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RECENT ADVANCES IN DERMATOLOGY

BY

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M.A., M.D.(Camb.), M.R.C.P.(Lond.).

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With Foreword

by

A. M. H. GRAY

C.B.E., M.D., F.R.C.P.(Lond.), F.R.C.S.(Eng.).

With 8 Coloured Plates and 50 Text Figures



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FOREWORD

THERE has never been, as far as I am aware, any work in the English language which has summarised the work done in Dermatology over a period of years. There are, of course, text-books which are constantly kept up to date, but which, owing to the exigencies of space and the necessity of adopting a more or less didactic style, cannot discuss at length various experiments that have led the authors to adopt their particular standpoint. On the other hand, the encyclopædias of dermatology compiled by many authors, though invaluable to the expert if conversant with the language (there are no such works in English), are apt to confuse anyone else by the very mass of material presented. There are also the very useful annual summaries of the principal papers published in each year. These, however, being limited to the work of a particular year, cannot give the same general survey of the subject as one which includes a period of years.

In the present work the author has reviewed the advances that have taken place in Dermatology over a period of some twenty years, approximately the post-war period. Naturally some of the roots of this work penetrate farther back than this, but as a general statement it would not be untrue to say that during the period mentioned, dermatological research has developed on different lines from those that existed before the war. For the twenty years or so before the war clinical observation was being supplemented—one might possibly in some cases almost say supplanted by an intensive investigation into the histology and bacteriology of skin diseases. Since the war, owing to the great developments in immunology, biochemistry, endocrinology, psychology, etc., a new orientation has occurred which, while not ignoring those aspects previously studied, has added a vast amount of new information to the subject and has,

at the same time, brought it into closer touch with general pathology and medicine.

As a result of this, however, Dermatology has lost much of its old simplicity. This may seem a curious word to use for those unfamiliar with the subject, who in former days looked on Dermatology as one of the most confusing branches of medicine, yet for dermatologists there can be no doubt that the subject was simple in those days compared with the present time. To-day all over the world various immunological experiments, often conflicting, are being carried out, which require almost from day to day a re-consideration of theories which had been based on previous experiments. The work on biochemistry becomes more and more complex and has long passed the comprehension of the average clinician; while the conflicts between the different schools in psychological medicine are apt to discourage any attempt on the part of the ordinary physician to try to understand anything about the subject.

The fact remains, however, that not only those who specialise in Dermatology, but also all those who are called upon to treat skin diseases, must have some knowledge of the progress that is being made in the subject. Such an opportunity is given them in the critical study which Dr. Goldsmith has provided, which not only deals with the advances in the science of Dermatology, but also very fully with the newer methods of diagnosis and treatment.

It is an especial privilege to me to be allowed to write this foreword, as Dr. Goldsmith has been associated with me at University College Hospital for nearly the whole period which this book surveys, and I know well his qualifications for the task which he has, in my view, so skilfully performed.

A. M. H. GRAY.

PREFACE

It is entirely due to Dr. A. M. H. Gray that I have had the privilege of contributing this volume to the well-known series, "Recent Advances," published by Messrs. J. & A. Churchill Ltd., and I am very happy to have the support of his kind foreword.

I have learnt a great deal through writing it. If someone is to profit from reading it, he will stand most chance, I think, by ploughing bravely through the chapters in their proper order (and then perhaps doing it again). For they have been arranged, as far as possible, in a logical sequence. Conclusions drawn from evidence sifted in the earlier chapters are taken for granted later. Thus, throughout the rest of the book, a familiarity is assumed with Lewis's work on the Triple Response, dealt with in Chapter I.: disorder of Lipoid Metabolism in Chapter VI. cannot be discussed without reference to the Reticulo-endothelial System, which has therefore been made the subject of Chapter V.: an understanding of the manifestations of Cutaneous Tuberculosis (Chapter VIII.) demands a careful study of the principles of Allergy, which I have tried to disentangle in Chapter VII. I must not multiply instances.

While many disorders, of which our knowledge has not materially advanced, have not been included, I have not shrunk from what may be considered somewhat lengthy and academic discussions of comparatively rare diseases, such as Xanthelasma, Amyloidosis and Addison's Disease, if they have seemed to me to illuminate important pathological processes of wider application.

Some conditions, *e.g.*, eczema, which may appear disappointingly inconspicuous in the Contents, will be found to make a much more arrogant display in the Index.

I have much pleasure in acknowledging my indebtedness to Dr. A. C. Roxburgh for kindly allowing the reproduction of several illustrations from the *British Journal of Dermatology*

and Syphilis, to Professor Jadassohn for similar permission with regard to his great Handbuch, to Dr. A. Miles with respect to the *Edinburgh Medical Journal*, and to Messrs. H. K. Lewis, Julius Springer and Masson for lending me blocks. Many colleagues in various countries have been good enough to supply me with original photographs or drawings: though its source is separately acknowledged beneath each picture, I wish here to express to them all my best thanks. Dr. W. Freudenthal has put me greatly in his debt for the beautiful drawings of Lichen Amyloidosus and Keratosis Senilis, made specially for this book.

The patience of publishers is (or should be) proverbial. I could hardly have put Messrs. J. & A. Churchill Ltd. to a severer test, but their courtesy and encouragement have been constant: I thank them cordially and crave their pardon.

Lastly my very grateful praise goes to my secretary, Miss R. Wilton, for the skill and zeal with which she has helped me preparing the drafts, revising the proofs and compiling the index; as well as for many clever suggestions and criticisms.

I hope that the book will be deemed a not unworthy homage to my great teachers, above all Dr. A. M. H. Gray and Professor J. Jadassohn.

W. N. G.

LONDON,
January.

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RECENT ADVANCES IN DERMATOLOGY

CHAPTER I

BLOOD-VESSELS

General Arrangement

LITTLE has been added to our knowledge of the gross anatomy since the classical description of Spalteholz in 1893. In his recent description (1927) he stresses the fact, pointed out long ago by Tomas, that the corium, although largely consisting of collagen and elastic fibres, possesses no blood-vessels of its own, *i.e.*, for its own use. One can see no blood-capillaries supplying the actual cutis itself apart from the papillæ, but only the epidermis and its derivatives. Even the finest arterioles in the upper half of the corium, hitherto looked upon as capillary-like, can contribute little or nothing to the nourishment of the corium, as they are surrounded by a mantle of circular muscle-fibres. Accordingly the true skin receives no arterial blood. For its nourishment it depends on the veins and possibly the lymph-vessels. The wall of the veins in the two superficial networks and also of the fine veins of the third plexus is constructed like that of the capillaries, entirely of endothelial cells and basement-membranes. In this respect the skin differs conspicuously from the other tissues composed mainly of connective tissue fibres. But Lewis says it is incorrect to regard the quite superficial capillary loops as the sole arterio-venous communications. There are occasional short communicating loops between the terminal arterioles and the collecting venules : they take a deeper and straighter course in the skin. Spalteholz describes the arteries of the cutaneous arterial network as possessing a thick muscular coat, which diminishes abruptly about the middle of the corium, where the vessels are

clothed by a single layer of muscle-cells. More distally this layer becomes imperfect, though muscle-elements are still discovered on the vessels of the subpapillary arteriolar plexus and even the terminal arterioles. For the sake of convenience in studying the behaviour of the blood-vessels, Lewis uses simple comprehensive terms, the relationship of which to Spalteholz's names I have set in the following table, which is slightly altered and elaborated from one given in Lewis's book.

Lewis's Names.	Spalteholz's Names.	
Strong arterioles	Main cutaneous arteries Cutaneous arterial network Arched arterioles	Strongly coated with muscle.
	Branches of arched arterioles Subpapillary arterial network Terminal arterioles	Slight covering of muscle.
Minute vessels Subpapillary venous plexus.	Capillaries Collecting venules 1st venous plexus 2nd venous plexus	Simple endothelial tubes, capable of nourishing surrounding tissues.
Deep veins	Communicating veins. 3rd venous plexus. Communicating veins. 4th venous plexus. Main cutaneous veins.	

The skin-area supplied by a branch of the subpapillary plexus averages 0·16 sq. mm.

The Colour of the Skin

The class of vessel that contributes most to the natural suffused redness is the subpapillary venous plexus, included in Lewis's "minute vessels." This can be simply demonstrated. If a glass slide is placed against the skin of the forearm and the vessels watched microscopically while a gently increasing pressure is exerted, the skin pales long before the capillaries empty and the most notable pallor develops at the moment when the venules of the subpapillary plexus collapse, and they are the first to do so. *Depth* of colour indicates the size of the minute vessels and throws no light on the rate of blood-flow. Ebbecke and Dale and Richards have pointed out that an area of

pale skin may be hotter than a red one. Thus it is *temperature* which expresses the relative rate of blood-flow. The *tint* is more complex in origin. It depends chiefly on the relative amounts of hæmoglobin and oxyhæmoglobin. Therefore a more rapid flow contributes to a redder tint. It is also redder if the superficial capillaries are dilated, as they hide the deeper venules. If the skin has natural warmth but is cyanotic, the arterial blood must be abnormal. The colour of the blood in the minute vessels depends, of course, also on the rate of oxygen-exchange with the tissues, but generally the rate of flow remains the preponderating factor. (Exceptionally skin may be red when little or no blood moves through it.)

Contractility of the Minute Vessels

When the skin is lightly stroked with a blunt point, there is an immediate pallor from mechanical emptying of the blood vessels; this almost immediately disappears. But within a further period of from 15–20 seconds the line of stroke again becomes visibly paler. The *pallor* reaches its full intensity in about 45 seconds. Soon it diminishes and after 5 minutes becomes indistinguishable. It is the tension or stretching of the skin that seems to be the effective stimulus. The white band is remarkably sharply defined, exactly mapping out the area stroked. This precision suggested to Müller in 1913 that the pallor might be due, not to contraction of the arterioles (which supply areas of more than 1–2 sq. mm.), but to the active contraction of the minute vessels responsible for skin-colour. That this is the case is proved by Lewis in the following way. The circulation in an arm is suddenly and completely interrupted by throwing the pressure of 300 mm. of mercury into an armlet. Under such circumstances the pressures in the arteries and veins become rapidly equal. The white reaction can be obtained in the skin of such a limb even up to 15 minutes after the interruption of circulation and does not differ from that in the opposite arm. Carrier and Parrisius have confirmed this and shown that each member of the minute vessel group is involved. The contraction

of the minute vessels after a short latent period in response to tension appears to be the direct result of stimulation of their walls. It is independent of nervous reflexes, central or local. Thus Ebbecke saw it occur on skin to which the nerve-supply had long been lost. Lewis estimates that when the minute vessels are contracted in response either to stroking or to adrenalin they are able to resist a minimal distending pressure of as much as 100 mm. of mercury, which is equal to, if it does not exceed, any pressure that can possibly be exerted on them from the arterial side.

The Triple Response

Whereas a gentle stroking or stretching of the skin produces the above described white reaction by directly stimulating the minute vessels to contract, stimulations of greater intensity evoke quite a different set of reactions. This set of reactions is composed of the following triad, called by Lewis "the triple response."

(1) Local Red Reaction. When the skin is *firmly* stroked with a blunt point, a subsequent red reaction along the line of pressure is invariable. It begins within about 3–15 seconds, reaches its height in about 45 seconds, and fades very gradually. The intensity and duration increase with the strength of stimulus and also if it is repeated. At first it is bright red, but later becomes bluish. It is precisely confined to the area stimulated. This fact suggested to Müller, as in the case of the white reaction, that the vessels mainly determining it must belong to the smallest orders. It is inconceivable that arterioles supplying more than a square millimetre of skin-surface or that veins, having more than a corresponding territory, could be responsible. That it is due to dilatation of the arterioles is disproved by the fact that the red reaction is still evoked when the circulation to a limb has been brought to a standstill; under such circumstances dilatation of the arterioles could only withdraw blood from the minute vessels. A contraction of the deep veins might conceivably force a little blood backwards towards the surface, but could not produce the vivid and sharply outlined reaction. It must, therefore, be due to an active relaxation of the minute

vessels themselves. It is seen equally well on skin to which the nerves have been cut and have degenerated.

(2) THE FLARE. When the skin is adequately susceptible or the stimulus strong enough, there occurs in addition to the above described red line, after a further delay of perhaps 15–30 seconds, a flushing of the neighbouring skin which Lewis calls "the flare." It increases in intensity and spreads for a greater and greater distance from the line. Its bright scarlet colour, which is maintained to the end, contrasts with the somewhat bluish tinge of the local red reaction; but it fades much earlier. While fading it is speckled, the speckles being at first most conspicuous at the edges. The flare fails to appear if the main vessels of the limb have previously been occluded, or if adrenalin has been injected beneath the skin. It is accompanied by very appreciable rise of temperature. If, on a skin showing the local red reaction and flare, a light stroke is made at right angles to the line, the normal white reaction will be seen within the area of the flare, but not where it crosses the local red line. Thus the contraction of the capillaries induced by gentle stretching can close them where they are passively distended by arteriolar dilatation but not where they are themselves actively dilated. Thus the evidence clearly establishes that the flare originates in dilatation of arterioles. The area supplied by a single arched arteriole is reckoned to measure a few millimetres across, which tallies with the size of the marginal crenations of the flare. These are therefore probably the most peripheral vessels that dilate and the smallest that possess a strong muscular coat. The flare is dependent on the integrity of the cutaneous nerves; the nervous path is discussed later.

(3) THE WHEAL. The above reactions may constitute the whole visible effect of firm strokes; but often these are followed by swelling of the skin, a local œdema, forming an urticarial wheal. The skin of certain individuals is peculiarly susceptible to stroking, and wheaing so produced is called "factitious urticaria" or "dermographism." The passage from a physiological to a pathological degree is insensible. Amongst healthy people a detectable swelling is found in about a fourth of those tested, and

in about 5% a conspicuous wheal is produced. The full reaction to stroking is not qualitatively pathological but only quantitatively. A wheal can be produced on the skin of the back of almost any normal subject by six to ten firm strokes accurately superimposed. The wheal habitually raised by a whip-lash is an example of the effect of a single strong stimulus on normal skin. Continued and hard friction wheals or blisters it. In factitious urticaria the wheal begins to appear in about 2 minutes and is generally at its height in about 4 minutes. It is at first red but shortly pales, the pallor being due to the pressure exerted by transuding fluid on the minute vessels. At first its margins are crisp and mark out precisely the borders of the local red line that precedes it. As time passes they become less sharp, since the fluid content being under pressure forces its way gradually into the surrounding skin. It may remain visible for one or many hours, but gradually disappears. The wheal is part and parcel of the total reaction; the stimulation needs to be relatively strong. It can be shown that the outpouring of fluid into the tissue-spaces is not the result of increased filtration-pressure, but of increased *permeability* of the vessel-walls. This permeability again is not the result of a simple stretching of the vessel-wall but of an independent change. Once it is established, the rate at which fluid is poured out is mainly governed by the rate of blood-flow. Ebbecke showed that, if trypan red is injected into the general blood-stream, the dye appears in a wheal while it is forming, but does not discolour a wheal already developed. This demonstrates the increased permeability, since vessels in their natural state retain this dye, and by this means he has shown that transudation ceases in about 5 minutes.

The triple response is a type-reaction and can be brought about by a great variety of stimuli: mechanical, electrical, thermal or chemical (including histamine). The similarity of the response to such a variety of stimuli is remarkable. It assumes still greater significance when one considers that the three essential parts of the response are independent of each other. Thus the flare is called forth through nervous channels, while the local dilatation

and œdema are not ; but the two last are also separable. Thus it becomes inconceivable that all the constituent parts of this complex response can be due directly to such different stimuli. There must be some common intermediate mechanism, which can evoke all the parts of the response and which can be called into play by all these stimuli. It is obviously most likely that this common factor is connected with *tissue-injury*.

Another method of reasoning brings us to a similar conception. In urticaria factitia the skin is hypersensitive to stroking. Now this susceptibility might be a general one or specific for the mechanical stimulus ; the latter is found to be the case. In such subjects electrical, thermal and chemical (including histamine) stimuli have no greater effect than in controls. Now, if the proneness of dermographic subjects to flare and to wheal depended on an unusual general reactivity of the vessels, then the stroke and the histamine and other stimuli should all yield exaggerated reactions. Thus for some reason a single stroke in a dermographic patient forms an adequate stimulus to the complex mechanism composed of nervous and vascular elements, which is no more than normally excitable. But since the stroke is a similar stroke to that applied on the skin of a control and which, if unrepeated, yields but limited response, it becomes doubtful whether the stroke itself provides the immediate impetus that sets the train of events in motion.

Responsibility of Diffusible Substances for Local Vaso-dilatation. The red line produced by a firm stroke on an arm in which the circulation has been stopped does not subside, but persists at a maximal intensity as long as circulatory arrest is maintained (tested up to 25 minutes). Thus the stimulus directly producing the line seems to persist in full force during the period of arrest and cannot therefore be the stroke itself.

Spread of Local Skin-Reaction. That wheals should spread is to be expected, as we have seen, because the fluid exuded under pressure forces its way into the neighbouring tissues. The following experiment is more significant. Venous pressure in a normal limb is first raised to about 200 mm. of mercury and the circulation then arrested. Histamine is now punctured into several

parts of the skin and the arm laid in a cold bath. (This preserves such increased permeability of the vessels as is produced by histamine.) Shortly small purple spots appear at the sites of puncture. They become and remain sharply defined but *increase in diameter*. No wheals form on them until the circulation is restored. Then wheals quickly appear and their diameters, *when they first become defined*, correspond accurately to the full diameters of the purple spots. Now enlargement of the purple spots under arrested circulation can only be due to diffusion of the histamine from the point of puncture. If in dermographic patients the experiment is repeated using a stroke instead of histamine-puncture, a similar spread of the purple line is observed. It is therefore concluded that the stroke has liberated within the skin a diffusible substance which acts like histamine as a direct stimulus, dilating and increasing the permeability of the vessels with which it comes in contact.

That the flare is also produced by a diffusible substance which acts similarly to histamine is shown as follows. If histamine is punctured into the skin of a limb in which the circulation has been arrested, and if it is kept arrested for 10 minutes after the puncture, the flare only appears after its release, persisting after the reactive hyperæmia of the rest of the limb has subsided. This delayed flare, though depending on a nervous reflex, cannot possibly be due directly to the original puncture. Here again a stroke in a dermographic subject shows the same phenomena.

Thus it is shown that a chemical substance is liberated, which yields a widespread arteriolar dilatation by acting on a local nervous mechanism; and also that the local reaction is due to a diffusible substance liberated in the skin, which acts directly on the vessel-wall. It would be gratuitous to postulate more than one substance since one would be enough.

THE IDENTITY OF THE DIFFUSIBLE SUBSTANCE. We have seen that the triple response to different stimuli depends on a common intermediate mechanism probably associated with tissue-damage, and that the most important part of this mechanism is a diffusible substance with an action similar to histamine. It is therefore likely that the diffusible substance is actually in every case

histamine or a substance closely related to it. Histamine is an amine produced when carbon dioxide is split off from histidine, a protein derivative occurring naturally in the body. It has been extracted from the mucous membrane of the gut and from liver and lung. If a drop of histamine 1 in 3,000 is placed on the normal skin and a prick made through it, a perfect triple response is evoked with constancy. The following facts further support the hypothesis that histamine is the responsible substance. Larger doses of histamine, introduced into the general circulation, produce profound effects of a kind very similar to those witnessed after extensive injuries of the tissues, such as shock following burns. In *shock* the main phase is characterised by fall of blood-pressure. There is relative emptiness of the heart, arteries and veins; but they are not dilated. The loss of volume is due to escape of plasma (the blood remaining in circulation being over-rich in corpuscles), as a result of dilatation of the minute vessels and an increase in their permeability. There are certain conditions in which urticaria and shock-symptoms occur together—namely, serum-sickness and classical experimental anaphylaxis. The symptoms of anaphylaxis have been proved to be due to the interaction of antigen and cell-fixed antibody. This interaction damages the cell to which the antibody is fixed. In a sensitised or anaphylactic individual a local urticarial response can often be evoked by pricking the antigen into the skin, the effects being exactly the same as those of pricking in histamine. It is probable, therefore, that the symptoms of anaphylaxis are the result of the setting free of histamine from cells damaged by the interaction of antigen with the antibody fixed to them.

THE TISSUE-ELEMENTS RESPONSIBLE FOR THE RELEASED SUBSTANCES. Lewis thinks that the cells mainly responsible for the release of H-substance in the skin are the living epidermal cells. A needle-prick just deep enough to penetrate through the horny layer and reach the living epidermis always yields a vascular response. Under the binocular microscope a needle can be passed into the skin between neighbouring capillary loops till a sharp prick is felt. The point is then seen to lie at the level of the tops of the capillary loops and does not penetrate nearly to

the true skin. After a triple response the epidermal cells frequently show signs of having been injured. All the stronger forms of stimulation usually employed, such as heating and freezing, are followed by desquamation. It is not until far stronger stimuli still are employed that deep layers of the skin are killed. That the substances are not released mainly from the endothelial walls of the minute vessels of the skin is indicated by the fact that these show no subsequent evidence of damage : *e.g.*, after the skin has been frozen sufficiently there forms a conspicuous wheal, and when this has subsided the capillaries are found to be intact and carrying blood.

That the released substances contain histamine and that their chief source is the epidermis have been corroborated by some more recent work of Harris. He showed that alcoholic extracts of human skin contain a substance that flushes and wheals it when pricked in. The extracts also contain a depressor substance and produce contraction of the guinea-pig uterus. From this and other evidence it is concluded that the extracts contain histamine. Its amount in normal skin is estimated at about 10 mgm. per kgm. Its concentration in the epidermis is six times greater than in the dermis. The epidermis contains 24 mgm. per kgm. = a solution of 1 in 40,000. Such a solution is more than adequate, if punctured into the skin from without, to flush it and wheal it. Therefore, the outpouring of the contents of a very few epidermal cells should suffice to produce a visible reaction. Skin when burnt or frozen contains no more and no less histamine than uninjured skin ; later its concentration actually diminishes. It therefore appears that the histamine is preformed in the cells and not produced by the injury. The latter causes it to escape from the cells into the tissue-spaces, and the subsequent diminution in concentration results from its absorption into the blood-stream. In blister-fluid its concentration in an *early* sample is higher than in the blood-plasma, but later approximates to it.

The Slower Reactions of the Skin to Ultra-violet Light and to some other Forms of Stimulation. Many familiar reactions of the skin that are preceded by considerable latent periods, *e.g.*, those provoked by ultra-violet and shorter-waved irradiations, by

bacterial toxins and by certain chemicals, receive from Lewis a similar interpretation to that of the acute reactions already discussed. In other words, the reaction of the skin is fundamentally the same to slowly acting as to quickly acting stimuli. The longer latency signifies the difference in the manner in which the stimulus acts upon the cell and represents the time during which the released substances are accumulating.

The Effects of Temperature upon the Minute Vessels. The only truly direct influence of moderate temperatures is that heat increases and cold lessens their tone. Temperature-change, however, also exerts an indirect influence by altering the amount of vasodilator substances in the tissue-spaces. Heat increases and cold diminishes their concentration, leading respectively to vasodilatation and to vasoconstriction. Thus the direct and indirect influences are in conflict. If one starts from the normal skin-temperature and ascends the scale, the direct influence is found to predominate and at a high temperature the metabolites accumulate enough to produce the triple response, even to blistering. On the other hand, as the scale is traced from normal downwards, the metabolites become reduced and the skin pales a little; but as the temperatures fall still lower the change in metabolic activity becomes less in degree and importance, and the direct paralytic influence of cold predominates, dilating the vessels. Eventually the temperature is low enough to damage cellular tissues, when flare, wheal and blister appear as an indirect effect.

Reactive Hyperæmia. Reactive hyperæmia, *i.e.*, such as occurs after prolonged pressure, is due chiefly to active dilatation of the minute vessels, the walls of which are essentially endothelial. This suggests that the reaction results from a local chemical change connected with tissue-metabolism. It is independent of nervous control, central or local. When the skin is deprived of blood, non-volatile metabolites accumulate slowly in the tissue-spaces and lead to vasodilatation. It is suggested that if the substances become sufficiently concentrated they lead to the more pronounced effects of the triple response. In the case of physical injuries release in relatively high concentration

is abrupt, whereas here it is slow. Thus reactive hyperæmia illustrates how vasodilatation may be produced by normal metabolic substances (it occurs so soon, viz. within a few seconds after interruption of blood-flow, that abnormal metabolites are unlikely). It also provides suggestive evidence that these normal metabolites gathered in sufficient concentration may yield the full triple response. Therefore it supports the contention that the H-substance is a normal metabolite. Because Lewis was unable to decide whether injuries to the skin bring about their vascular responses solely through the action of a common normal metabolite or whether this is eventually supplemented by disintegration products, he allows the definition of H-substance to embrace more than one substance.

Nerve-Supply of the Cutaneous Blood-Vessels

Constrictors. These are all derived from the sympathetic in the normal manner.

Sympathectomy. The modern operation consists in the removal, for disorders of the upper limbs, of the inferior cervical and first and second dorsal ganglia, and for the lower limbs, of the second, third and fourth lumbar ganglia; in both cases together with the intervening portions of the sympathetic chain. It is very beneficial in many disorders arising from spasm of the arterioles, such as Raynaud's disease, very severe chilblains, certain "trophic" ulcers of the legs, sclerodactyly and even thrombo-angiitis obliterans. Lake says that the effects of the modern operation, as opposed to Leriche's periarterial method, are permanent; the final result is, however, sometimes worse and sometimes better than the early one. Disorders of the lower limbs are more amenable than those of the upper. Sometimes after a unilateral sympathectomy there is an immediate improvement on *both* sides. This is thought to be due to the setting free of H-substance from damaged tissue and, on the unoperated side, soon disappears again.

Dilators. These have a much wider origin and run a very varied course. A large part of the *scalp and the adjoining mucous*

membranes receives its dilators by way of the cranial nerves (trigeminal, facial, glossopharyngeal, laryngeal branch of the vagus). In addition the cervical sympathetic is said by Dastre and Morat to provide dilating fibres for the skin of the ear, cheeks, lips and their neighbourhood; they come from the upper part of the thoracic cord and leave it by the ventral roots. But Feldberg and Schilf think that these fibres are secretory and that the vascular dilatation is a secondary metabolic effect.

In contrast with the above, the dilators for the skin of the *trunk and limbs* leave the cord, between the lower cervical segments and the first sacral segment, through the *posterior roots* and run with the spinal nerves to the periphery without making connection with the sympathetic chain.

As long ago as 1876 Stricker observed that the skin of the limbs flushes when the cut posterior roots of the spinal nerves are stimulated peripherally. Foerster noted that the areas of flushing correspond closely with Head's zones, which were determined on the basis of "trophic" disorders. A similar reaction is seen if the sensory nerves are excited distal to the ganglia (Bayliss). The fibres concerned belong to the posterior root system, degenerating when the root-ganglia are removed but not when the roots are cut between the cord and the ganglia. Bayliss concluded that they are identical with the afferent fibres and capable both of conducting stimuli from the skin to the cord and also, as far as they are in connection with blood-vessels, of producing changes in the periphery resulting in their dilatation. He speaks of an "antidromic conduction." This view is widely accepted in modern literature, but Hirt in 1928 showed that the spinal ganglia, in addition to the somatic cells, contain many autonomic ones, including some which send long processes to the periphery. As it is with great probability that an efferent conduction can be ascribed to them, he thinks there no longer remains any necessity to assume an antidromal action, especially as this assumption is not supported in any other department of nerve-physiology.

The Nervous Mechanism of the Flare. The flare still occurs if the peripheral sensory nerves have been interrupted by cutting or injection (Lewis and Grant). But when they have been cut

it only remains obtainable for 7 days. After that it fails, presumably because the nerves have degenerated. Lewis therefore ascribes it to a short "axon-reflex," further explained as follows: Woollard states that the plexuses found on the arteries are of two kinds, non-medullated (sympathetic) and medullated (sensory). The latter chiefly participate in innervating the smaller arteries and arterioles. When traced peripherally the sensory fibres are seen to throw off collaterals ending in special terminations in the adventitial walls of the arterioles, in the surrounding fatty connective tissue, in Pacinian bodies, and presumably also in nerve-endings to the skin. He has shown that one and the same sensory fibre may by division supply the arteriolar wall and special sensory nerve-endings. Bruce thinks that the stimulus ascends such an afferent nerve-fibre to a bifurcation and then goes over into the other branch, by which it returns to the arterioles. This reflex seems to form a mechanism of defence peculiar to superficial and sensitive structures such as the skin and conjunctiva. But if Hirt's views are right it may be that the fibres to the arterioles contain some purely efferent autonomic twigs which are stimulated by the histamine.

Innervation of the Minute Vessels. Stöhr has shown with the new silver methods the presence of very fine nerve-twigs which reach the capillaries, accompanying or entwining them in portions of their length and then switching off to other capillaries, so bringing about a kind of nervous cross-connection for a group of such vessels. That the tone of the minute vessels can be changed by nervous action independently of the arterioles has been demonstrated in the case of *the constrictors* by Harris and Marvin in 1927. They showed in the rabbit's ear that stimulation of the sympathetic caused the blood to be expelled from the capillaries after the circulation in them had been brought to a complete standstill by compressing the arteries.

Active *dilatation* of capillaries may also result from nerve-stimulation. The impulse is conveyed by way of the sensory nerves. It is likely that the dilatation ensues indirectly by a chemical change, for, as von Frey points out, the constricting and dilating nerves are not antagonistic in the sense that their effects

cancel each other. If both are stimulated together, constriction occurs first and dilatation later. Lewis was led to the same idea, partly by the consideration of herpes zoster, the skin-lesions of which he thought were caused by the damage to the posterior root ganglion. We know now that this is not the case, the skin-lesions being the result of the local presence of virus (see page 382). But it led him to investigate whether stimulation of sensory nerves did in fact release H-substance. He used the median nerve of a cat, from which the sympathetic fibres had been destroyed by excising the stellate ganglion at least 3 weeks before. (This would not, however, remove the autonomic fibres of Hirt.) Stimulation of this sensory nerve produced a very long-lasting flush, gradually increasing to a maximum over a period of about 30 seconds of stimulation, and then declining over a period of 5–10 minutes. This suggests the gradual accumulation and subsequent removal of a vasodilator substance. A further and more conclusive experiment shows that the vasodilatation can be postponed by arresting the circulation to the limb. [The real vasomotor (constrictor) nerve, on the other hand, produces its effect immediately and this disappears rapidly after cessation of stimulation and is not postponed by arresting the circulation.]

Though zoster itself can no longer be cited, there are other significant clinical instances. Weir Mitchell described cases in which a nerve, though not transected, is damaged and subsequently caught up in the scar. The limb so affected is guarded by the patient with utmost precaution, not only from injuries, but from contacts of any kind. The affected skin is glossy, red, smooth, hairless, acutely sensitive and painful, and sometimes the seat of herpetiform eruptions, single or repeated. These lesions are clearly irritative, judging by the pain, and not paralytic (trophic) nor caused by trauma.

Irresponsiveness and Refractoriness

Under certain circumstances, chiefly after a reaction to histamine, freezing, etc., the minute vessels remain dilated and refuse

to respond fully or at all to the vasoconstrictor substances on the one hand (irresponsiveness), and, on the other, to histamine or equivalent substances in so far as these cause increased permeability (refractoriness). The explanation is not quite understood.

Mottling of the Skin

Some degree of mottling is normal; no part of the skin is exempt. Often the whole body, with exception of the face, is mottled. The fine speckles on the hand and the larger mottlings on the limbs are essentially similar, for they behave alike in all conditions of test. Lewis says that the areas comprised are relatively constant in form and in position in any individual over long periods of time, and concludes that they must depend on a permanent arrangement of some structures in the skin. This is also strongly suggested by the similarity of the pattern in form and size in different individuals. The paleness is not due to a difference in the number of vessels as compared with the dark areas, but to difference in their size, and this is explained by differences in tone. Thus the pale areas withstand considerable venous pressure before they suffuse. Mottling is independent of nervous influences.

So-called "erythema ab igne" corresponds in pattern with the ordinary mottling. Its outline would not be so distinct if the pattern were continually changing. In a case of erythema ab igne the dark pigmented areas were found to be irresponsive to adrenalin and refractory to histamine. The average temperature of the pale areas was actually slightly higher than that of the dark. In the neighbouring skin, which showed marked ordinary mottling, the dark parts were also irresponsive to adrenalin, though not so completely.

Considering the evidence as a whole, Lewis inclines to the old view of Adamson and others that there is a correspondence between areas of mottling and main arteriolar territories. The maximal points of supply being in the centre of the pale areas would explain the greater capillary tone. In the marginal areas the vessels, having a slightly less blood-flow, would be more

susceptible to damage and, their tone being originally low, would tend to become more or less permanently inefficient, irresponsive or even completely refractory.

But Lewis's opinion that the fine speckles on the hand are essentially similar is not quite in harmony with the findings of some other observers. Thus Ebbecke noticed that the appearance of the skin-surface, especially the palms, in the same individual varies greatly, especially if it is warmed. Then one sees white and red spots of a few millimetres' diameter. Prolonged observation of these shows that there is both spontaneous change in the width of the arteries and also, quite clearly distinct from that, in the width of the local capillaries. The distinctness of the spots varies in an irregular rhythm once or a few times in a minute. Carrier found that within a certain area some capillaries were almost permanently open, whilst others rapidly shut and opened again. Microscopical comparison of various regions showed that areas of a few millimetres in diameter, in which only a few capillaries were open and the deeper vessels were difficult to see, alternated with other areas in which most capillaries were open and the deep vessels were clearly visible. There is, therefore, a fluctuation not only in the general blood-supply of the skin, but of the tiniest areas.

Von Frey concludes that, though the width of the capillaries is largely determined by local metabolic changes, it is doubtful whether there can be metabolic differences so close together as to account for the variations in tone observed by Carrier in neighbouring capillaries. Perhaps there is some automatic rhythm such as has been demonstrated in arteries (Meyer, Rothlin). They need not be attributed to nerves, as Schmidt has noticed them in the nerve-free vessels of the umbilical cord.

Morbid Eruptions

In attempting to explain morbid eruptions in terms of the triple response, Lewis distinguishes two parts of it and emphasises some of their characteristic points. In the *first type* (independent of nerve-supply) the fully developed colour is

intense but rapidly becomes dull-red or purplish; the margins are crisp; there is frequent association with swelling; the reactivity of the vessels to adrenalin and histamine is reduced. This type especially tends to be followed by pigmentation. In the *second type* (dependent on nerve-supply when due to a local injury) there is a diffuse scarlet blush of irregular outline, becoming speckled. It is blanched by adrenalin and its response to histamine is normal. There is a distinct rise of skin-temperature. Taken separately, these two types may be compared broadly to the macular or morbilliform type of eruption and the scarlatiniform respectively. He thinks that H-substance can be released either by direct injury of cutaneous cells, by circulating or entrapped poisons, or through the medium of efferent impulses in the sensory nerves.

URTICARIA. The phenomena are characterised by acuteness and suggest its being due invariably to the almost instant and full poisoning of the cells, whereby H-substance is released quickly and in quantity.

THE BLISTER. This represents a modification of the first type, especially associated with a prolonged stimulus and response.

HÆMORRHAGIC ERUPTIONS. These belong essentially to Type I.

SCARLATINIFORM RASHES. It is suggested that the responsible poison acts either directly upon the sensory nerve terminations, as does histamine in the axon-reflex, or upon the strong arterioles themselves.

CENTRIFUGALLY SPREADING LESIONS. If an inflammatory lesion creeps slowly through the skin radially or in one direction, the intensity of the reaction being fully maintained at its moving edge, Lewis thinks the lesion is due to a poison introduced into the skin locally and not diffusely. For marginal advance indicates that the stimulus to which the skin surrounding the original lesion is responding is reaching it radially from the central focus. No movement of H-substance released at a centre point can account for a form of progression in which the reaction is maintained at its full intensity. The poison is, therefore, probably a living bacterial agent. The obvious example is erysipelas, but

other instances of creeping lesions should, Lewis thinks, be interpreted similarly. The flattening or healing in the centre is not due to the original poison being exhausted there, because that would assume that the poison, still existing at the margin, is free to move outwards but not inwards. It is due to the vessels that reacted first having gradually become refractory to stimulation and simultaneously lost their increased permeability. This also explains why, when two active margins meet, they do not become superimposed but subside.

LUPUS ERYTHEMATOSUS AND ROSACEA. These favour areas in which the vessels are prone to become irresponsive.

RAYNAUD'S DISEASE. Recent work of Lewis suggests that the essential abnormality lies in the small arteries themselves and is independent of the vasomotor nerves. The phenomena are caused by a temporary complete closure of the arterioles, brought about by cold, to which they are abnormally sensitive. In addition there is in most cases some thickening of the intima, which adds to their tendency to occlusion. Given vessels already in this abnormal condition, the vasomotor nerves, if stimulated by emotion or exposure of the whole body to cold, may precipitate an attack by exerting their normal constrictor action.

Bibliography

CARRIER, E. B. "The Reaction of the Human Skin Capillaries to Drugs and Other Stimuli," *Amer. Journ. of Physiol.*, 1922, **61**, 528 (*cit.* W. Spalteholz).

EBBECKE, U. (*a*) "Die lokale vasomotorische Reaktion der Haut und der inneren Organe," *Pflügers Arch. f. d. ges. Physiol.*, 1917, **169**, 1 (*cit.* von Frey); (*b*) "Gefässreaktionen," *Erg. Physiol.*, 1923, **22**, 401 (*cit.* von Frey).

VON FREY, M. "The Blood Vessels of the Skin and their Changes of Tone," *Jadassohn's Handbuch der Haut u. Geschlechtskr.*, I/2, 21.

HARRIS, K. E. "Observations upon Histamine-like Substances in Skin Extracts," *Heart*, 1927, **14**, 161.

HIRT, A. "Ueber den Aufbau des Spinalganglions und seine Beziehungen zum Sympathicus," *Zeitschr. Anat.* 1928, **87**, 275 (*cit.* von Frey).

KROGH, A. "Anatomy and Physiology of the Capillaries," translated by Ebbecke, Berlin, 1924 (*cit.* W. Spalteholz).

LAKE, N. C. "Sympathetic Surgery in the Treatment of Cutaneous Lesions," *Brit. Journ. Derm.*, 1935, **47**, 143.

LEWIS, T. (*a*) "The Blood Vessels of the Human Skin and their Responses." London: Shaw & Sons, 1927; (*b*) "Raynaud's Disease, with Special Reference to the Nature of the Malady," *Trans. St. John's Hosp. Dermat. Soc.*, 1932, 60.

SPALTEHOLZ, W. "Blood Vessels of the Skin," *Jadassohn's Handbuch der Haut u. Geschlechtskr.*, **I/1**, 379.

STÖHR, P. H., JUN. "Die peripherische Nervenfasen," *Handbuch der microscop. Anat.*, 1928, **4**, 1 (*cit.* von Frey).

WOOLLARD, H. H. "The Innervation of Blood Vessels," *Heart*, 1926, **13**, 319 (*cit.* T. Lewis).

CHAPTER II

THE GLANDS OF THE SKIN

THERE are three kinds of skin-glands.

A. Sebaceous glands, which are derived from, and in principle always open into, a hair-follicle.

B. The small coil-glands, which open on to the free skin-surface, or true sweat-glands.

C. The large coil-glands, which, as a rule, open into a hair-follicle.

The glands of the skin are differentiated, according to their mode of secretion, into holocrine and merocrine (Ranvier).

HOLOCRINE GLANDS. The secretion from these entails and is formed by complete disintegration of the gland-cells. The sebaceous glands and even the whole epidermis are examples.

MEROCRINE GLANDS. The gland-cells produce a secretion but themselves survive. It is either only a more or less fluid secretion or composed of a part of the cell itself. Examples are the coil-glands, referred to in common as sweat-glands.

These merocrine glands are further subdivided (Schiefferdecker, 1921) into eccrine and apocrine. The *eccrine* glands give off a clear secretion, the cells remaining intact. The *apocrine* glands also give off a fluid secretion, but in addition the tips of the actual cells disintegrate and are shed into the lumen.

Epidermis

The secreting cells are represented by the stratum germinativum. As they multiply they degenerate and are extruded towards the surface. In the course of this process, on the one hand, they produce a wax-like substance (keratohyalin, eleidin, horn-fat), and, on the other hand, the remains of the cells are

transformed into horn. The chief component of this is *keratin*, a protein distinguished by its high content of cystine and its resistance to chemical and mechanical attack. The horn-fat is distinguished from sebum by its rich content of cholesterol esters and free cholesterol. Sebum and horn-fat have, like lecithin and lanolin, the important property of holding water in considerable quantity and impeding the absorption and loss of water by the skin without entirely preventing it.

Sebaceous Glands

Nothing of importance has been added to our knowledge of these in recent years. Besides the regular sebaceous glands associated with every hair there are others, arranged irregularly, singly or in groups and sometimes visible to the naked eye. They are found particularly at junctions of mucous membrane with skin, in the mouth and in the skin of the genital regions, nipple and areola (cf. possibly meibomian glands of eyelid). Even some of these are attached to more or less well-developed hairs, but sometimes the hair-follicle is vestigial or absent. On the lips and mucous membrane of the cheeks they are visible as tiny, yellowish, round, scarcely raised nodules in about 50% of males and rather less often in females. They only develop at puberty. The appearance is generally referred to as "Fordyce's Disease," but it was described by Koelliker as long ago as 1862. Its main importance lies in its being apt to be confused with lichen planus.

SEBUM. This contains a small quantity of fat (triglyceride), but chiefly the esters of the high molecular alcohols and fatty acids; cholesterol is only present in traces. It has the function, with horn-fat, of hindering rapid evaporation and conserving warmth. This conforms with the fact that cold, which produces goose-skin, must at the same time, by action of the erectors, express sebum from the glands. The sebaceous glands are most densely situated where subcutaneous fat is minimal, *e.g.*, scalp, nose, lip, chin, the middle line of the front and back of the trunk, *i.e.*, those areas which specially need to be protected against loss of heat. This is particularly well illustrated by the tip of the nose.

Seborrhœa. Dependence of the activity of sebaceous glands on direct nerve-supply is very doubtful, but, as in the case of the apocrine sweat-glands, they are influenced by psychical and sexual processes, probably through a hormonal mechanism.

The explanation of *Vernix caseosa* is still uncertain. Stein thinks that during pregnancy the same substances which stimulate the skin-glands, and especially the mammary gland, of the mother also actively stimulate the sebaceous glands of the fœtus; after birth this stimulus of course disappears and the sebaceous glands in childhood become inconspicuous. They spring into activity again at puberty, when once more fully developed sexual glands supply the necessary hormones. Up to the age of 5 years there is a great tendency to seborrhœa of the scalp. This often disappears between the ages of 5 and 15 years, reappearing at puberty. A third period of heightened function is associated with senile changes. When the papillæ cease to produce hairs the sebaceous glands often grow and secrete more intensively, a last flicker before senile shrinkage.

Local asphyxial and cyanotic states also increase the secretion.

Post-encephalitic Seborrhœa. The most definite evidence of the influence of the vegetative nervous system on sebaceous secretion is afforded by the occurrence of extreme degrees of facial seborrhœa after encephalitis lethargica. It was first noticed by Cohn in 1920 in early or acute cases and thought to be a manifestation of the nervous lesions. Krestin gave a full account of it in 1927. He only included cases in which the history was quite definite that the skin-condition only appeared after the infection. The skin of the face is swollen, doughy and covered with sebum, often giving the impression that some ointment has been applied. It is made worse by excitement, heat and sweating. In old-standing cases a scaly eruption on a hyperæmic base is common, especially over the forehead, resembling the scaly seborrhoid met with on the chest in non-neurological cases. A mild degree of blepharitis is usual. When seen soon after the acute pyrexial period the face shows a diffuse pink flush, which after a time disappears, often leaving telangiectases over the cheeks. The mouths of the sebaceous glands are

patulous and frequently occupied by black keratinous plugs. In old-standing cases there may be papular, acneiform or pustular lesions, leaving pitted scars. Pityriasis capitis is almost invariable, usually dating from the acute illness. If previously present, it nearly always increases with the encephalitis.

This seborrhœic condition is generally associated with Parkinsonian rigidity and excessive salivation. The onset of the skin-changes is difficult to determine, but in most cases they appear with muscular rigidity between 6 and 18 months after the acute phase. The seborrhœa and sialorrhœa diminish with time and to some extent with the administration of hyoscine or belladonna, though the muscular disability may remain stationary or get worse. The seborrhœa is most marked in young subjects and almost constantly associated with the mask-like facies. The same skin-condition was also seen in other disorders presenting Parkinsonism, such as paralysis agitans, as well as in some patients with mixed pyramidal and extra-pyramidal lesions.

The association of secretory disorders of at least two sets of glands, the skin and salivary, with manifestations of gross lesions of the brain-stem suggests that the disturbance is probably *central*. The Parkinsonian syndrome is generally attributed to pathological changes in the corpus striatum. Damage to the substantia nigra has been demonstrated by Marinesco, McKinley and others in post-encephalitic Parkinsonism and in paralysis agitans. Clinical and experimental observations have shown the importance of the nuclei at the base of the thalamus and third ventricle in connection with vegetative disturbance. That the affected nuclei are near the median line is suggested by the fact that the seborrhœa is always bilateral.

Seborrhœa Oleosa. It is still a little puzzling how this excessive oily coating of the face and hair arises. Histological examination shows beyond doubt that the sebum at the moment when it leaves the glands and surrounds the hair is still half solid and plastic. This could never produce a fluid coating on the surface of the skin, which is at a lower temperature. If oily seborrhœa comes from the sebaceous glands they must therefore be producing an abnormally fluid secretion. This has not been proved

to be the case. Even in seborrhœics, squeezing of the skin ejects the usual half-solid worm-like follicular contents. Unna even thinks that oily "seborrhœa" depends on a hyperhidrosis. Seborrhœa of the face is not only troublesome in itself but in *holding particles of dust and fumes*, a fact of great importance in certain occupations, rendering dermatitis more likely and determining its distribution. Races and sections of the community engaged in much muscular labour are less affected than brain-workers.

SEBORRHŒA SICCA. It is still not settled whether *dandruff*, or pityriasis capitis, is only a form of seborrhœa in which the secretion dries to form scales, or whether it is due to an infection. Stein takes the former view and looks on seborrhœic eczema as a direct sequel to seborrhœa. The observations of Krestin, quoted above, speak in the same sense. We have seen that it is really more difficult to explain liquid oily seborrhœa than seborrhœa sicca; since sebum is the result of disintegration of the gland-cells, one would expect to find cellular detritus in dried sebum. However, in some cases the scales are clearly exfoliated surface-epithelium; for these conditions there is probably some other cause and they will be considered again in Chapter X.

TREATMENT. There has, unfortunately, been no great advance. It is generally advised to restrict carbohydrates, foods that favour constipation and putrefaction, and strong coffee and tea; exercise is beneficial. The various *sulphur* preparations, such as Sulphur Lotion B.P.C. and Chlorosulphol, are very useful. The most effective form in my experience is a mild peeling paste composed of *six per cent. sulphur and six per cent. resorcin in zinc paste.* Stein strongly recommends combining sulphur with a modification of Unna's alum paste, which was itself based on a centuries-old formula: it is made up as follows:—

Solution 1.		*Solution* 2.	
Dried egg albumen . .	17	Alum	8
Distilled water . .	70	Distilled water . .	70

Solution (2) is added hot to cold solution (1) and the mixture evaporated to 87 gm. Then one adds tincture of benzoin 3:

almond-oil to 100. This is called "pasta albuminis aluminata." When applied to the skin it forms a firm plaster-like covering and is very suitable for use at night. It has a strong whitening, degreasing and anti-inflammatory action. But it is of most use in the oily seborrhœa. It is made more effective and also more easily applicable as follows :—

Pasta albuminis aluminata . . .	20
Sulphur	2

Add acetum odoratum and hydrous wool fat equal parts to produce a soft paste.

A good powder is :—

Zinc oxide	10
Red bolus	15
White bolus	15
Mag. carbonate	15
Rice starch	to 100

Not only is this skin-coloured, but bolus absorbs fluids, especially fat. Magnesium carbonate is also absorbent. Two per cent. of sulphur can be added if desired.

If the skin becomes intolerant of these applications, the best alternative is *ultra-violet rays* given for a prolonged period in mild erythema doses. *X-rays* are very effective in diminishing glandular secretion, but when given in safe doses only produce very temporary benefit; they should therefore only be used at long intervals in exceptionally severe cases.

Small doses of *arsenic* have seemed to me of service.

Sweat-Glands

There is no part of the skin where these are not present. For a long time a distinction has been drawn between the large and the small sweat-glands, and between the superficial and deep coils. But it was not until 1921 that Schiefferdecker showed that there were two different biological types.

The Small Coil-Glands. These are the ordinary human form and dip directly from the surface-epithelium into the corium, the long duct being sometimes straight but usually tortuous and ending in a coil. This is made up half of excretory duct and half of gland-tubule. Their epithelium is sharply defined towards the lumen, which is evenly circular in cross-sections, the cells being all of the same height.

They have no relationship with hairs either embryologically or later. Schiefferdecker calls them *eccrine* glands : the cells excrete fluid and do not lose any part of their substance. It is in man alone that they are found all over the body. In the palms and soles they constitute the only epidermal appendages.

INNERVATION. The nerves of the sweat-glands belong to the sympathetic. They arise from the thoracic and upper lumbar segments and leave the cord, at the same level as their origin, with the ventral roots (D1–D12, L1–L3). The cells of origin lie chiefly in the lateral horn of the grey matter. The sweat-nerves run *viâ* the white rami to the sympathetic chain, in the ganglia of which they end and are succeeded by the post-ganglional fibres. These run partly with the cervical sympathetic to the sweat-glands of the head and partly with the peripheral somatic nerves to the limbs and trunk (Spiegel).

They are co-ordinated by a centre in the basal and medial portion of the mid-brain, which coincides with that for heat-regulation. But this is not the only part of the brain that can stimulate sweating. It has been produced by stimulating the frontal lobes. Emotional sweating is well known.

But the sweat-nerves can be brought into action by local influence independently. Thus, if an arm is placed in a hot-air chamber, sweating is confined to that limb, but only occurs if its innervation is intact ; it probably depends on a spinal reflex. It occurs even in a limb emptied of blood by an Esmarch bandage and is therefore largely independent of circulation (Dieden).

It is interesting that the *pharmacodynamic* behaviour is opposite to that of other organs supplied by the sympathetic, in that adrenalin has no effect, whilst pilocarpine and muscarine excite sweating and atropine diminishes it. The explanation that the

secretory nerves are really parasympathetic does not hold, except perhaps in the face.

Guttmann has shown that the nervous control of sweating is exercised by a series of reflex arcs which stimulate and inhibit each other. The first neuron goes from the cortex through the inner capsule to the subcortical ganglia, probably the hypothalamus; the second, from the hypothalamus to the vegetative oblongata nucleus; the third, from here to the lateral horn of the cord; the fourth, from the lateral horn nucleus through the white ramus communicans to the ganglion of the sympathetic chain; and the fifth from this through the grey ramus communicans to the peripheral nerve to the sweat-gland. According to Braeucker the secretory fibres to the upper extremity leave the cord at the fourth to ninth thoracic segments and run by way of the anterior roots and white rami to the sympathetic chain. They then ascend to the lowest cervical ganglion, which they leave by the grey rami to join the brachial plexus. The special fibres for the hand leave the cord at the first thoracic and seventh and eighth cervical segments. Those for the feet leave the cord at the eleventh thoracic to the third lumbar segments, and descend in the sympathetic chain to leave it by the grey rami of L4, L5, S1 and S2 to run with the mixed peripheral nerves.

Consequently disturbances of sweating can be produced by disorders of any part of this long chain. Total division of peripheral mixed nerves results (except in the case of the face) in an anhidrosis, which corresponds with the area of analgesia. In the face, in addition to the main sympathetic secretory fibres, there seem to be independent parasympathetic bulbar fibres running with the facial nerve.

THE SIGNIFICANCE OF SWEATING. Some rather surprising results emerge from Yas Kuno's careful experiments. The sweating caused by *heating* invariably appeared all over the body-surface and never only locally, even when the heating was confined to a small area. [This is in contradiction to the experiments of Dieden quoted above, showing that when an arm is placed in a hot-air chamber sweating is confined to it.] But the palms and soles, though in them the sweat-glands are more abundant and the so-

called "invisible perspiration" is greater, did not, he asserts, perspire under high atmospheric temperatures. They did, however, increase their secretion, and they alone, under any intense sensory stimulation, and especially under *mental stress*, such as was experimentally obtained by means of mental arithmetic. Moreover, sweating on the palms or soles due to any cause always appeared on all four parts. Generally speaking, heat caused the head, neck, anterior and posterior surface of the trunk and the dorsum of the hand to sweat most, and the axillæ and internal surfaces of the thighs least. This seems at a glance to be contrary to daily experience; but according to his observations they become wet, not because sweating is excessive, but because the sweat evaporates there with difficulty. The abundant sweating of the head, neck and trunk is advantageous for the dissipation of heat. The sweating of the palms and soles must have some purposeful relationship to mental stress, its most frequent cause. Moistening of the palms increases the friction between them and the object grasped; consequently muscular work is facilitated and the sense of touch sharpened. In human beings mental stress is not necessarily accompanied by muscular action, but it is almost invariably so in animals. The sweating in human palms and soles may be regarded as a phenomenon transmitted from animal life. The normal secretion plays an essential part in keeping the thickened horny layers of these parts supple.

Medicaments stimulate sweating by acting (*a*) on the brain, especially antipyretics; (*b*) on the spinal centres, *e.g.*, strychnine, camphor, ammonia compounds; (*c*) on the peripheral endings, *e.g.*, muscarine, physostigmine and pilocarpine.

Treatment of Hyperhidrosis. *Internal Remedies.* These have the disadvantage that they affect regions where one may not wish to diminish secretion. Thus *atropine* leads to a very unpleasant dryness in the mouth. It is, however, definitely of use, especially in tuberculous sweats. It is given in pills of 1/120–1/60 gr. Popularly *sage* has long been in use. The antihidrotic principle seems to be an ethereal oil, which acts directly on the sweat-centre. A preparation has lately become available called "*Salvysat* (*Bürger*)," which contains all the active components

from fresh sage-leaves. It is given in doses of 15–25 drops three times a day. After some weeks it is wise to allow an interval of a few days to avoid habituation. Katz, Zöckler and other authors report that the diminution of sweating sets in within a few days and that there are no symptoms of intoxication. The effect lasts for some time after its administration ceases. Zwerg has had success with *camphor* given by mouth in tablets coated with gelatine to avoid irritation of the stomach. According to Yas Kuno's experiments the type of hyperhidrosis which the dermatologist is most often called upon to treat, namely, that of the palms and soles, is due to emotional causes. It would, therefore, be rational apart from environmental treatment to administer sedatives, such as bromide or luminal.

Local Treatment. X-rays. This is the only certain method of curing hyperhidrosis. It is often necessary to irradiate until there is considerable atrophy of the sweat-glands; this is likely to be accompanied by more or less atrophy of other appendages and of the true skin. But the results of suitable dosage on the palms and soles and axillæ are very good. The average dose recommended by McKee is ¾ E.D. with moderate filter once a month; four to six exposures may be required. Treatment should be stopped a little before the full desired effect has been obtained.

Formalin is the best known application, but it is not always satisfactory and is apt to sensitise the skin. As a 10% powder it helps to diminish maceration and decomposition, but is no good for really profuse sweating. It can be added to cold foot-baths in a strength of 1 teaspoonful to 3 pints. It is contraindicated if there are cracks or excoriations. Recently von Brunn has recommended using undiluted formalin as follows: about every 4 weeks, on one or two consecutive evenings, it is swabbed on to the hands or feet before going to bed. The interdigital folds should be excluded. He reports lasting success in himself and forty other patients; only in one case a trifling eczema developed. "Solution of Formaldehyde with Soap" B.P.C. may be used as a ½–1% solution or 20–30% ointment.

In cases where erosions and fissures are present Lengefeld

recommends powdering with *aluminium acetate,* either pure or mixed with an equal quantity of indifferent powder. Signs of irritation are not observed. Its effect when once secured can be maintained by using it once a week.

Von Bültzings-Löwen (1924) and others report favourably on "Resorcin Percutol," a mixture of about 40% resorcin and 60% salicylic acid ester. It is fluid, almost colourless and smells only faintly; it is used undiluted, a few drops being rubbed in at first daily and later at longer intervals. As a rule 4 to 6 weeks' treatment is enough.

Sympathectomy. The peri-arterial method is irrational and ineffective. Braeucker, by cutting the rami communicantes, brought about complete and permanent cessation of sweating of the hands and feet and the same result follows the modern operation of removing the appropriate ganglia and intervening portions of the sympathetic chain.

Pompholyx. Tilbury Fox, who first described this condition, looked upon the blisters as retention-cysts of the sweat-ducts and called it "dyshidrosis." But Hutchinson, who is responsible for the name "cheiropompholyx," rejected all connection with the sweat-glands. It is characterised by deep-seated blisters which resemble sago-grains and are firm to the touch. They appear, generally in large numbers, on the sides of the fingers, especially between the index and thumb, the next most favoured sites being palms and soles. Except in the severer cases it is unaccompanied by signs of inflammation. The vesicles may become confluent but have little tendency to rupture and so cause weeping. Itching may or may not be present, but is usually slight. The duration is limited: generally within 14 days the contents of the blisters dry and the roofs are thrown off as dry scales; this may be hardly noticeable clinically. Only in a small percentage there develop the symptoms of a weeping eczema which prolongs its duration. The disorder is, as a rule, strictly confined to the hot period of the year. The *histology* shows no connection with the sweat-glands and is indistinguishable from that of eczema.

The condition is therefore now generally looked upon as a

variety of eczema, and capable accordingly of being evoked by a multiplicity of causes. Its peculiarities, such as the deep-seatedness of the blisters and relative absence of inflammatory signs, are explained as depending on the thickness of the horny layer. Thus, when it spreads on to the back of the hand or up the leg, one can sometimes see side by side typical eczema where the horny layer is thin and pompholyx where it is thick. But in the majority of cases it is characteristic that the eruption, unlike most examples of eczema, *does not* tend to spread beyond the sites of election.

As regards the *ætiology* Török has sometimes seen it coincide clearly with menstruation. The French attach importance to dyspepsia. MacLeod mentions nervous derangements, especially mental worry. He quotes a case in a girl aged 15 years with left-sided hemiplegia who was subject to attacks just in warm weather. It was always much more marked on the paralysed side, where it did not so readily respond to treatment. Whitfield was the first to demonstrate that in many cases of interdigital vesicular eruptions the blisters contained ringworm-fungus. This and other aspects of its ætiology are more fully discussed on pp. 353 to 357. Excessive sweating, which is not always present, would favour the growth of fungus and could also act as an eczema-producing irritant.

The *treatment* depends on the ætiology. Suitable symptomatic remedies are *astringent lotions*, such as resorcin and tannic acid of each 1%, or solution of aluminium acetate B.P.C. dr. 1 to ℥ 1 of water. The lotion should be followed by a bland *powder*. Constant recurrences may often be checked for a considerable period by a few small doses of *X-rays*.

The Large Coil-Glands. Now, in certain parts of the body only the second type of sweat-gland is present. These glands correspond with what were known as the large sweat-glands; but they are sharply distinguished from the first small eccrine type both histologically and functionally. They do not arise directly from the surface-epithelium: their opening (and origin) is in the lower wall of hair-follicles above the sebaceous gland, and the slightly tortuous duct extends deep into the corium and ends in

a large coil of wide tubes. They are called "the *apocrine* glands of Schiefferdecker," for they excrete not only fluid but also part of their cell-substance. Their tubes are formed of large cells, which vary in appearance according to the stage of secretion. Either they are flat and sharply defined towards the lumen as in the case of eccrine cells, or else their inner end projects as a dome. This dome is thrown off and mixes itself with the fluid secretion. In animals glands like these are widely distributed, and the conformity of the large apocrine glands to the animal type, which always empties into hair-follicles, is incontestable. In man they are localised to the axillæ, genital regions and breasts. These are regions with a special hair-formation (cf. also Moll's glands attached to the eyelashes and the lanugo-follicles of the external auditory meatus). The apocrine coil-glands develop to a greater degree and earlier in women than in men, namely, in boys at about puberty, and girls at about the age of 9 years. The mammillary apocrine glands are of peculiar interest. They differ somewhat from the others and form a link between the apocrine sweat-glands and the mammary glands themselves and may even be looked on as small accessory breasts. A connection between hair-complexes and milk-glands can be traced through the whole series of mammals. Apocrine glands produce a *smell*, which plays a very important *rôle* in animals as a sexual stimulant, the glands being specially active during "heat." Primitive races have more odour-glands than white races, and women more than men (labia, buttocks, axillæ); they are very active during pregnancy and menstruation and may really be looked upon as cutaneous sex-glands.

There are two diseases which would appear to concern the apocrine glands.

Fox-Fordyce Disease. In 1902 these authors described a peculiar condition which has since been studied by Rasch, Kissmeyer and others. It is almost confined to women, though just a few cases have been described in men. It is essentially regional, involving the axillæ, pubis, labia majora, perinæum, nipples and sometimes the region of the umbilicus; briefly, wherever the apocrine glands are met with; but quite often only

one or two of these territories are touched. The eruption consists of a profusion of little papules, hemispherical or slightly conical, firm, about the colour of the normal skin and sometimes rather translucent. The intervening and neighbouring skin is generally pigmented but not lichenified (see Fig. 1). Itching is variable:

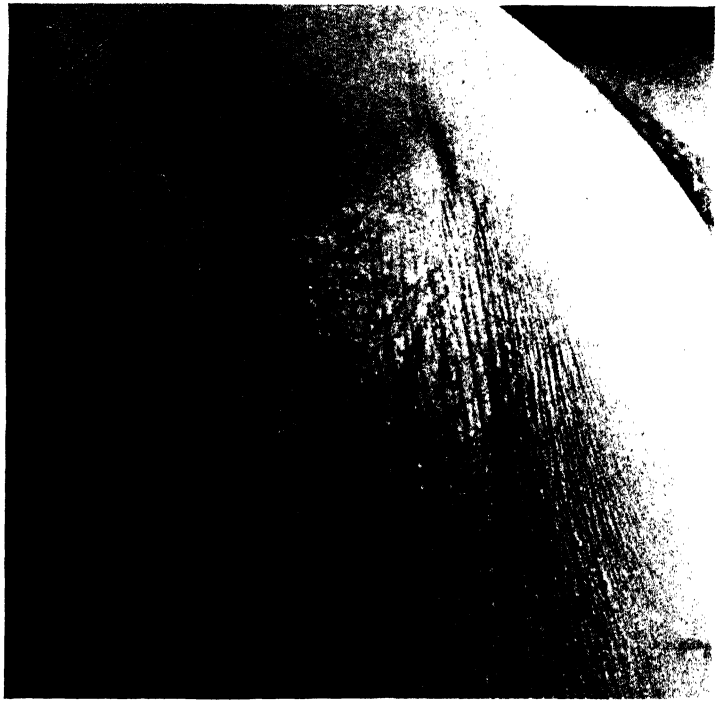


FIG. 1. Fox-Fordyce Disease (Author's Case).

sometimes there is hardly any but generally it is intense, especially during menstruation, and may precede the eruption. In addition to acanthosis, hyperkeratosis, periglandular and perivascular infiltration, the *histology* shows a marked dilatation, sometimes cystic, of the apocrine glands. The reasons which lead one to think that these glands form a part of the sexual apparatus

suggest the probability that this disorder depends on an endocrine disturbance. As a fact, *ovarian* medication is stated to be efficacious, and it would be rational to combine this with *X-ray* treatment, which is an undoubtedly useful symptomatic remedy.

SYRINGOCYSTADENOMATA. The connection of this eruption with apocrine glands is much more doubtful, and it is only the form referred to by Jacquet and Darier as "eruptive hydradenomata" that comes into question. It is rare, appearing mostly at the time of puberty in the form of numerous firm oval elevations on the anterior surface of the chest and neck, of pale rose colour, somewhat resembling syphilitic papules, but not scaly. They may persist indefinitely or can disappear. Occasionally they are scattered on the abdomen, arms and face. This disease too is almost confined to women. That, together with the fact that it does not appear till puberty, has led to the idea that the apocrine glands are concerned; but the distribution makes this very doubtful. Moreover, I have lately seen the typical condition in a man, who stated that the eruption had been present since birth, at any rate long before puberty. The *histology* is different from that of Fox-Fordyce disease. One sees in the corium cylindrical and branched epithelial tracts, in places dilated into minute cysts. It was till recently generally held that the tumours were nævoid growths originating from rudimentary sweat-glands. Nowadays the idea put forward by Krompecher and others of the possibility of new formation in the adult of cutaneous glands, imperfect or more or less abnormal, obliges us to consider such an origin for hydradenomata.

Bibliography

BRAEUCKER, M. "Die Innervation der Schweissdrüsen und die chirurgische Behandlung der Hyperhidrosis," *Arch. Klin. Chir.*, 1928, **149**, 718; and *Klin. Woch.*, 1928, **7**, 683 (*cit.* J. K. Mayr).

VON BRUNN. "Zur Therapie der Hyperhidrosis," *Münch. med. Wschr.*, 1925, **16**, 569 (*cit.* J. K. Mayr).

FOX, G. H., and FORDYCE, J. A. "A Rare Papular Disease affecting the Axillary Region," *Journ. Cut. Dis.*, 1902, **20**, 1.

VON FREY. "Die Drüsen der menschlichen Haut," *Jadassohn's Handbuch der Haut u. Geschlechtskr.*, **I/2**, 33.

GUTTMANN, L. "Die nervösen Leitungsbahnen der Schweiszsekretion beim Menschen," *Dtsch. Z. Nervenheilk.*, 1928, 107 (*cit.* J. K. Mayr).

KRESTIN, D. "The Seborrhœic Facies as a Manifestation of Post-encephalitic Parkinsonism and Allied Disorders," *Quart. Journ. Med.*, 1927, **21**, 177.

KUNO, YAS. "The Significance of Sweating in Man," *Lancet*, 1930, 912.

MAYR, J. K. "Die Erkrankungen der Schweissdrüsen," *Jadassohn's Handbuch der Haut u. Geschlechtskr.*, **XIII/I**, 1.

PINKUS, F. "Die normalen Anatomie der Haut," *Jadassohn's Handbuch der Haut u. Geschlechtskr.*, **I/I**, 1.

SCHÄFFER, J. "Über die Hautdrüsen," *Wien. klin. Woch.*, 1926, **39**, 1 (*cit.* F. Pinkus).

SCHIEFFERDECKER, P. (*a*) "Über morphologische Sekretionserscheinungen in den ekkrinen Hautdrüsen des Menschen," *Arch. f. Derm. u. Syph.*, 1921, **132**, 130 ; (*b*) "Die Hautdrüsen des Menschen u. der Säugetiere, ihre biologische rassenanatomische Bedeutung," Stuttgart : Schweizerbart, 1922 (*cit.* F. Pinkus).

STEIN, R. O. "Die Erkrankungen der Talgdrüsen," *Jadassohn's Handbuch der Haut u. Geschlechtskr.*, **XIII/I**, 48.

ZÖCKLER, O. "Salvia officinalis (Salvysatum Bürger) in der Therapie der Nachtschweisse und der Hyperhidrosis verschiedener Aetiologie," *Dtsch. Arch. klin. Med.*, 1926, **154**, 88 (*cit.* J. K. Mayr).

CHAPTER III

PIGMENTATION

THE physiological pigmentation of the skin is produced by a corpuscular organic pigment (melanin), varying from pale yellow to deep black, which is found in all animals. It is distinguished from blood-pigment by being iron-free. It is almost entirely contained in the cytoplasm of various cells, some of which have made it (melanoblasts), whilst others have only taken it up (melanophores). In histological sections of the skin the granules are normally seen in the basal cell layer of the epidermis, especially as a little dome above the nuclei, in the corresponding portion of the hair-follicles, in the hairs themselves and in some spindle-shaped cells in the corium. In recent years a great deal of work has been done on the nature and origin of melanin and on the character and origin of melanoblasts. The most important is that of Bruno Bloch and of P. Masson, and their conclusions are at variance.

Melanin

It cannot be derived from blood-pigment (hæmatin) because it contains no iron; moreover it may be observed in tissue-cultures, frog embryos, etc., where there is no blood. The idea that it is derived by *oxidation* from a colourless mother-substance was suggested by the observation of such a process on the cut surface of apples and potatoes and in the darkening of resins. That the oxidation is activated by a *ferment* was suggested by Joshida's discovery of laccase, the ferment which darkens the sap of the Japanese lacquer-tree. Bertrand and others have demonstrated the wide distribution of such oxidases in the vegetable world (fungi, potatoes, etc.). In particular he discovered tyrosinase, which acts almost specifically on tyrosin, producing

a melanin closely resembling natural melanin. Tyrosinase was later found in meal-worms and in the ink-glands of cephalopods. Pryde states that natural melanin contains 8·5% of nitrogen and no sulphur. It is bleached by hydrogen peroxide and blackened by silver nitrate. Natural melanins, found in the retina, hair, feathers, skin, melanotic tumours and the sepia of cuttle-fish, may not all be one and the same and may not be identical with the melanin formed from tyrosin by tyrosinase: but they are probably closely related. Raper, using tyrosinase from the meal-worm, found that when it acts on tyrosin in the presence of oxygen the following series of products result:—Tyrosin + tyrosinase + oxygen → 3 : 4-dihydroxyphenylalanin (= dopa) → corresponding quinone → 5 : 6-dihydroxydihydroindole-2-carboxylic acid → corresponding quinone (= red substance) → 5 : 6-dihydroxyindole or its 2-carboxylic acid. The last two are extremely easily oxidised in contact with air and are regarded as the immediate precursors of melanin. The ferment is not actually needed for the stages from the red substance onwards; but *3 : 4-dihydroxyphenylalanin* (*dopa*) is readily oxidised by it and much more rapidly than is tyrosin itself.

Free tyrosin, however, has never been found in extracts from the skin of mammals, nor has tyrosinase been demonstrated in the higher warm-blooded animals. But using the first product in the above series, namely 3 : 4-dioxyphenylalanin shortened to "dopa," as his melanogen and employing skin-sections instead of extracts, Bloch has elaborated the very important "dopa reaction" (1917). He chose "dopa" as his new substrate on account of its close chemical relationship to adrenalin and its great sensitiveness for oxidases. The use of skin-sections enabled him to observe the exact points in the normal skin-structure where the pigmentation took place. Dopa is a colourless toxic catabolite.

Dopa-Reaction. Frozen sections of fresh skin are immersed in a 1 in 1,000 watery solution of dopa with a *p*H value of 7·3 to 7·4 and afterwards washed in distilled water. It will now be observed that certain cells are coloured grey to black. These cells, therefore, must contain a ferment which has converted the

dopa into melanin: it is referred to as "Dopa-oxidase." The change occurs exclusively in the cytoplasm. The reaction is negative in albinos and in scars and leucodermia. It is intensified in all cases where there is a tendency to hyperpigmentation, especially after all irradiations, such as ultra-violet and X-rays. In the human skin the cells that react in this way are the basal cells of the epidermis and of the hair-follicles, and these cells are, therefore, called *melanoblasts*. In such preparations the melanoblasts mostly show a dendritic shape.

The spindle-shaped cells in the corium, which normally contain some pigment-granules, are not darkened by being immersed in dopa, and it is therefore concluded that they do not make the pigment but merely take up pigment-granules that have escaped into the corium from the basal cells. As they only carry pigment, they are called *melanophores*.

Bloch states that the reaction is specific for dopa, and consequently that dopa-oxidase is not identical with tyrosinase. There is, however, a difference of opinion as to its strict specificity. Kreibich and Meirowsky claim to have obtained it with "rongalite-white" and also with paraphenylenediamine and other easily oxidisable bodies. Mulzer and Schmalfuss (1931) claim that 3,4-dioxyphenylethylamine (oxytyramine) is oxidised by skin just as strongly as dopa. But Bloch and Schaaf, Peck and others (1932) maintain that dopa-oxidase only reacts with the natural l-3,4-dioxyphenylalanine and not even with Harington's optical isomer d-3, 4-dioxyphenylalanine. Meirowsky admits that, whereas dopa produces all shades from the lightest grey to deep black, paraphenylenediamine, etc., only cause a slight, though distinct, darkening of the protoplasm. Moncorps (1924) obtained from the urine in two cases of melanosarcoma a melanogen which he identified as homoprotocatechuic acid. This he then oxidised with a specific ferment (pyrocatechinase) to melanin. He could show that freshly pigmented skin was responsive to several pyrocatechinic derivatives and that the formation of pigment depended on the co-operation of a pyrocatechinase. Meirowsky also points to Spitzer's observations (1931), that even where dopa and its ferment can be demonstrated, namely

in apples and pears, no true melanin-formation takes place, but only a diffuse dark brown discoloration ; and he concludes that the dopa-reaction does not represent the whole of the final natural formation of melanin.

In addition to the basal cells and the corresponding cells of the hair-complexes, a positive dopa-reaction is also given by certain melanoblasts in the corium, which will be referred to later. Moreover it is positive in certain cells in which pigment-formation does not naturally occur, for example, the leucocytes of the tissue and of the blood. (Meirowsky also mentions nerve-fibres, striated muscle, ganglion-cells, sweat-glands, kerato-hyaline, red blood-cells.) This makes it probable that those cells which naturally produce pigment also *provide their own pro-pigment.* Other reasons for this view are the demonstration of pigment-formation after warming or exposure to U. V. R. in skin separated from the body (Meirowsky), the melanin-production in cells of malignant melanomata, in which condition pro-pigments are found in the urine (Moncorps), and the manner of melanogenesis in artificial tissue-culture of pigment-cells (Carrel, Smith and Luna). This tissue-culture of pigment-forming epidermal cells is also a strong argument against the old view that the epidermal pigment came from the corium ; this is also make unlikely by the dopa-reaction, the fact that if the corium is experimentally saturated with a dye-stuff none of it is taken up by the epidermis, and also by the fact that pigment first appears in the human skin shortly before birth when none can be seen in the corium.

What is the fate of melanin ? Some, as we have seen, escapes into the corium, is phagocytosed by the melanophores and presumably eventually absorbed. The rest is carried up into the superficial layers of the epidermis, where it is converted into some colourless substance, a small proportion persisting and being cast off as such with the horny layer.

Melanoblasts. What sort of cells are they and what is their origin ? During a phase of active pigment-formation, either natural or as a result of the dopa-reaction, a large proportion, but not the whole, of the pigmented cells are seen to have a *dendritic* shape. Pigmented dendritic cells are also present in

the sheaths of nerves, especially the pia mater, and Weidenreich thinks that the pia pigment is the remains of a phylogenetically old general pigment-mantle of the nervous system. It is only in the retina and the epidermis that there appear to be pigment-cells that are not dendritic. In the human skin these dendritic cells are only seen in the basal layer and in pigmented nævi and in Mongol spots.

Mongol Spot. In all new-born babies of the Mongolian race, but in only two to three of every thousand European babies, a blue patch can be seen in the sacral region and sometimes other parts of the body. It generally vanishes by about the age of seven years. Histologically it is found to be caused by the presence of very large branched cells deep in the corium, which give a positive dopa-reaction. Bloch says that even in a normal new-born baby histological examination reveals a few such "Mongol cells," though not enough to cause a clinical discoloration. The Mongol spots seem to represent a vestige of the mesodermal pigmentation which is predominant in animals; for the epidermal mode of pigmentation is only highly developed in man, and in him it hardly begins before birth. When melanin is present in the corium and is not cloaked by overlying epidermal pigment, it gives the skin a blue colour, just as the lamp-black used in tattooing looks blue when viewed through the overlying layers of skin. Such blue skin is particularly well seen in certain monkeys. As to the racial frequency of the Mongol spot, Mayerhoffer (1928) has shown that its presence in Europeans does not depend on intermixture with Mongols. It can occur in all races, but in those with greater pigment-content it is more pronounced and lasts longer. Jadassohn has described *blue nævi*, little raised blue tumours in which these Mongol cells are massed together. Blue nævi bear the same relationship to Mongol spots as the ordinary brown moles do to normal pigmented skin. When they become malignant (if they are of mesodermal origin) we have perhaps the only true examples of melanosarcoma.

Thus we see that in the higher mammals pigmentation is chiefly a function of dendritic cells in the dermis, thought to be mesodermal; whilst in man it is a function mainly of similar cells

in the epidermis, which Bloch thinks are only modified basal cells. If we accept his view, then we are faced with the rather extraordinary situation that in the higher mammals and in man pigment is a function of cells of similar appearance, but in the former they are of mesodermal and in the latter of epidermal origin. So there are three views as to the nature of the epidermal melanoblasts :—(1) Every basal cell is always dendritic but only a few are identified as such by their contained pigment. That is to say, unless they contain pigment at the time of examination their dendrites are not obvious. (2) The ordinary basal cell becomes dendritic on functional stimulation: *i.e.*, active or excessive pigment-production (Bloch). (3) Dendritic are genetically different from non-dendritic cells (Ribbert, Masson).

According to Miescher, the epidermal dendritic pigment-cell is distinguished from the ordinary basal cell by (1) its varied, often bizarre, form and branched processes, (2) the absence of protoplasm-fibrillation and intercellular bridges, (3) the peculiarity of its position, at right angles or obliquely to the ordinary basal cells, which are sometimes surrounded by the former's processes in a kind of basket, (4) its relatively intensive pigmentary activity and strong dopa reaction. Thus it appears like a foreign element among the basal cells.

Becker (1927) found that dendritic cells are more frequent in normal (*i.e.*, not hyperpigmented) skin and oral mucosa than is generally supposed. They vary in the different regions, and even in the same region in different individuals, both as regards their size and shape and also with regard to their numerical relation to non-dendritic pigmented cells. They are predominant in the pharynx, about equal in the buccal mucosa and then diminish relatively, being least in the epidermis of the nipple and abdomen. But even here he saw some in 25% of cases. The thicker the epithelium (*e.g.*, in the buccal mucosa and acanthotic processes) the larger and more branched are the cells. In pathological hyperpigmentation the increased pigment is in some cases (*e.g.*, acanthotic lesions) seen chiefly in dendritic and in other cases (*e.g.*, Addison's disease) in non-dendritic cells. In skin from the nipple there may be marked pigmentation of the basal cell layer

without any identifiable dendritic cells. Conversely, in the buccal mucosa the dendritics are present in large numbers though pigmentation is slight. Sometimes even in the same section the degree of pigmentation and proportion of dendritic cells both vary, but without regular relationship. Even more than in hyperpigmentary processes, it is in *acanthotic* conditions, such as condylomas, lichen ruber and pemphigus vegetans and in beginning nævi and melanocarcinomas, that the dendritics are increased. They may project into the dermis or even lie in it with their branches coursing into the epidermis, but have never been seen in the dermis in their entirety. He agrees that they never have intercellular fibres and they show no mitotic figures.

Becker's findings do not quite tally with Bloch's view. They suggest that the dendritic cells are not the same as the basal cells, but that both can independently form pigment. But against this are the observations of Peck, who found that in the course of a Thorium X reaction the proportion of dendritic cells, as compared with ordinary basal cells, increased from 10% to 40% and afterwards sank again. If they were independent, such an increase, he argues, would require karyokinetic activity, but mitoses have never been seen in them.

Pautrier, Lévy and Diss think that corium and epidermis, derived from different germinal layers, are spacially and functionally bound together into an indivisible whole. In the process of pigment-formation they ascribe an important function to the "Langerhans cells." [I must now explain that according to Bloch and Miescher the "Langerhans cells," which are also dendritic, are quite distinct from the pigment-forming dendritic cells, whilst Pautrier and Masson consider them identical. Langerhans used a special gold method; their demonstration depends not on a silver or gold impregnation of the separate pigment-granules, but on a darkening of the protoplasm, which has a reducing power not possessed by that of the dendritic pigment-cells. The histo-chemical properties of the Langerhans bodies have a neuroid character. They are found in the *upper* layers of the epidermis and in pigmentless regions, *e.g.*, the palms.] Pautrier's idea is that the pigment formed in "the Langerhans

cells " is given off through their dendrites to the cells of the rete and also into the corium, which is thereby, so to speak, tattooed by the epidermis. The " Langerhans cells " also give pigment-granules to the endothelium of the capillaries in the papillæ. The dopa and Fontana methods show that in the " Langerhans cells " there are two streams of pigment-substances, a chromogenic from the corium into the epidermis carrying forerunners of melanin, and an opposite stream bringing the finished pigment back into the corium. Pautrier observed these relations between corium and epidermis, as did Masson, in cases of xanthoma tuberosum. The lipoid droplets are seen in the endothelium of the capillaries, in the " Langerhans cells " and in the cells of the rete mucosum, always intracellular. In Schamberg's disease and in hæmochromatosis, in which there is a deposit of hæmosiderin, the granules seem to show the same interconnection of tissue-elements. Pautrier set up the hypothesis that this is a trophic system, representing the peripheral portion of the reticulo-endothelial system of Ribbert, Goldmann and Aschoff. Hueck thinks that the dendritic cells of the epidermis and the pigment-forming cells of the corium belong genetically, morphologically and functionally together. He deprecates the sharp distinction between ectodermal epithelium and mesodermal connective tissue; for connective tissue is a syncytial structure, originally a protoplasmic network free from nuclei between the germinal layers. Into this protoplasmic network nuclei penetrate, and cells from both layers anastomose with each other. The original form of the epithelial and the connective tissue cells is the dendritic.

Pigmented Nævi and Melanomata

The question of the origin of the normal melanoblast naturally leads to that of the origin of pigmented tumour-cells. The term " melanoma " is given to any abnormal collection of melanin-pigment cells, whether in the skin or elsewhere.

Benign Melanomata. Macular and Cellular Nævi. *Freckles.* In a freckle small groups of basal cells become intensely pigmented. As it fades the transport-cells of the corium increase in number

around the blood-vessels in direct proportion to the lessening of the pigment in the basal cells. Clinically, freckles are sharply demarcated from the surrounding pigment-poor skin and often have a somewhat zigzag outline. Though more obvious in the spring and summer than in winter, large ones may remain conspicuous throughout the year. But even the others do not really disappear; for when they are no longer visible in ordinary light they are still obvious when viewed by Wood's light (see p. 359). They are most conspicuous in areas exposed to light but can be made apparent even in covered parts by pressure, rubbing or chemical irritation. They appear very early in life, and the predisposition to them is an inherited dominant character. In uniovular twins their exact location is almost identical (Siemens), and in an individual they are wont to recur at exactly the same spots. Siemens and Arning think that the tendency to freckles is due to racial intermixture. Adachi points out that they are extremely rare in Japanese but very common in mixtures between Europeans and Asiatics.

Even in relatively dark regions of normal skin, non-pigmented cells can be seen microscopically between groups of basal-cells in which the pigment is concentrated. Generally in freckled persons the rest of the skin is under-pigmented, but, according to Habermann, by no means unable to form pigment; indeed, it may sometimes get so dark that the freckles can no longer be distinguished. Meirowsky thinks that freckles represent an exaggeration of this normal flecking, and are already determined in the germ-plasm. He considers that a sharp differentiation cannot be made between freckles, *nævi spili* (flat pigmented moles) and *lentigo*, between which there are transition-forms. Darier says that even typical flat nævi often become darker and larger under various influences, such as pregnancy and sunlight, and Meirowsky is certain that pigmented nævi as well as freckles can be increased or made to appear for the first time by infections, trauma or X-rays. Jadassohn has pointed out that perfectly typical freckles may be unilateral. Histologically, the pigment in flat benign melanomata is confined to the basal layer, except in the darkest examples, when it is also copious in the chromato-

phores of the corium. In lentigo two-thirds of the cases show the cell-islands characteristic of soft moles, and all are more intensely pigmented than freckles or nævi spili.

It is of great interest that the nests or columns of special nævus-cells, situated close under the epidermis or penetrating deeply into the corium, which characterise raised pigmented moles, give a positive dopa-reaction. In this they behave similarly to the pigment-forming basal cells and are therefore probably of the same origin. If Bloch's view is right, then nævus-cells are epithelial.

This view is strongly supported by the recent investigations of Dawson. He considers a freckle the simplest form of pigmented nævus, containing as yet no nævus-cells in the corium. By histological preparations of a large number of lesions, he tries to show all stages in the transition from such a simple group of pigmented basal cells to the nævic cell-nests. This transition starts with a proliferation of the deeper layers of the surface-epidermis and rete-pegs. The individual cells of the swollen pegs lose their prickles and become distinct from each other. Nearly all of them are spindle-shaped or branching and they may contain much pigment. The bulbous tips of the rete-pegs (or similar buds from the surface-epidermis) give way, and their cells, individually or in groups, become structural constituents of the papillary body. New connective tissue grows in behind them and cuts them off from the epidermis. The exposed cells go on to form columns or nests in the corium, each cell being surrounded by delicate connective tissue fibrils. They mostly assume a polygonal shape, and, in the final stage of a quiescent cellular nævus, have an atrophic aspect. Most of them may be unpigmented, but among them are branching pigmented cells. By further proliferation they can be traced right up to the systematised and giant nævi, without any essential difference in structure.

Not only can nævi first make their appearance at any age, but they can also disappear altogether or change into other forms.

Malignant Melanomata. The most striking characteristic of the malignant tumours that arise from pigmented nævi is the diversity of the histological picture. Dawson classes them as follows :—

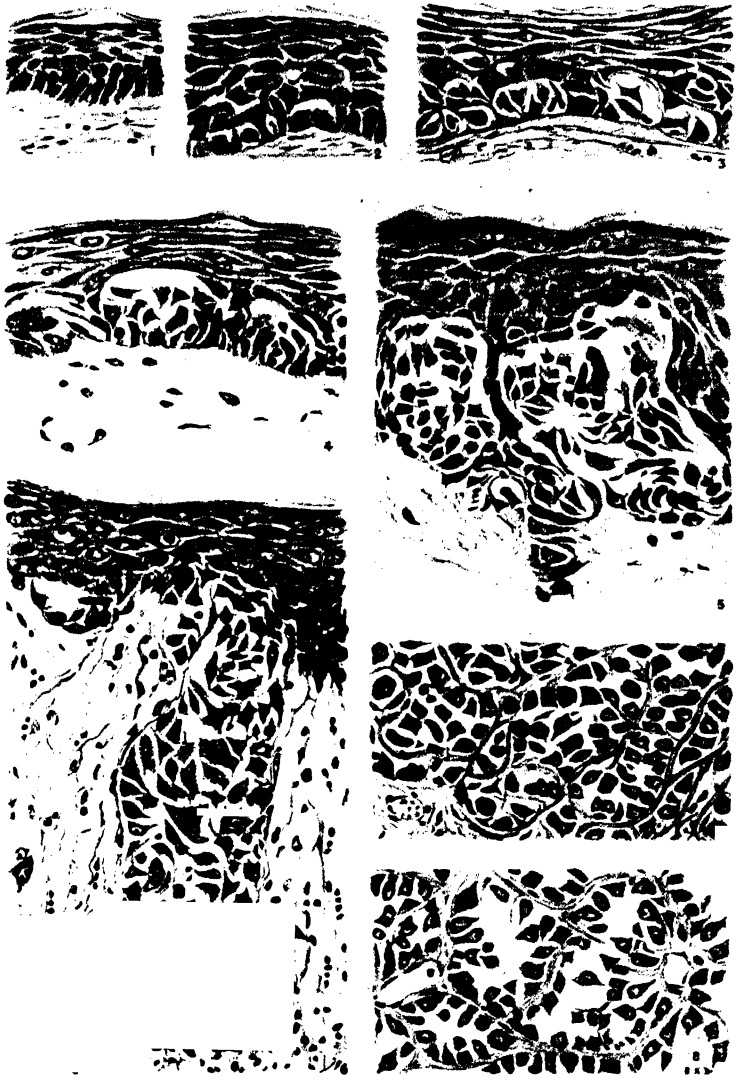


FIG. 2.—Stages of Evolution of a Melano-Carcinoma. (J. W. Dawson, *Ed. Med. Journ.*, 1925, p. 501.) (Reduced.)

(*a*) Melanocarcinoma, in which cells of epithelial appearance are arranged in alveoli.

(*b*) "Melanosarcoma" with spindle-shaped cells and, less frequently, round cells.

(*c*) "Melanoendothelioma" and "perithelioma," the former having sheets of large protoplasmic cells often arranged as in some endocrine glands; the latter having large cells arranged on a central papillary or vascular core.

(*d*) "Melanofibrosarcoma" (rarest) with fibrocellular interweaving strands.

There are numerous instances of transitions between these types.

Development of Melanocarcinoma. Fig. 2 illustrates a series of changes taking place in the surface-epithelium between the rete-pegs. At the vascular margin of a growing mole individual isolated cells of the basal layer show a clear non-staining rim round the nucleus. The cytoplasm increases in amount and becomes vacuolated, the nucleus is vesicular and the prickles are lost. Such detached individualised cells form small groups.

Fig. 2, (*3*) *and* (*4*), show them becoming polymorphic, elongated, spindle-shaped or branching. As the surface-epithelium is traced towards the growth these intraepidermal cell-groups become larger and bulge towards the corium and the constituent cells completely separate from the normal cells and from each other (Darier's "segregation").

Fig. 2 (*5*) shows the detached cells, often deeply pigmented to the tips of their finely branching processes. As the cell becomes more and more laden with pigment it may round off and burst and the free pigment is carried into the transition-zone between epidermis and corium. It is at this stage that a lymphocytic reaction becomes definite. The proliferating tumour-cells, having penetrated into the corium, retain their characteristic nucleus and intense pigmentation. They have become free and amœboid and have long processes.

Fig. 2 (*6*) (*upper part*). As they reach the deeper layers of the corium they arrange themselves in the dilated tissue-spaces in an areolar manner.

Fig. 2, (*7*) *and* (*8*). The pigmentation lessens as the deeper

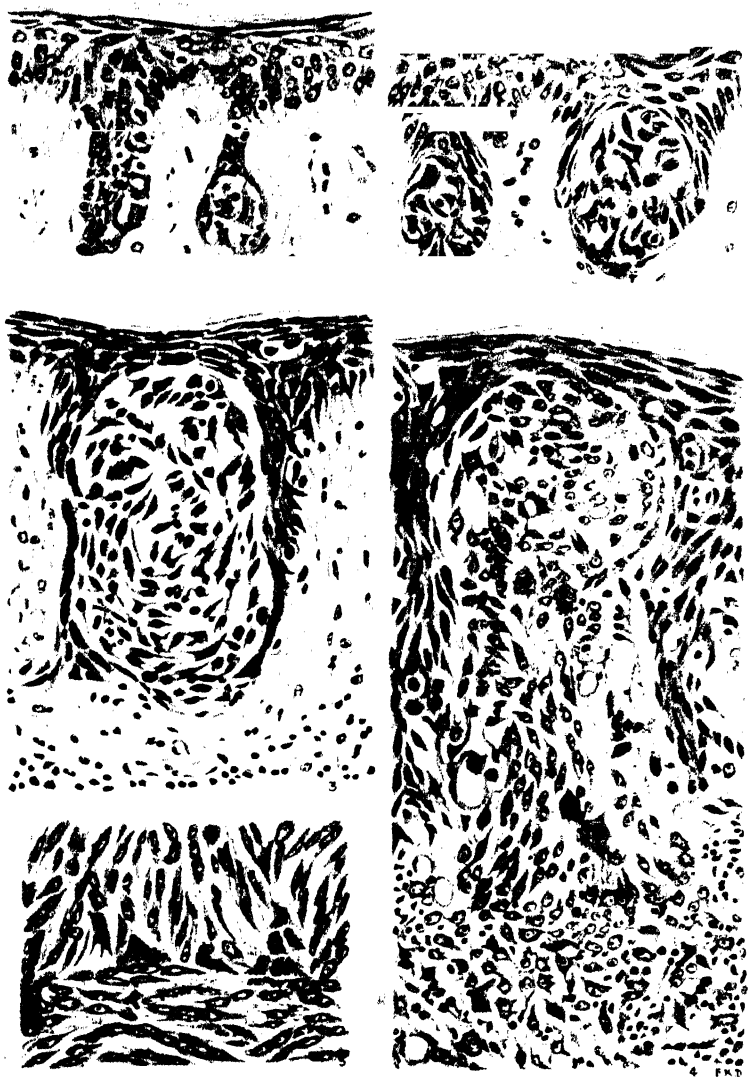


FIG. 3.—Stages of Evolution of a Melano-Sarcoma. (J. W. Dawson, *Ed. Med. Journ.*, 1925, p. 501.) (Reduced.)

layers are reached; perhaps the young cells have not yet gained the power of producing pigment. Even here branched or rounded cells containing globular masses of pigment may be found in the fibrous tissue septa, but they are readily recognised as phagocytic cells which have been carried in the lymphatics from the upper pigmented portion of the tumour.

Development of "Melanosarcoma." Fig. 3 illustrates a series of cell-transformations in rete-pegs traced from normal epidermis towards the tumour; a process exactly analogous to that of melanocarcinoma.

Fig. 3 (*3*) shows the rupturing of the swollen rete-peg and the setting free of amœboid epidermal cells, which penetrate the corium and proliferate to form a cellular mass of spindle-shaped or polymorphic cells.

Fig. 3, (*4*) *and* (*5*). Soon after penetration the tumour-cells are large and branching and much pigmented. When they reach the deeper tissue they are less pigmented and more uniformly spindle-shaped. Thus, morphologically, the growth is a spindle-celled melanotic sarcoma, but Dawson is convinced that the tumour-cells, both pigmented and non-pigmented, have one common origin, namely, the intraepithelial cell-nests. There is an entire absence of changes in the dermis, except of an inflammatory reactive kind, till they have ruptured into it.

He traces the development of the melanomata that show an endothelioma-like or perithelioma-like or fibrosarcoma-like structure from exactly similar beginnings in the epidermis. This study illustrates the amazing power of anaplasia (reversion to a more primitive embryonic type) and redifferentiation possessed by the epidermal cell.

The two possible sources of the malignant cells are:—(1) multiplication of nævus-cells hitherto lying quiescent in the corium, *i.e.*, malignant change; (2) a repetition or continuation of the original process by which these nævus-cells come to lie there, *i.e.*, a genetic process. In the former mode the small atrophic cells take on larger protoplasmic shapes, become free from the columns and nests and form new masses of polymorphic cells. This may take place side by side with a genetic process in the overlying epithelium

and the two are essentially similar. According to this view, one would have to consider all nævi to be essentially malignant melanomata in which the genetic process has, temporarily or permanently, come to a standstill. In any melanotic tumour there are two types of cells that may contain melanin :—(1) the true tumour-cells which make pigment and reproduce cells that do so ; (2) the phagocytic cells of connective tissue or endothelial origin.

Dawson entirely agrees with Bloch as to the relationship of the dendritic epidermal melanoblasts to the ordinary basal cells (see p. 42). But compared with other observers he seems to have had unusual difficulty in seeing branched cells in the normal skin.

von Recklinghausen's Disease. Pigmented patches like nævi spili occur in association with little molluscous tumours and nerve-tumours. It has been maintained by some that the pigment-patches are different from the pigment-nævi occurring independently of Recklinghausen's disease. Thus Siemens states that those in Recklinghausen's disease have an even border, whilst the majority of others have a jagged one. But Meirowsky is certain that, whether with or without Recklinghausen's disease, both kinds of border can be seen, and that there are intermediate degrees of jaggedness. Pollio describes three histological groups in Recklinghausen's disease :—(1) pure pigment-spots, (2) pigmented soft moles, and (3) pigmented spots without cell-nests, but with acanthosis and inflammatory cell-infiltration of the cutis. Ganz has found transition-forms between the three groups and also between these and definitely papillomatous nævi. Sometimes the pigment-spots develop gradually into pendulous sacs with crinkled surface, which microscopically show fibromatous connective tissue and atrophic nerve-fibres pressed together and tangled and occasionally swollen out into club-shaped forms (Andreew, 1930). Bürkle, who agrees that there are no fundamental differences between the pigment-nævi of otherwise sound individuals and of those with Recklinghausen's disease, has shown in both that the nerves ascending from the subcutaneous fat divide, and in places become accompanied by peculiar fibromatous

tissue-strands, which mostly begin at the boundary of cutis and subcutis. There are not always cell-nests but often a retiform structure. In the strands of this network are nerve-fibres. He thinks that pigmented moles often represent the first recognisable fibromatous changes of the connective tissue of skin-nerves, and that there are all stages of transition from pigmented nævi to the largest molluscous tumours. The histological structure of the latter was described by Clenet and Ingelrans in 1923 as including peri- and endo-lymphangitis, capillary hæmangioma, mucous change in the connective tissue suggestive of embryonal malformation, sub-epidermal pigmented cell-nests and formations which, owing to their resemblance to Meissner and Pacini bodies, they called "pseudo-Pacinian neuromas."

Masson's Researches on the Melanomata. Briefly, Masson reached the conclusion that not only those associated with Recklinghausen's disease but *all* pigmented nævi are *terminal neuromas of tactile nerves*. He had accepted Bloch's theory and admitted the "segregation" of Darier as characterising the initial differentiation of the nævic cells when separating from the epidermis, and also admitted with Unna the descent of the segregated cells into the dermis. But in 1923, resuming the study of nævi with a new technique, he was struck by the appearance of the deep cells, which now looked like the cells of Schwann. Further work confirmed the constancy of this "métaplasie schwannienne," the frequency of myoid cells and the non-existence of metaplasia of the connective tissue. His new technique consisted essentially in the use of a trichrome stain of iron hæmatoxyline, ponceau-fuchsin and aniline blue.

He found that the nævus showing its nervous connections most clearly is the scalp-nævus, which is generally only slightly pigmented to the naked eye. These tumours result from the localised proliferation of a whole collection of elements of nervous origin attached to myelinated nerves of the dermis. These elements, associated in a plexus of non-myelinated fibres, are capable of becoming differentiated into structures closely resembling certain tactile end-organs, namely, corpuscles of Wagner-Meissner (nævic corpuscles) and cells of Merkel-Ranvier (epithelioid nævus-cells).

The comparative study of normal Merkel-Ranvier cells and epithelioid nævus-cells on the other hand, and of the cells of Langerhans on the other hand, seems to show that they are connected by intermediate forms and correspond to various functional adaptations of the same cellular stock (that which constitutes the mass of the nævus and also certain normal tactile



FIG. 4. Normal skin of the wrist; clear cells in the basal layer, spaced out uniformly; many are turgid and projecting into the dermis. (P. Masson, *Ann. d'anat. pathol.*, 1926, p. 442.)

apparatus of the papillary body and epidermis). Thus the cells of Langerhans or epidermal melanoblasts seem to be in man of the same descent as the tactile cells and the neuroglia of the tactile nerves. The epithelioid cells exist throughout the whole thickness of the nævus, but only preponderate in the superficial stratum, where they appear to continue the direction of the bundles of fibres.

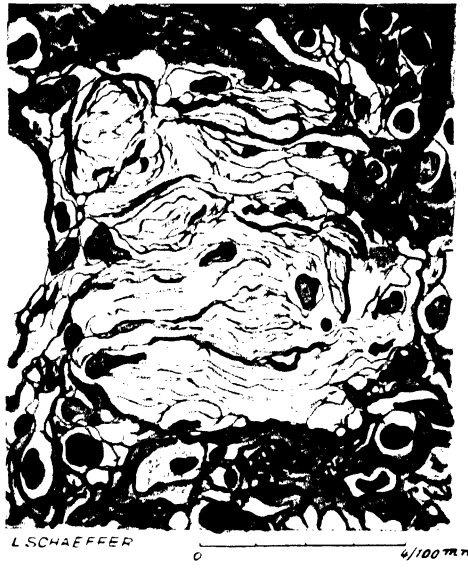
Between epithelioid cells, nervous fibres and the " folded-leaf " corpuscles (Wagner-Meissner bodies) one again finds intermediate forms. The single nævic cells on close examination have flexuous cytoplasmic prolongations sheathed with collagen, which anastomose with similar prolongations from sister-cells and are in continuity with the neuroid fibres connected to the deep bundles. The " cells " probably represent nuclear enlargements in the course of the fibres (see Plate I, *a*). Similar epithelioid cells can be found in the epidermis, generally in contact with the basal layer and distinguishable from the rete-cells by their size and clarity and lack of prickles (" clear cells ") (see Fig. 4). From their deep pole emerges a similar prolongation, which penetrates into the dermis (see Plate I., *b*). There are also upward prolongations from the apical poles, which tunnel among the rete-cells.

The cells of Langerhans are found in just those regions where there are no Merkel-Ranvier cells, and both are pigmented. The pigmentary function of the skin belongs then to cells of the same stock as those of a nævus. Again, these are of the same species as that part of the sensory nervous system represented by the corpuscles of Wagner-Meissner and tactile cells of Merkel-Ranvier. The cells of Langerhans appear to distribute pigment both to the epidermis and the dermis, and Masson has called them " trophomélaniques " (cf. pp. 43, 44).

The epidermis covering a nævus shows abnormality of the basal layer, in that it is interrupted by excessive numbers of Langerhans cells, more or less modified, which, in contact with basal cells, seem to attack them and take their place. The larger groups appear to force up the rete-cells from the basal membrane. When contiguous with each other they may lose their branches, becoming most of them globular. He denies that these segregated cells can be the result of modification of basal cells, because he could see no intermediate forms between the peripheral cells of a Langerhans group and the surrounding rete-cells. On the contrary, the latter appear flattened and rolled back. The clusters seem clearly formed by proliferation *in situ* of Langerhans cells.

There is great technical difficulty in demonstrating neurites themselves, as opposed to neuroglia. But by silver impregnation

PLATE IX.



Nævic corpuscle in longitudinal section. Note its lamellar structure. Its shape is roughly square. From its four corners there escape sinuous nævic fibres, cut through at different angles and forming at the upper right and lower left corners little bundles. Some fibres are isolated in the connective tissue in the form of bands or narrow circles, pink with a thin blue sheath. They swell at their nuclei. When the nuclear swellings are cut transversally they give the impression of spherical epithelial cells isolated in the connective tissue. (P. Masson, *Ann. d'anat. pathol.*, 1926, p. 452.)

[*To face p.* 54.

PLATE Ib.



Normal skin of the wrist ; two clear cells of the basal layer (note colour of cytoplasm) ; they have downward prolongations, in the course of which are nuclear enlargements ; each is a Langerhans cell ; the fibre is a nerve-fibre without myelin, of which one sees by this method only the Schwannian elements. (P. Masson, *Ann. d'anat. pathol.*, 1926, p. 452.)

To face p. 54.

he has shown neurites derived from the deep nerve-bundles, which gradually fade out in the central mass of neuroid symplasm. Again, he has demonstrated superficial neurites among the nævic corpuscles and surrounding and penetrating epithelioid cell-nests. There are incomparably more neurites in cellular nævi than in normal dermis. They seem to have the same relationship to the nævus-cells as normal neurites have to the true cells of Schwann and the tactile cells. Cellular nævi are tumours resulting from proliferation at the same time of neurites and surrounding neuroglia. Since the latter presents differentiated forms comparable to the tactile corpuscles, one may consider that the nerves that ramify in them are tactile nerves. It is interesting that cellular nævi can be found everywhere except on the volar surface of the fingers and toes, just where typical Merkel-Ranvier cells and Wagner-Meissner corpuscles are fully developed. The fact observed in beginning nævi that the epithelioid cells arise from intraepidermal cells of Langerhans proves that they are of the same stock. If then the nævus-cells, by virtue of their evolution and their connections with neurites, represent peripheral neuroglial elements, then the cells of Langerhans, which give rise to them, must also be considered neuroglial.

In the development of every cellular nævus there occur simultaneously, on the one hand, the segregation and dropping-off into the cutis of cells from the epidermis, and, on the other, a cellular infiltration deep in the dermis containing myelinated nerve-fibrils. Thus it has two distinct planes of departure, one epidermal and the other intradermal and nervous. The elements arising from these two planes proceed towards each other across the dermis and unite. In an adult nævus some of the deeper neuroglial fibres contain neurites, whilst the superficial glioma consists of schwannian fibres without neurites. Its behaviour reminds one of the peripheral glioma and central neuroglioma of a cut nerve. If they are too far apart they remain separated; so the macule will remain macule and the neuroglioma will become voluminous, as in Recklinghausen's disease. If near together they will push towards each other and unite; some of the central neurites will inhabit neuroglia derived from the epidermis. The lesion, which

originally separated the two, probably dates from the early development of the epidermal sensory nerves.

The views of Bloch and of Masson are not reconcilable and a verdict cannot yet be given. We have seen that there is difficulty in accepting the implication of Bloch that the mesodermal mode of pigmentation prevalent in higher mammals has vanished in man except for Mongol cells. This difficulty would disappear if, as Masson thinks, all the pigment-forming cells are of nervous origin, whether they happen to be situated in the dermis or epidermis or elsewhere. [Meirowsky, indeed, still maintains that in man melanin is also formed by the cells in the cutis which are dopa-negative and which most authorities consider only carriers. Miescher (1933) entirely disbelieves Meirowsky's idea and disposes of his argument that in certain conditions, such as vitiligo and skin painted with tar, chromatophores may be abundant whilst the epidermis is free of pigment, by explaining that the pigment in chromatophores may outlast that in the epidermis by many years. It may also depend on a high degree of "incontinence" of the epidermal cells; this can be shown, for instance, in pre-cancerous processes, in which one finds very little pigment in the epidermis in spite of a strongly positive dopa-reaction; while at the same time there is a mass of chromatophores.]

Masson and Pautrier's "réseau trophomélanique" Miescher considers to be no more than a hypothesis.

As regards the attempt to relate all the pigment-cells together and trace them back to a single ancestral pigment-cell, he points out its difficulty or impossibility in view of the fact that pigment-formation in the higher animals begins so late, at a time when the individual germinal layers are far advanced towards maturity. Thus epidermal pigmentation only appears shortly before or even after birth.

Miescher does not accept Masson's identification of the dendritic pigment-cells with Langerhans cells (see p. 43). If, as Masson thinks, pigment-formation is a function exclusively of the dendritic cells and the ordinary basal cells only receive it from them, it is difficult to understand why the dopa-reaction is occasionally

more strongly positive in ordinary basal cells than in the dendritics. There is no doubt that the nævus-cells are closely related to the dendritic cells, as they have many common morphological features, such as pale protoplasm, absence of prickles and often typical branches. But Miescher is convinced that he constantly sees metamorphosis of ordinary basal cells into nævus-cells, such a metamorphosis being rendered more likely by the fact that mitoses have never been seen either in the intraepidermal nævus-cells or in the dendritic melanoblasts. He therefore agrees with Bloch as to the close relationship of basal to dendritic cells, and he holds that it has not been satisfactorily established that either dendritic pigment-cells or intraepidermal nævous elements are connected directly with nerve-fibres.

Miescher and von Albertini have studied nævi with Masson's technique and also with hæmalum-erythrosin-saffron, and agree with him that the apparent symplasts in the dermis contain formations which morphologically most resemble certain nervous end-organs, especially the Wagner-Meissner touch-corpuscles. They have also occasionally seen transitions between the fibres of the deep symplasm, composed probably of schwannian cylinders with connective tissue mantle, and normal nerve-fibres. More often they have observed at the base of a nævus distinct changes in the ascending nerve-twigs, such as loosening of the sheath and abnormal increase of nuclei. The frequency of these observations has increased with improvement in their technique.

Thus Miescher confirms Masson as regards the deeper portion of cellular nævi but not as regards the superficial changes, where Masson too felt himself to be on less certain ground. He thinks it unlikely that nævi are formed exclusively through epidermal "Abtropfung" (dropping-off, or budding-off). Probably they are organoid malformations, in which epidermis, connective tissue and probably the nervous system are all involved. It has not yet been made clear whether, as Masson thinks, the nerve-like structures are a fundamental feature of nævi or whether they are only occasionally associated with nævus-formation.

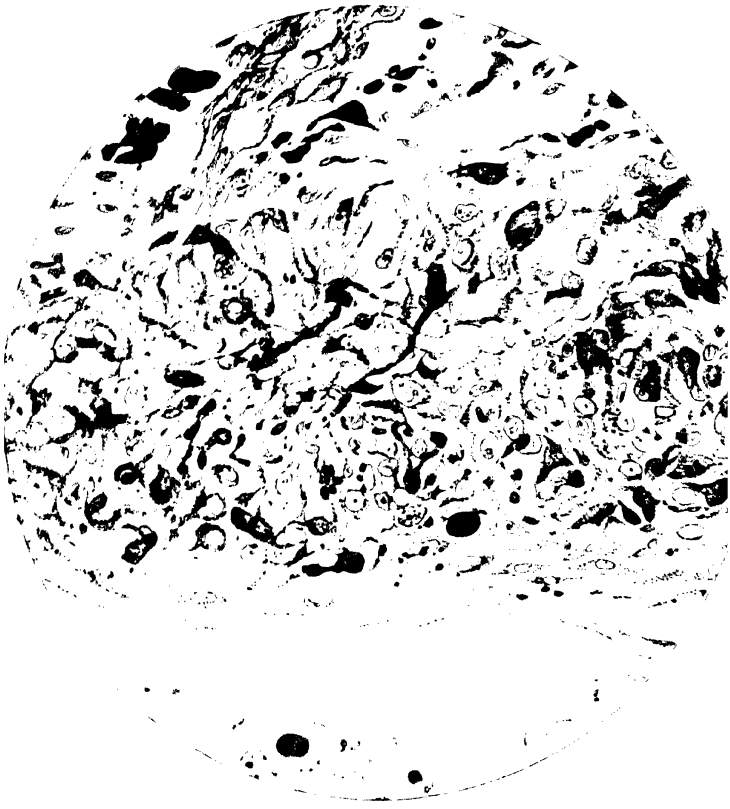
Though the majority of *malignant melanomata* start from nævi,

others originate from melanotic precanceroses, and a few spontaneously. Sometimes the invasion of the cutis is not confined to localised nests, but all along the line cells appear to be pouring down like rain from the epidermis (Dubreuilh and Miescher). Though mitoses are not seen in the intraepidermal cell-nests nor in the non-malignant nests in the cutis, they appear in malignant tumours after the cells have invaded the cutis and constitute the most important sign of the beginning of malignancy. This apparent massive metamorphosis of epidermal cells (see Plate II.) and their flooding into the corium without any mitoses Miescher thinks is against Masson's view that they are all derived from special cells.

We have seen that Masson's views still lack full confirmation and are open to many objections. There are, however, a few further points which seem to me in favour of his view rather than Bloch's. If the melanoblasts are ordinary basal cells why do scars remain unpigmented? It looks as if the pigment-forming cells must have arrived in the epidermis in the course of development from below and are not present when the epithelium grows over a wound from the side. If melanoblasts are basal cells it is remarkable that malignant melanomas so seldom, if ever, develop from the common basal cell epitheliomas, even when they are irritated by repeated inadequate treatment. The histology of their mode of origin as well as their sites of election are quite different. Further, why should the melanomata be so strikingly less vulnerable to X-rays and radium than basal-celled epitheliomas? It is well known that nervous tissue is especially insensitive.

"Amelanotic Melanomas." Under the title "amelano-sarcoma" Deelmann (1922) described 8 cases of skin-tumours, in which the history showed origin from a nævus and the histology was characteristic of melanoma, except for the absence of pigment. Since then Horwitz has published as many as 49 cases in which, in spite of absence of pigment, the clinical picture, malignancy and the histological structure compelled a diagnosis of malignant melanoma. Many earlier authors had pointed out that certain of the metastases or the primary tumour may contain little or

PLATE II.



Melanocarcinoma. Epithelium from the margin, massive development of pigment-laden dendritic cells. (G. Miescher, *Jadassohn's Handbuch*, XII 3, p. 1062.)

[*To face p.* 58.

no pigment. They are of interest in showing that the amount of pigment bears no relationship to malignancy.

Leucodermia

"Leucodermia" is not easy to define; confusion arises with mere relative paleness compared with hyperpigmentation and with areas protected by scales from the prevailing discoloration, as in psoriasis treated with chrysarobin. Wertheim defines it as follows:—"More or less numerous disseminate secondarily originating pigment-poor or pigment-free spots of roundish shape with normal or hyper-pigmented surrounding." But I think it unwise to restrict the term to secondarily originating achromia and important, on the other hand, to add that there is not merely absence of pigment, but inability, perhaps only temporary, to form pigment. This is demonstrated by negative dopa-reaction and failure to darken on irradiation.

Depigmentation, like hyperpigmentation, may follow various inflammatory processes and eruptions.

Syphilitic Leucodermia. The usual form is composed of small, round, pale areas without sharp outline, between which the skin is normal or possibly over-pigmented. It is most conspicuous and often only seen on the neck. The whole process is now considered primarily a depigmentation rather than a hyperpigmentation with spared islands. It is consequently more often noticed in dark individuals. Moreover, Ehrmann showed that it could be brought out on the trunk too by irradiation with quartz-light. Habermann takes the view of Simon and Neisser that the leucodermia follows an exanthem and that it is only noticed if and where the skin is otherwise pigmented. Even if there is no clinical preceding rash the leucodermic patches show histologically signs of mild inflammatory perivascular infiltrate. Hoffmann established that wherever Treponema pallidum penetrated there was a progressive loss of pigment, though this might be preceded by a trifling increase.

There is no real support for the hypothesis of Kerl and others that there is a cerebral pigment-centre somewhere in the mid-

brain, the specific damage of which is responsible for the pigment-anomalies in syphilis.

The leucodermia of syphilis can be closely imitated by that of psoriasis, guttate parapsoriasis, eczema, pityriasis rosea and various dermatomycoses. Freudenthal (1928) described under the name "Luische Leucomelanodermie in Form einer Pseudo-vitiligo" a case of seropositive syphilis in which he observed the development of large patches of leucodermia out of an erythematous serpiginous late exanthem. In one stage it consisted of large white patches surrounded by a narrow ring of erythema but not of hyperpigmentation. These leucodermia-like syphilides may be mistaken for vitiligo. He doubts whether true vitiligo ever has an inflammatory border.

Tinea Versicolor. Occasionally this superficial fungous infection, instead of causing the usual brown discoloration, appears as white spots. It is often first noticed after exposure to the sun has pigmented the rest of the skin. In a case recently seen by me copious fungus could be demonstrated within the white areas. It is not merely due to protection against the light by the fungus or scales, for the infection can cause actual depigmentation in negroes.

Psoriasis. That the leucodermia may be a true one has been established by histological examination and by its failure to react to light.

Vitiligo. The usual course is that quite gradually small round or oval white spots appear which grow peripherally with convex outline. They can come to a standstill at any stage, remain stationary for a long time, and then suddenly progress again. Their progressive character distinguishes them from congenital achromic or leucodermic patches, which are quite fixed. The whole body-surface may be involved. The pale areas are surrounded by hyperpigmentation, which is most accentuated in their immediate neighbourhood, gradually fading towards the periphery. A regression of the spots is, without doubt, very rare, though it has been reported by a number of observers (Trim and Sequeira). Complete cases, from which the last patches of pigmentation have disappeared, are sometimes falsely reported as

cures. Apart from the colour-changes the skin appears clinically normal. It is not generally recognised that vitiligo of the scalp may take the form of white hairs scattered among the normal ones, and not necessarily in a circumscribed clump (Goldsmith).

The white patches cannot be made to pigment by light or other irritants, but Jadassohn showed that they are more easily inflamed than normal skin. This is supported by Schultz, who used carbolic acid, and by Takigawa (1931), who found that intracutaneous injections of old tuberculin, diphtheria toxin, etc., produced stronger reactions in the pale areas and that their resorption was slower than in the healthy skin. Other observers have reported opposite findings. Thus Kreibich had a case of eczema due to pediculosis, in which a vitiligo patch was completely spared though framed by a sharply defined cord-like inflammatory border. (May this have been syphilitic leucodermia?) He thought the vitiligo must interfere with the nervous reflex responsible for the inflammatory process; but we have seen that, according to Lewis, an intact nervous supply is not required for a local inflammatory reaction. Experimentally he found that croton oil produced blistering of the neighbourhood but not of vitiligo-patches themselves; he had the same result in syphilitic leucodermia. Hanava, using cantharides, iodine and CO_2 snow, and Burgess and Warner, using mustard-plaster, have corroborated Kreibich. Fischer has recently described cases in which rubbing of clothes, etc., has produced lichenified zones immediately around the depigmented areas, but not within them. But Roxburgh, testing vitiligo-patches by Lewis's methods (by stroking and pricking-in histamine and adrenalin and also by injecting pilocarpine), failed to elicit any striking or constant difference in the behaviour of the superficial blood-vessels as compared with unaffected areas.

Histology reveals complete disappearance of melanin and a negative dopa-reaction. Several authors have observed inflammatory infiltrates. They may be considered either the remains of an inflammatory process which caused the leucodermia or might in some instances be a reaction to light owing to deprivation of protective pigment. In many cases atrophic changes have

been observed, but never great enough to be noticeable clinically.

ÆTIOLOGY. In 1925 Flarer investigated 20 cases: 16 were women. In 4 it began with menstruation, in 6 with the menopause, and in 2 during pregnancy. Of the 4 men two were partially impotent; the skin was of feminine type with diminished sebaceous secretion and increased sweating. There was a tendency to adiposity. The vascular system showed in 15 cases a noticeable instability, the vaso-constrictors reacting with abnormal intensity to adrenalin, and the dilators to pilocarpine. In 13 cases dermographism and the pilomotor reflex were less marked on the leucodermic patches than elsewhere. Hypofunction of the pituitary was observed in 6 cases, and of the ovaries in 6. There seems, therefore, to be some disturbance of the endocrino-sympathetic system, but it is hard to define. It is sometimes associated with hypothyroidism, but more commonly with hyperthyroidism, and occasionally with suprarenal damage, for example Addison's disease. Lindberg (1922) thinks the Addisonian cases are coincidental. Sometimes it may be that the Addisonian hyperpigmentation merely shows up pre-existing leucodermia. But in Hern's case we noticed that the vitiligo was especially pronounced in the areas usually most deeply pigmented: both adrenals were found to be grossly atrophied as to cortex and medulla. Takigawa (1931) found sympathicotonia and vagotonia in equal frequency in ordinary cases of vitiligo. Psychical disturbances are popularly blamed, especially when it involves the hair; but the latent period varies from a day to 3 years. Oesterlen (1931) brings forward other forcible arguments against the idea that whitening of the hair can be produced by fright. In particular he emphasises the impossibility of a disturbance of pigment in a fully developed hair-shaft and rejects the supposition of Landois that the loss of colour is caused by the entrance of air. It is always a matter of substitution of dark by colourless hairs.

Relationship of Vitiligo to Alopecia Areata. In addition to the well-known fact that the new hair growing on an alopecia areata patch is frequently white, cases have been reported in which there are at first patchy losses of pigment in skin and hairs and only after some months alopecia in the same sites (Bettmann

and Sabouraud). In others, next to areas of typical alopecia were patches showing only depigmentation of hairs which did not fall. Schein has noted and Sabouraud confirmed that in cases of alopecia occurring in patients with early senile canities only the dark hairs fall out. The argument is used that both vitiligo and alopecia areata occur in Graves' disease and that experimentally in hens the administration of thyroid extract from cases of Graves' disease leads to fall of feathers and their replacement by colourless ones. But in true vitiligo fall of hair is very rare, and Barthélemy objected long ago that it is wrong to identify a permanent condition such as vitiligo with a curable one such as alopecia areata. Roxburgh finds in his own statistics no reason for associating the two diseases.

As to the actual pathogenesis it seems likely that the dark border is the result of stimulating inflammatory processes in the spreading zone. The depigmentation is best, but not adequately, explained by Schein's "exhaustion-theory." This is based on the fact that dark individuals exposed to an equal stimulus respond with a greater increase of pigmentation than fair, and that in the same individual an analogous difference is found according to the region. Now dark skin reaches earlier the maximal limit of its pigment-forming power, so that a further increase of stimulus finally paralyses pigment-production. Bloch, too, sees in vitiligo a kind of exhaustion of a primarily weak cell-function, as measured by the dopa-reaction. The complete disappearance of pigment already formed is, however, still unexplained.

Acquired Hyperpigmentation

The physiological elaboration of pigment can be increased by many different causes, local and general. But the response to both varies in degree within wide limits according to the predisposition of the individual.

Chemical and Toxic Melanodermia. Bloch calls attention to the fact that those chemical irritants that especially cause pigmentation, *e.g.*, tar and arsenic, have the potentiality in common with

actinic influences (which, incidentally, they enhance) of eventually leading to carcinoma, when their action is prolonged.

Petroleum, Coal and Tar Melanoses. These cases have only aroused interest since the beginning of the Great War, when lubricating oils, etc., were used in a crude state, especially in Germany and Austria. Thus Oppenheim demonstrated a case of typical lubricating oil melanosis, in which there was such an intense brown-black discoloration of the face and neck, that it was thought to be an arsenical pigmentation. Many other cases were afterwards reported from the use of impure vaseline. In addition to pigmentation some develop lichenoid or bullous lesions. The eruption is not strictly confined to areas exposed to the offending substance; though most intense and evenly distributed on the parts exposed to light, it only fades *gradually* at the junction with the covered areas. It does not, therefore, appear to be caused by the external action of the tar-product, nor can light be more than one of the determining factors. Hoffmann and others thought the cause might be the inhaling of small quantities of tar-vapour and proposed the name "melanodermitis toxica lichenoides et bullosa."

When due to crude petroleum or the above derivatives, it depends on inadequate removal of the harmful components, especially anthracine and anthraquinone-acridine compounds. These substances cause sensitisation of the skin to light, but they can bring about quite similar discoloration on covered parts with the help of intertrigo or friction. The same condition has also been seen to result from long occupation with hard or soft coal and also with various derivatives of coal, but only those distillation-products with high boiling point, *e.g.*, coal-tar, pitch and asphalt. Sometimes localised melanoses are caused by articles made from asphalt, *e.g.*, on the ears from radio earphones in which acridine is present. The toxic effects of tar on the skin are similar to those of crude petroleum, though the tendency to pigmentation is slightly greater, whilst that to hyperkeratosis is less.

All these substances appear to act more by inhalation in the form of dust than by external exposure. Though hardly any area



Beginning Professional Melanodermitis in a Gas-worker.
(R. Habermann, *Jadassohn's Handbuch*, IV, 2, p. 838.)

[*To face p.* 65.

of the body is immune, the favoured sites, in order, are the face and neck, upper limbs, lower limbs, groins and navel. It is also characteristic and almost pathognomonic for the sclerotics to be stained. The colour varies from dark brown-red through red-violet to dirty brown or slaty black. The arrangement is flecked, reticular or figurate (see Plate III.). Examination with the lens generally reveals a still finer network, in which the immediate neighbourhood of the hair-follicles is spared (Habermann). This is an additional point against its exogenous causation. In the majority the discoloration is accompanied by other changes, *e.g.*, diffuse swelling and infiltration, scaling, hyperkeratosis, follicular plugs, papulo-pustules, comedos or papules resembling lichen ruber. Finally, in long-standing cases there are signs of atrophy, such as a shiny appearance, crinkling and telangiectasis, giving a picture resembling radiodermatitis, poikilodermia of Jacobi or xerodermia pigmentosa (Habermann). There are no constant internal symptoms, and it seems that very small quantities are required to sensitise the skin.

"Riehl's Melanosis." Though in certain individuals the above condition can be produced by the inhalation of ordinary coal-dust, it has been much rarer in countries that were spared the blockade and the multifarious substitution-products in which petroleum was largely used, even for food, *e.g.*, margarine. The similar clinical picture described in 1917 by Riehl was at first thought by him to be due to other food-factors. But the only distinction may be that in Riehl's cases the intoxication with petroleum was by the alimentary route. But in non-Germanic countries the term "Riehl's Melanosis" has, on the contrary, come to be used just for cases with a known exogenous noxa, *e.g.*, tar-vapour (Burnier and Eliascheff), lubricating oil (Louste and Lévy-Franckel) and in metal-workers (Cole and Driver).

In 1922 Civatte, when still unaware of the newer observations on tar-melanosis, described an exactly similar condition under the name "poikilodermie réticulée et pigmentaire." Habermann states that Civatte eventually recognised without qualification the complete identity of his disease with tar-melanosis; but Civatte, in a personal communication (September 21st, 1933), tells

me that he identified his poikilodermie with the first cases of Riehl but that he is sure that his cases, and he thinks several of Riehl's, were not due to tar. He considers it probable that not only tar but also other causes, as yet ill-defined, may lead to the same melanodermia.

Several cases have been described in England under the title "poikilodermia of Civatte" by Barber, Graham Little and others, chiefly in women. None of them had apparently been exposed to oil or tar-derivatives.

Arsenical Melanosis. There are two types:—(1) diffuse, which may include the whole body-surface, and (2) flecked; the latter is commoner. The diffuse is probably always a primary arsenical manifestation. In the second type the flecking is sometimes due to an eruption such as psoriasis or lichen planus, for which the arsenic has been given; but even uncomplicated arsenical pigmentation is usually flecked, giving rise to the raindrop appearance. In contrast with tar-melanoses the pigmentation due to arsenic, though also a sensitiser to light, is generally more marked on the trunk than on the exposed parts. It occasionally but rarely involves the oral mucosa. There is great variation in individual predisposition. It can follow all forms of arsenic. Histology shows that the pigment is entirely melanin. Arsenic is a very strong catalyser of oxidising and reducing processes: it therefore probably acts by hastening and intensifying the normal pigmentary mechanism.

Endocrine Influences. Addison's Disease. The pigmentation is seen microscopically to consist of an increase of melanin in the deeper layers of the rete. It can be shown that there is no increased activity of the oxidase, as there is in actinic pigmentation. It can, therefore, be further greatly increased by irradiation. Consequently it generally fades somewhat in the autumn and winter; this must be remembered when evaluating remedies. If, then, the oxidase is not increased, it is natural to suspect an increased supply of melanogen, especially in view of the very close relationship between adrenalin and dopa and the associated disease of the adrenal glands.

Ætiology. The fatal disease often develops on a basis of con-

stitutional hypoadrenalism, as a result of some added endogenous or exogenous noxa. The leading place is taken by tuberculosis of the adrenals. Very acute cases are often without pigmentation; they depend on a destruction of the adrenals by hæmorrhage, thrombosis or embolism; generally only on one side. When this is so some authors hypothesize a reflex disturbance of function of the sound side. When the adrenals are not grossly involved Furuta remarks that not enough attention is paid to finer cortical changes, which can bring about typical manifestations of insufficiency. Involvement of the different parts of the adrenal system produces separate effects, though of course these are generally combined.

Medulla and Chromaffine System. Constitutional inferiority of the chromaffine apparatus has been emphasised in status thymicus and lymphaticus; but just in typical thymo-lymphatic patients there is generally a pale skin. Tuberculosis is said most often to attack primarily the medulla. Bannwart reported a case of Addison's disease in which a lymphangio-endothelioma had destroyed only the medulla and sympathetic chain. Chromaffine insufficiency is generally considered to be signalised by hypotonia, adynamia, low blood-sugar, raised glucose-tolerance, absence of elementary and adrenalin-glycosuria, and melanodermia.

Cortex and Interrenal System. Numerous authors, including Marchand and Hansemann, have contested the importance attributed to the medulla. For the cortex, they say, is sometimes severely diseased without the medulla showing any changes. Instances of elective amyloidosis, sclerosis or atrophy of the cortex have been reported. These authors see in the cortical damage the chief cause of Addisonism, and new work on the cortical hormone points to its close relationship with pigmentation. Youthful cases of Addison's disease often show delay in growth and atrophy of bones (cf. progeria). To insufficiency of the cortex are ascribed gastro-intestinal and toxic manifestations and nervous and psychical disturbances (convulsions, delirium and coma).

Sympathetic Nerves. Addison himself recognised the importance of the sympathetic. According to Sézary it is normally stimulated by the chromaffine system and acts as inhibitor of pigmentation.

Its paralysis could therefore lead to melanodermia (Chauffard and Wiesel). In lower animals in which the pigment-cells are still under the control of the nervous system the sympathicotropic action of adrenalin results in their contraction. Pende thinks that in man too the parasympathetic stimulates pigmentation and the sympathetic inhibits it. But in the War severe and varied injuries of the sympathetic produced no melanodermia. To this it has been objected that in the presence of anatomical damage there may have developed a new hormonal equilibrium, just as, conversely, there can be a functional disturbance without gross structural change. Warthin, Kren and Jackson saw a case of Addison's disease with pigmentation following infiltration of the solar plexus by lymphosarcoma. On the whole, the evidence as to the importance of sympathetic involvement is conflicting.

The Functional Unity of the Interrenal and Adrenal Systems. Most authors think that Addison's disease is the result of a disturbance in the ordered interplay of the two systems. But even in recent literature conscientiously analysed cases have been reported in which no changes could be found in either portion of the suprarenals. Sergent says that there may be suprarenal insufficiency without pathological anatomic findings. Conversely, there may be severe destruction without clinical manifestations, so long as there remains enough adequately functioning gland. Whilst Falta (1925) ascribes *all* symptoms to failure of the chromaffine apparatus, most recent authors have reached the conclusion that in extirpation of the adrenals a small remainder of cortex is enough to prolong life, and that complete absence of chromaffine substance causes no grave disturbances (Lewis and Houssay, 1923; Banting and Gairns, 1926, *et al.*). Cortical remains easily undergo hypertrophy. A hormone-like extract of cortex named "Cortin" or "Interrenin" has been reported in many cases to have caused improvement in Addisonian symptoms, including pigmentation, for which it is more effective than adrenalin.

Adrenalin. Most authorities now derive it from certain cyclical cleavage-products of albumen. As to its place of origin, the early view favoured the medulla. But many years ago Oliver and

Schaaf pointed out the importance of both portions, and gradually the view has strengthened that adrenalin is formed in the cortex and passes into the medulla, which mainly acts as a reservoir (Hartman).

Relationship of Adrenalin to Melanin. The idea that adrenalin and promelanin are derived from the same substance has not been established. But the black oxidation-product of adrenalin is thought by Gallerani (1928) to be identical with Raper's tyrosin-black.

Cortin (*Interrenin*) was isolated by Kühl (1926), and the method improved by Swingle and Pfiffner. Experimental and practical experiences in America have led Hartman, McArthur and many others to the unanimous conclusion that the effects of extirpation of the adrenals and the clinical symptoms of Addison's disease, including pigmentation, can be largely abolished by its injection.

The precise relationship of the adrenal disturbance and Addisonian pigmentation still remains obscure.

THYROID. The frequency of pigmentary changes complicating Graves' disease is variously computed as 3% up to 70%; Haldin Davis gives 50%. He describes it as a slight diffuse pigmentation of the trunk, especially the abdomen. It occurs with other enlargements of the thyroid, too, but less often. Chvostek distinguishes two types, the Addisonian and chloasma. In the former there may be a combination with real Addisonism. It is probably not caused through the vegetative nervous system, since in Graves' disease the sympathetic, generally regarded as a pigment-inhibitor, is usually hypertonic. Kocher saw many instances of disappearance of the pigmentation after thyroidectomy. Thyroxine, like adrenalin, is a derivative of tyrosin.

OVARIES. Experimental investigations by Bloch and Schrall on the influence of ovarian hormones on pigment-formation led them to the following conclusions. (1) In castrated and normal male guinea-pigs implantation of ovaries or injection or feeding of female sexual hormones (folliculin or œstroglandol) produce a hyperpigmentation of the nipple and areola. It is just as intense as the corresponding change in pregnant females. Prolan,

i.e., anterior pituitary hormone, does not have this effect. (2) The action of the follicular hormone consists in the activating and enhancing of the already present pigmentary capacity of the epidermal melanoblasts by virtue of their dopa-oxidase. It does not occur in albino nipples or in the completely pigmentless portions of partially coloured areolæ. (3) There is some parallelism between the duration and intensity of the hyperpigmentation and the other changes in the breast brought about by the hormone, *e.g.*, growth and development of the mamma. But in the pigmentation there is much more marked individual variation. Thus the injection of folliculin produces a growth of the nipple up to a maximum of about two and a half times with little individual variation. But the final intensity of pigmentation varies very greatly, depending on its intensity before the administration of folliculin. It sometimes reaches a degree only equalled in pregnant females with a naturally dark skin. This proves that the hyperpigmentation is a direct effect of the ovarian hormone and not merely secondary to the growth of the breast, which it may even precede. Besides, the mamma is not the only region where pregnancy-hyperpigmentation takes place, and in the other areas there is no evidence of increased cell-proliferation. Both processes last for some time after discontinuance of the hormone. This does not seem to stimulate the pigmentary apparatus of the whole skin but only certain regions; and within these only certain cells, namely, those which normally produce pigment.

Pregnancy-Pigmentation and Chloasma. In *pregnancy* all pigmented areas get darker, including nævi, which it may even bring out for the first time.

There is, according to Hofbauer, a hyperplasia of the adrenals, thyroid and hypophysis, the over-action of which can be considerably counteracted by giving ovarian extract. This is in contradiction to the work of Bloch and Schrafl, which at present constitutes the most direct evidence of the important *rôle* of the ovaries in the hyperpigmentation of pregnancy. Enlargement of the adrenals in pregnancy and the demonstration of an increase of adrenalin in the blood by Neu led Meirowsky to the view that hyperadrenalism is the most important factor. But we have seen

that adrenalin itself does not act as a propigment of epidermal melanin; if it acts as a stimulator of the sympathetic it would have a depigmenting action; further, in Addison's disease there is certainly no increase of adrenalin but rather a diminution, though there may be an increase of its mother-substance. Meirowsky's conclusion, therefore, seems unjustified.

Chloasma. The name is given to patches of pigmentation resembling freckles, only much larger, which are increased by, but are not dependent on, light. Chloasma is characterised by its sharp demarcation, which distinguishes it, according to Darier, from pigmentation produced by light or heat. It affects the face, and Fig. 5 depicts the characteristic distribution according to Sellei. He thinks seborrhœa is a predisposing factor. It has been attributed to pregnancy, the climacteric and various disorders of the pelvic organs; but it may occur in males or virgins, and out of 20 cases Sellei could only find dysmenorrhœa or other gynæcological disorder in 7. Its sharp demarcation and strict localisation suggest that it is aetiologically similar to freckles and that pregnancy only serves to bring it into evidence, as it can other nævi.

Yet a similar appearance, a brown ring on the forehead with arched margins, has been described by Anderson and Wernoe (1930), together with some cutaneous dystrophy and pigmentation of the linea alba, in patients with encephalitis, brain-tumours or organic brain-injury. They ascribe the pigmentation to central vegetative damage, probably in the corpus striatum.

Avitaminoses. Deficiency of *vitamin A* can lead in man, in addition to dryness and papular lesions, to intense pigmentation. Even areas not otherwise changed may become darker, including the conjunctiva (Wright and Kirkpatrick, 1927), which becomes light grey to dark grey-brown, especially near the inner canthus. Frazier has seen the pigmentation precede keratomalacia. It disappears on giving "A," but more slowly than the keratomalacia. Possibly it is related to the pigmentation in vagabonds, where also there is involvement of the conjunctiva.

Vitamin D. Feer observed browning of the skin of children treated with Vigantol. Bernheim-Karrer and Zaruski tested

uniovular twins. They were kept under the same conditions, including light-environment, but one was given Vigantol. The

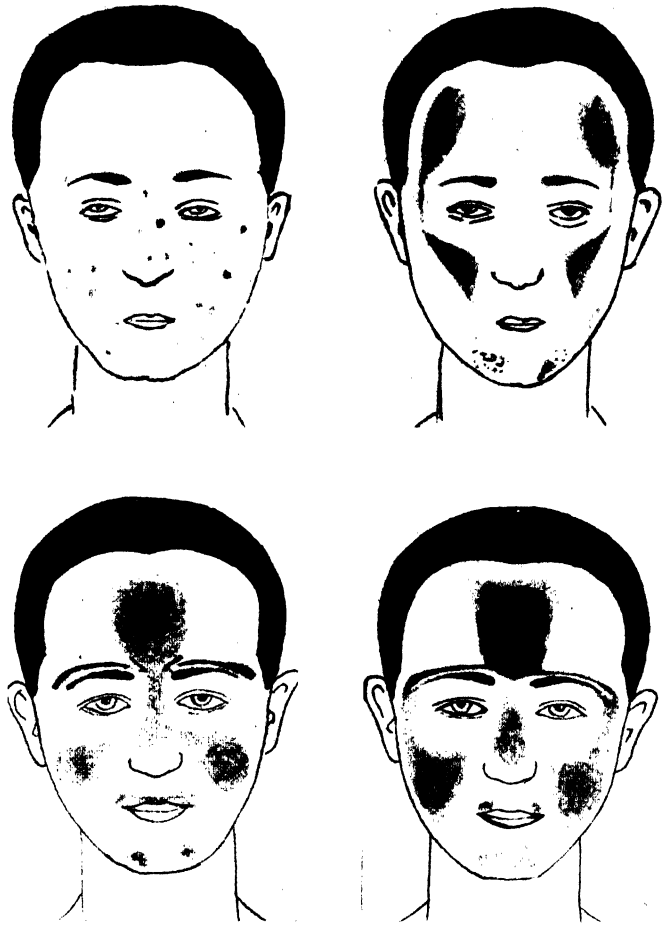


FIG. 5.—Forms of Chloasma Uterinum. (J. Sellei, *Dermat. Zeit.*, 1930, p. 19.

latter developed deep pigmentation, especially of the back of the hands, the axillæ, circum-mammillary region and the part of the

back exposed to light. These cases appear, therefore, to be due to an excess of vitamin D. According to Thoens it can be counteracted by increasing "A."

Nervous System. Peripheral Nerves. Depigmentation has often been reported in the distribution of irritated peripheral nerves, as in neuritis and neuralgia. Foerster described increase of pigment after gunshot-wounds involving peripheral nerves, though complete nervous interruption generally caused no pigmentary changes.

Spinal Column. Attention has also been drawn to streaks of pigmentation which may supervene on anæsthetic or paræsthetic areas resulting from affections of the spinal column (Thomas) and in half-girdle-form in zona (Souques). Simons studied the results of war-wounds of the spinal cord. In one case, within a fortnight after injury of the cervical cord, he observed numerous small pigmented spots in the area of distribution, which ceased abruptly towards the middle line as well as above and below. But, as a rule, months or even years elapse before the appearance of such spots. Sometimes depigmentation has been observed under similar circumstances. Thomas thinks destruction of the grey substance is essential for the genesis of the pigmentation. Most authors assume a disturbance of the sympathetic, but Sézary (1926) declares that there is no clinical evidence for such a view and thinks that melanodermia can only occur from disturbance of nutrition and of internal secretion, in which the sympathetic would play only a secondary *rôle*. Sometimes the pigmented streaks may really be analogous to the systematised nævi and systematised dermatoses, such as lichen planus, which occasionally occur in a zoniform pattern so far unexplained. The "system" is thought to correspond with the inherited factors which determine the striped markings in animals.

Neuroses and Psychoses. Wigert (1926) described 5 cases of general melanodermia in catatonic schizophrenia. In none was there any sign of disorder of the adrenals, though the pigmentation was Addisonian in character. It faded *pari passu* with the regression of the stupor and agitation. He thought there was

probably a toxic factor which worked *viâ* the nervous system on the internal secretion. Kaufmann has frequently noticed increased pigmentation in hypochondriacal psychoses with hallucinations.

Buccal Pigmentation. Buccal pigmentation in patches or streaks occurs not only in Addison's disease, but also in the absence of any indication of suprarenal insufficiency. It has been seen in pediculosis, exophthalmic goitre, tar-melanosis and exceptionally in arsenicalism. It must also be remembered that it may be racial; among Europeans it is commonest in Roumanians.

Treatment

Nævi. Freckles. Matarasso (1932) recommends CO_2 *snow*. Each spot on the face is given 3 seconds' application of a carefully shaped pencil; on the hands 4 seconds are necessary. After a week the spot desquamates, and he reports that the freckle does not recur. Roxburgh advises the application to each individually of liquefied *phenol*. For small numbers Pokorny and Sellei prefer the *galvano-cautery* with a very fine point. These treatments can usefully be preceded by irradiation to render all the lesions conspicuous. For large numbers *desquamation* can be produced by applying mercury perchloride 0·1–0·5% in spirit or a 10–20% white precipitate ointment. But these peeling procedures generally have only a temporary effect. Moreover, strong mercurial preparations sometimes even aggravate pigmentation.

Flat Moles. These can be removed by superficial scraping with electrically driven *burrs* (Kromayer). The best local anæsthetic for relatively small areas is ethylchloride, which has the advantage of hardening and demarcating the area. The cutis propria is not involved, scars are avoided, and the results are good. Lazar (1926) recommends the intracutaneous injection of 0·3% *hydrogen peroxide* and claims completely scarless results. My own favourite method is *fulguration* with a small high-frequency machine and pointed applicator. This converts the tissues into a dry powder which can be easily brushed off, there being little

difficulty in gauging the necessary depth. It has the advantage that there is practically no subsequent inflammatory reaction.

CELLULAR NÆVI. After the removal of any hairs by *electrolysis*, these too are banished most satisfactorily by *fulguration*, if not too large, when they are best *excised*.

MALIGNANT MELANOMATA. If there are signs of malignancy (growth, especially after the age of 25, subjective symptoms, red or pigmented halo), a margin of apparently healthy skin must be included; Belot considers 8 mm. adequate. A local anæsthetic is dangerous. *Electro-coagulation* is probably safest, as it fixes the cells. This is not the case with the diathermy knife, which Louste and Thibaut (1931), as a result of a bad experience, consider just as dangerous as the surgical knife. Ravaut recommends first coagulating a barrier around and beneath the lesion. Electro-coagulation is radical and has the advantage that the open healing allows of rapid detection of relapses. But the massive destruction of tissue leaves considerable scarring. *X-rays* and *radium*, in contrast to earlier views, are now realised to be sometimes effective. Cases whose cure has lasted over 5 years have been frequently reported (Miescher, Evans *et al.*), and they have the advantage of being more conservative. But it remains true that a larger proportion of melanomas than of other malignant neoplasms prove ray-resistant. *Excision* should only be used when it is possible to operate at a great distance from the primary growth; for example amputation of the finger for a melanoma of the nail-region. More than in any other type of tumour there is an indication for early extirpation of regional lymph-glands, with perhaps subsequent irradiation. The prognosis is now realised to be not so hopeless as formerly, unless metastasis has occurred. Those on the face have the best and those on the foot the worst outlook.

Chloasma. Treatment is only required if spontaneous disappearance fails. Leszchinsky recommends *folliculin* for hyperfunction of the pituitary and *insulin* for hyperthyroidism at the climacteric. But Recasens (1930) failed to get an ideal result with hormone-treatment, autohæmotherapy, or ovarian implantations. Sellei finds it remarkably effective to combine

vitamin C internally (juice of 3–4 lemons daily) with "*mercurol*" (ammoniated mercury, bismuth subnitrate, glycerine, oil of sesame, equal parts) externally. The treatment needs to be continued for 3–4 months. Neither of these measures singly is nearly so successful.

Vitiligo. Internal treatments by themselves have been useless. *Irradiation*, even with sensitisers, such as oil of bergamot, has only been partially successful in a few cases. Cohen and also Burgess have, however, recently achieved complete cure by the following combined method. A 10% alcoholic solution of *oil of bergamot* is applied to the affected areas twice a day. Once a week they are exposed to a *mercury vapour lamp* after the intravenous injection of *sanocrysin* 0·05 gm. Pigmentation began at the end of 3 weeks and was complete in 10 weeks. Bucky and Wolffenstein have reported entire success by means of *Borderline-rays* (see p. 451), and an elaborate combined method is advocated by Jausion and Pagès (see p. 443).

Bibliography

Becker, S. W. "Melanin Pigmentation," *Arch. of Derm. and Syph.*, 1927, **16**, 259.

Bloch, B. "Das Pigment," *Jadassohn's Handbuch der Haut- u. Geschlechtskr.*, **I/1**, 434.

Bloch, B., and Schrafl, A. "Experimental Investigations on the Influence of Ovarian Hormones on Pigment-Formation," *Arch. für Derm. und Syph.*, 1932, **165**, 268.

Bucky, G. "Alopecie und Vitiligo. Beeinflussung durch allgemeine Grenzbestrahlung," *Zbl. Hautkrank.*, 1932, **42**, 564 (*cit.* Habermann).

Burgess, N. "Successful Treatment of Vitiligo with Report of a Case," *Brit. Journ. Derm. and Syph.*, 1934, **46**, 313.

Burgess, N., and Warner, E. C. "A Case of Addison's Disease associated with Hyperthyroidism and Vitiligo," *Guy's Hosp. Report*, 1926, **76**, 280 (*cit.* Habermann).

Bürkle, H. de la Camp. "Pigmentnævi und Neurofibromatosis," *Arch. klin. Chir.*, 1931, **167**, 167 (*cit.* Meirowsky).

Civatte, A. "Poikilodermie réticulée pigmentaire du visage et du cou," *Ann. de derm. et de syph.*, 1923, **4**, 605 (*cit.* Bloch).

Cohen, M. "Successful Treatment of Vitiligo," *Arch. of Derm. and Syph.*, 1933, **28**, 215.

Dawson, J. W. "The Melanomata," *Edin. Med. Journ.*, 1925, 501.

Deelman, H. T. "Über pigmentlose Nævusgeschwülste," *Acta dermato-vener.* (Stockholm), 1922, **3**, 212 (*cit.* Miescher).

Evans, W. A., and Leucutia, T. "Treatment of Melanotic Tumours of the Skin," *Amer. Journ. Roentgenol.*, 1931, **26**, 236 (*cit.* Miescher).

FLARER, F. "Richerche sul sistema endocrino-simpatico in alcuni casi di vitiligine," *Giorn. ital. di derm. e sif.*, 1925, **66**, 957 (*cit.* Bloch).

FRAZIER, C. N., CH'UAN-K'UEI HU. "Cutaneous Lesions associated with Vitamine A Deficiency in Man," Dermat. Congress, Copenhagen, 1930, 482.

FREUDENTHAL, W. "Luetische Leukomelanodermie in Form einer Pseudo-Vitiligo," *Arch. für Derm. und Syph.*, 1928, **156**, 142.

GOLDSMITH, W. N. "Canities in a Youth aged 17," *Proc. Roy. Soc. Med.*, 1932, **25**, 1549.

HABERMANN, R. "Paratypische Pigmentanomalien," *Jadassohn's Handbuch der Haut- u. Geschlechtskr.*, **IV 2**, 830.

HARTMAN, F. A., AARON, H. H., and CULP, J. E. "The Use of Cortin in Addison's Disease," *Endocrinology*, 1932, **16**, 43 (*cit.* Kaufmann).

HORWITZ, A. "Melanotic Tumours. Non-melanotic Melano-epitheliomas and their Relation to the Melano-epitheliomas," *Ann. Surg.*, 1928, **87**, 917 (*cit.* Miescher).

KAUFMANN, E. "Die pathologischen Pigmentierungen der Haut in innerer Medizin, Neurologie und Psychiatrie," *Jadassohn's Handbuch der Haut- u. Geschlechtskr.*, **IV 2**, 1011.

KINNEAR, J. "A Case of Riehl's Melanosis," *Brit. Journ. Derm. and Syph.*, 1935, **45**, 191.

LINDBERG, K. "Etiologie et pathogénie du vitiligo," Paris: Jouvet et Cie., 1922 (*cit.* Habermann).

MASSON, P. "Les nævi pigmentaires, tumeurs nerveuses," *Ann. d'anat. path.*, 1926, **3**, 417.

MATARASSO, M. "Treatment of Freckles," *Ann. de Derm. et de Syph.*, 1932, **3**, 818. (Abst. *Brit. Journ. Derm. and Syph.*, 1933, **45**, 168.)

MEIROWSKY, E. "Idiotypische Pigmentanomalien," *Jadassohn's Handbuch der Haut- u. Geschlechtskr.*, **IV 2**, 588.

MIESCHER, G. "Melanom," *Jadassohn's Handbuch der Haut- u. Geschlechtskr.*, **XII 3**, 1005.

MONCORPS, C. "Studien zur Genese des normalen Oberhautpigmentes," *Arch. für Derm. und Syph.*, 1924, **148**, 2 (*cit.* Meirowsky).

OESTERLEN, O. "Haarergrauen durch Schreck," *Med. Welt*, 1931, **5**, 1129 (*cit.* Habermann).

PAUTRIER, L. M., LÉVY, G., and DISS, A. "Dermo-epidermic Interchanges as Controlled by the Study of Melanic Pigment, the Esters of Cholesterol (Xanthoma) and Hæmosiderin (Schamberg's Disease)," *Arch. of Derm. and Syph.*, 1928, **17**, 1 (*cit.* Meirowsky).

PECK, S. M. "Pigment (Melanin) Studies of the Human Skin after Application of Thorium X," *Arch. of Derm. and Syph.*, 1930, **21**, 916 (*cit.* Miescher).

PRYDE, J. "Recent Advances in Biochemistry." London: Churchill, 1931.

RAPER, H. "Tyrosinase-tyrosin Reaction; Production from Tyrosine of 5 : 6-dihydroxyindole and 5 : 6-dihydroxyindole-2-carboxylic acid; the Precursors of Melanin," *Biochem. Journ.*, 1927, **21**, 89 (*cit.* Pryde).

ROXBURGH, A. C. "The Ætiology of Alopecia Areata and its Relation to Vitiligo and Sclerodermia," *Brit. Journ. Derm. and Syph.*, 1929, **41**, 351.

TRIM, E. A., and SEQUEIRA, J. H. "Vitiligo in an African; Spontaneous Improvement in Hospital," *Brit. Journ. Derm. and Syph.*, 1931, **43**, 592.

SELLEI, J. "Formen und Ursachen der als Chloasma uterinum benannten Hyperpigmentation des Gesichtes," *Derm. Zeit.*, 1930, **58**, 17 (*cit.* Meirowsky).

SMITH, D. T. "Evidence showing the Existence of Two Distinct Types of Pigment Cells," *Bull. Hopkins Hosp.*, 1925, **36**, 185 (*cit.* Meirowsky).

WOLFFENSTEIN, W. "Behandlung der Vitiligo mit Grenz-Allgemeinbestrahlungen," *Zbl. Hautkrank.*, 1931, **36**, 160 (*cit.* Habermann).

CHAPTER IV

ENDOCRINE NERVOUS AND MENTAL INFLUENCES

The Endocrine System

THERE is a particularly close functional interrelationship between the endocrine glands, the vegetative nervous apparatus and the mind, so that it is difficult or impossible to define the effects of the disorder of one portion of this great system without regard to associated changes in the rest.

Thyroid. The lowered metabolism in *hypothyroidism* explains the tendency to accumulation of fat. The lowered excretion of nitrogen is not appreciably raised by increasing its ingestion. Its consequent accumulation in the tissues leads to retention of water, *i.e.*, œdema. Popper found that the skin of thyroidectomised animals when immersed in $\frac{N}{10}$ HCl could absorb as much as 8 times the quantity taken up by normal skin.

The state of the thyroid has an influence in varying the sensitiveness to drugs. Thyroidectomised animals are more sensitive to mercury. Conversely, Bram showed that patients with Graves' disease have a heightened tolerance of quinine. Bauer suggests that individual over-sensitiveness to various medicaments may at least partly depend on the state of the internal secretions. A similar function is exerted in infections, a connection having been shown experimentally between the endocrine organs and bactericidal power, phagocytosis and antibody-formation. The defence-forces are lessened by removing the thyroid and restored by giving it by mouth.

GRAVES' DISEASE. In this condition, which may represent a dysfunction rather than a pure overaction, there is generally copious growth of the scalp-hair and the skin is thin and smooth.

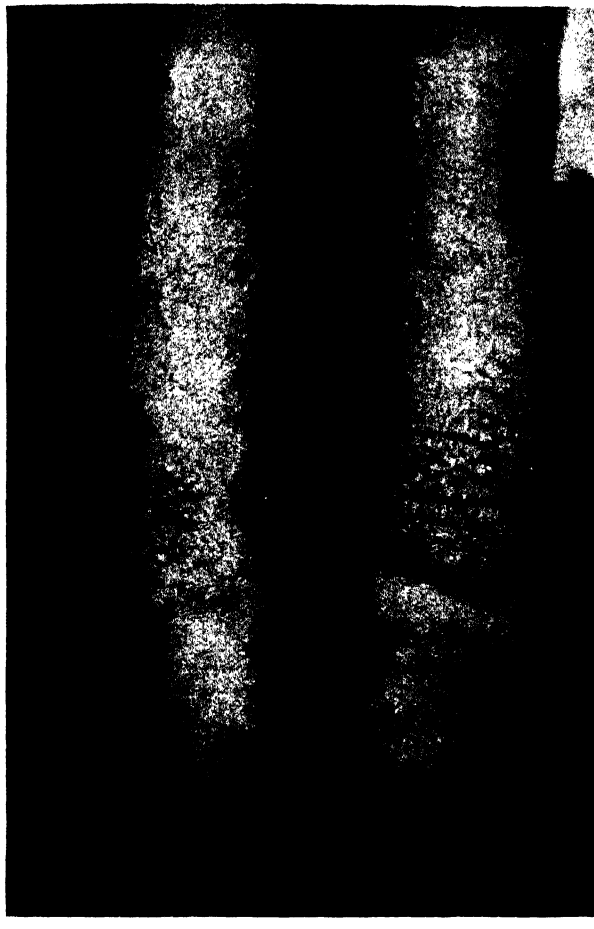


FIG. 6.—Showing myxomatous plaques on lower anterior aspect of legs, separated from similar plaques on feet by a band of normal skin corresponding to shoe-strap. (J. T. Ingram, *Brit. Journ. Derm. and Syph.*, 1933, p. 21.)

There is often hyperhidrosis, either diffuse, circumscribed, or even unilateral. The pigmentary changes are mentioned on p. 69. Sometimes there are changes resembling those of hypothyroidism,

namely, a myxœdema-like condition with dry skin, hypotrichosis, premature canities, and dryness and brittleness of the nails.

Circumscribed myxœdema has been recorded from time to time during the past 30 years, sometimes associated with hypothyroidism, but also quite often in Graves' disease. Ingram (1933) observed it in a patient with advanced Graves' disease, which was eventually fatal. In the skin of the legs and dorsum of the feet were several plaques, which were thickened, firm, rugose, coarse and showing prominent pores (see Fig. 6). They persisted in spite of many months' absolute rest in bed. A marked feature was the sweating of the unaffected skin of the feet and legs. Histologically the plaques showed normal epithelium, beneath which was a narrow zone of myxomatous tissue made up of fine fibres and star-shaped cells with long radiating processes; deeper still was a thick layer of rather hyaline fibres arranged in interlacing strands, with clear spaces, evidently resulting from œdema, between them. O'Leary in 1930 reported 8 cases: in 7 of these Graves' disease was already present, associated with auricular fibrillation and œdema of the legs. After an initial improvement caused by thyroidectomy, all these symptoms relapsed together. In one of his cases it appeared 6 months before the onset of the Graves' disease. He noted that the condition only occurred on the legs and was always associated with cardiac failure. Pillsbury and Stokes, in 1931, reviewing the literature, found 20 cases, 12 of which were associated with hyperthyroidism and œdema of the legs: to these they added 3 cases of their own. Reuter, who studied the histology of circumscribed myxœdema, noted that mucin occurs normally in the skin. He thought that the essential changes of myxomatous degeneration depend on primary œdema. Ingram concluded that circumscribed patches of myxomatous degeneration on the legs may be associated with and dependent upon hyperthyroidism, and that the determining factor is chronic œdema due to cardiac failure. But McMenemey later described a case in which there was no cardiac failure or other causes of œdema.

Jadassohn points to some relationship between *calcinosis cutis* and myxœdema.

Circumscribed *sclerodermia* may also occur in cases of Graves' disease. In the early stages the resemblance to localised myxœdema may be very great and the two conditions may occur together in the same patient. Vallery-Radot, Hillemand and Chomereau-Lamott described a case of Graves' disease in which there developed first myxœdema and eventually generalised sclerodermia.

Parathyroids. The tetany which follows extirpation or destruction of these glands is accompanied among other things by *hypotrichosis* and *atrophy of the nails*, which may fall. There is some evidence that the alopecia resulting from the administration of thallium acetate is due to its action upon the parathyroids. Mice poisoned with thallium develop, in addition to the fall of hair, skeletal symptoms and cataract. That the latter is not due to a local toxic action is shown by the fact that if the thallium is introduced into the conjunctiva or anterior chamber of the eye no cataract follows.

Impetigo Herpetiformis. Friedmann in 1932 reported a typical but benign case of Hebra's impetigo herpetiformis, which he observed over a period of 10 years. The young woman was three times pregnant, each pregnancy being accompanied throughout by diarrhœa. During the two first pregnancies (the third was artificially terminated at an early stage) there was first a loosening of the hair. In the second half of the first two pregnancies there was an outbreak of impetigo herpetiformis. The beginning of the second attack could be watched. Within 2 days the exanthem developed evenly and rapidly to its maximum. At its peak precipitately the child was born, after which the cutaneous manifestations rapidly subsided. In both pregnancies the uterus emptied itself prematurely and with great rapidity at the acme of the skin-eruption. Both babies died almost immediately after birth. She also had chloasma, temporary loss of nails and hair, tetany, and some atrophy of the optic nerves, pronounced nightblindness following the illness. During the subsequent period of observation there was never a relapse, even after the premature interruption of the third pregnancy.

In two other cases of impetigo herpetiformis cataract has been

described. Since the disease can occur in men the origin cannot lie in the pregnancy itself or the female sex-glands. Schardorn considers it due mainly to damage of the parathyroids. Since his publication in 1921 most described cases have had tetany, and in those that came to autopsy there was absence of the parathyroids. Friedmann doubts the existence of true impetigo herpetiformis without inadequacy of the parathyroids. As in the case of tetany, the majority of cases occur in the spring. The exact source of the toxin which damages the parathyroids is not known.

Sex-Glands. TESTES. The skin of castrated males becomes more or less thin, dry and lustreless, as if the activity of the cutaneous *glands* were inhibited. The face becomes greyish and wrinkled: the lanugo-hairs there are scanty and are altogether absent on the body. The pubic *hairs* are absent or of the female type. The scalp-hair is sometimes strikingly copious, though dry and lustreless. This conforms with the normal physiological observation that at puberty, in addition to the hair-changes, there is an increase of sebaceous and sweat-gland activity.

The absence of testicular secretion seems to favour the development of *cancer*. It was found by Maisin, Desmedt and Jacqmin that tar-cancer could be produced much more quickly in castrated than in non-castrated mice, and metastases occurred in the internal organs in 73% of castrated as compared with 33% in the non-castrated.

THE OVARIES. These have a definite relationship to *pigmentation*, as has been proved by the experiments of Bloch and Schraft described on p. 69.

Bloch and Stauffer point out some association between dermatoses of the *poikilodermia* type and atrophies of the ovaries and testes.

Adrenals. Their relationship to pigmentation has been fully discussed in the last chapter.

Overactivity of the cortex in the male, if it begins in early life, is associated with premature puberty. After puberty, however, when virility is established, no further change in this direction is possible.

But it is in the female that cortical hyperplasia leads to the

most striking changes. If it begins before puberty, the child becomes obese and develops *hair* on the face and pubic region, the *skin* becomes coarse and dry, the clitoris enlarges, the internal genitalia diminish and frequently menstruation fails to appear. If it begins after puberty, there ensue amenorrhœa, loss of sexual interest, hyperpiesia, *hirsutism* and the usual signs of virilism : sometimes there is partial *baldness* of the scalp in the typical male distribution. Unilateral adrenalectomy in several such cases has had definitely beneficial effects upon hair-distribution and other symptoms, without impairing the general health (Broster). But manifest virilism may be unaccompanied by obvious hyperplasia of the adrenals. It is supposed that in such cases their internal secretion responsible for masculinisation is abnormally active.

Histological investigation of the adrenal glands reveals that in all cases of virilism the cortical cytoplasm has an affinity for fuchsin which is not observed in normal glands (Broster and Vines). It is natural to suspect that the substance so stained may be closely related to the hormone or its precursor responsible for masculinisation. The same fuchsinophil reaction is also given by the eosinophil cells of the anterior pituitary, the interstitial cells of the testis and the peripheral cells of young corpora lutea.

The above facts led to the view that overactivity of the suprarenal cortex stimulates all mechanisms associated with masculinisation. Some doubt as to this has been caused by 2 cases recently described by Cecil, in which young men aged 26 and 27 years showed pronounced changes in the direction of femininity as the result of hypernephromata. It must, however, be realised that, whilst neoplastic cells may continue the functional activity of the normal cells from which they arose (*e.g.*, the eosinophilic and basophilic tumours of the anterior lobe of the pituitary which cause acromegalic gigantism and Cushing's pituitary syndrome respectively), a neoplasm may arise in an endocrine gland which destroys the hormone-producing cells and therefore diminishes or abolishes its specific activity. Thus ovarian tumours may lead to virilism in women. A greater difficulty for the masculinisation theory is the fact that Cleghorn

(1932) failed to obtain any effect on the growth and maturation of male mice by the injection of cortical extracts prepared by Swingle and Pfiffner's method.

Pituitary. HYPOPITUITARISM. Underaction of the anterior lobe causes a condition resembling eunuchism. In Fröhlich's "dystrophia adiposo-genitalis" the *skin* is alabaster-white, thin, dry and slightly scaly and feels cold. *Urticaria* and *dermographism* are common, and sometimes increased *sweating*. *Striæ albicantes* are often observed, perhaps due to stretching of the skin by increased subcutaneous fat. In Simmonds' "cachexia hypophyseopriva" or "dystrophia marantogenitalis (Simmonds' type)," which is caused by inhibited function of the pituitary and probably also the neighbouring centres of the base of the brain, the skin-changes resemble senile *atrophy*.

ACROMEGALY. This is due to hyperfunction chiefly of the anterior portion. There are thickening and roughness of the *skin* and often *pigmentation* and *mollusca pendula*. *Sebaceous* secretion is increased; sometimes there are outbreaks of profuse *sweating*. Hypertrichosis is not uncommon; the scalp *hair* is dense and individual hairs are coarse; the beard and moustache are bristly and eyebrows bushy; there is overgrowth of lanugo; the *nails* are thickened and brittle and grow rapidly. In 400 cases studied by Rowe, Winter and Lawrence, in which changes in the pituitary, mostly hyperfunction, were present, the commonest cutaneous manifestation was hypertrichosis, which occurred in 28%. According to Falta it is characteristic of the skin in acromegaly, in contra-distinction to myxœdema, that it can be *lifted in folds*. Sometimes the skin of the hands may somewhat resemble the early turgid stage of diffuse generalised sclerodermia.

Cutis Verticis Gyrata ("Bull-dog scalp"). In this rare condition the scalp is thrown into thick folds. It has been relatively often met with in microcephalic idiots and in subjects of acromegaly (Weber), possibly because the skull is too small for the scalp or the scalp too large for the skull (Truffi). In acromegalic patients folding of the skin has also been noticed on the face and even the hands. But a precisely similar clinical appearance of the

scalp has been observed alone or associated with myxœdema, pluriglandular insufficiency and non-microcephalic idiocy. Moreover, its histology is far more varied than its clinical appearance. Sometimes there are no microscopical abnormalities, except perhaps thickening of the cutis. But in others, which Jordan would distinguish as *pseudo*-cutis verticis gyrata, the histology has been that of a cellular nævus, neurinoma, neuronævus, nævofibroma or neurofibroma and occasionally a leucæmic or inflammatory infiltration. In many cases of pseudo-cutis verticis there have also been multiple tumours on the body, considered to be ordinary nævi, or, rarely, classical von Recklinghausen's disease. In neurofibromatosis it has recently been realised that changes occur in the skull which may include enlargement or contraction of the sella turcica, but without abnormality of the hypophysis. It is possibly significant that most of the cases of neurofibromatosis with alteration of the sella turcica have involved the scalp; such a mixed malformation of soft tissue and underlying bone finds an analogy in spina bifida. Widening of the sella turcica without involvement of the pituitary has also been observed in association with other nævi of the scalp or elsewhere. The correlation between histological type of cutis verticis gyrata and endocrine disorder has not been clearly worked out.

Strandberg and Weber emphasise that the effects of endocrine disturbance may be localised. Thus circulatory disturbances are most noticeable at the extremities. The sweating in hyperthyroidism is often regional: pigmentation may be confined to the axillary folds. In eunuchoidism the fat-accumulations are especially evident in certain areas, as is the hypertrichosis. In acromegaly there are often scattered warts and fibromas and the characteristic thickening of the skin can be confined to the hands and feet.

Basophilic Hyperpituitarism (Cushing's Endocrine Pituitary Syndrome). As was pointed out in discussing adrenal cortical tumours, adenomata can be functionally active structures producing hypersecretory effects: even minute tumours can give rise to striking and characteristic clinical symptoms. The growth-provoking and sex-maturing principles, the former almost certainly

elaborated by the acidophil and the latter presumably by the basophil elements of the anterior lobe, are chemically separable hormones.

Anterior pituitary adenomas composed of basophil elements were first described 20 years ago by Erdheim, but were looked upon as curiosities of morbid anatomy. Cushing described in 1932 a series of cases presenting a certain symptom-complex, including changes in the skin. The following features are characteristic of all cases :—(1) Rapidly acquired, peculiarly disposed and usually painful adiposity, confined to face, neck and trunk. (2) A tendency to kyphosis, associated with lumbar spinal pains. (3) Sexual dystrophy, shown by early amenorrhœa in females and ultimate functional impotence in males. (4) *Hypertrichosis of face and trunk* in all the females and in the preadolescent males and possibly the reverse in adult males. (5) *Dusky or plethoric appearance of the skin with purplish lineæ atrophicæ.* (6) Vascular hypertension. (7) Erythremia. (8) Backaches, abdominal pains, fatigability and ultimate extreme weakness. Other features less constantly recorded include *acrocyanosis, purpura-like ecchymoses* and *dryness* and *pigmentation of the skin.*

In 9 fatal cases the average age of onset was 18 years, and the average duration from onset to death 5 years. Death was ascribable to, or associated with, *multiple cutaneous abscesses and ulcers, intercurrent erysipelas,* acute pulmonary complications, intercurrent meningitis, streptococcal phlegmon or pancreatic necrosis. A basophilic adenoma of the pituitary was definitely demonstrated in 3 cases, an undifferentiated adenoma in 2, an adenoma-like structure in a fibrosed area of the anterior lobe in 1, and in 2 cases the gland was said to be normal.

There remain some difficulties in attributing the symptoms to the basophilic cells, especially if these are responsible for maturation and the ovulatory mechanism. For example, whereas premature sexual maturity characterises the disorder in children of either sex, why, in adult women, should there be amenorrhœa with an apparent reversal of the secondary sexual characters ? It is nevertheless of impressive significance that the syndrome has been found at autopsy in 6 out of 8 cases to be associated

with a pituitary adenoma, which in the 3 most carefully studied was definitely shown to be composed of basophilic elements.

Parkes Weber, in 1926, had described a similar syndrome under the heading "cutaneous striæ, purpura, high blood-pressure, amenorrhœa and obesity," and he says (1932) that he should have added, to complete the clinical title, "with severe trophic changes



FIG. 7. Upper front of body to show cutaneous hæmorrhages and striæ. (F. P. Weber, *Brit. Journ. Derm. & Syph.*, 1926, p. 10.)

in the skin of the legs" (see Fig. 7). The *purpura* recurred from time to time in the form of crops of cutaneous petechiæ and ecchymoses, which could be readily produced by constriction of the veins of the arm. The legs and thighs showed transverse *striæ*, petechiæ and a peculiar *brownish discoloration*, especially over the anterior surface, where a good deal of the skin had become shiny or *parchment-like*. A minute basophilic adenoma was found in the anterior lobe by Bock.

The Nervous System

Symmetrical areas of skin are in close nervous relationship. It was previously known that in the frog irritation of a certain area produces constriction or dilatation of the blood-vessels, not only on the stimulated but also on the opposite side, the distribution having a segmental limitation. Recent observations of Bourguignon and of Thomas have shown quite similar phenomena in man, namely, symmetrical changes of motor, sensory and vegetative excitability through unilateral causes.

The Vegetative Nervous System. Foerster, Kroll and Altenburger investigated the relationship of the vegetative nervous system to skin-sensitivity. They found that the excitability of the sensory system is diminished by the sympathetic, as also by calcium chloride, adrenalin, scopolamine, parathyroid and corpus luteum, whilst it is raised by potassium chloride, choline, pilocarpine, physostigmine, thyroid, ovary, posterior pituitary and insulin. These effects are not fully explained by changes in the circulation.

An important indicator of the functional state of the vegetative system is the differential blood-picture, which is influenced by reflexes from the skin through the vegetative nervous system. Müller first demonstrated the regular occurrence of a drop in the leucocyte-count after intracutaneous injection of various substances, *e.g.*, Aolan (lactalbumin). Hoff found that with this diminution of leucocytes the blood-pressure also falls, pointing to a reflex on to the whole vegetative system. It might be argued that the process is humoral; but Emden and Wolf showed that the leucocyte-count does not sink, if one has previously cut the vegetative nerve-fibres around the arteries supplying the area from which the blood is taken. As to whether it is the sympathetic or the parasympathetic tone that is raised by intracutaneous injections, the most recent investigations of Schilling seem to show that they constitute an amphotropic stimulus, rendering both the sympathetic and also the vagus and parasympathetic more responsive. This can be shown experimentally, for, if one injects a specific vegetative stimulant subcutaneously and at the same time

provides an unspecific intracutaneous stimulus, then the latter enhances the former. Similar effects are probably produced by physical therapy.

Trophic Changes in Organic Diseases of the Nervous System. In injuries of peripheral nerves Foerster says that trophic disturbances in the skin are hardly ever absent. In a severe lesion (total division) the skin is inelastic, dry and covered with numerous small scales, or even hyperkeratotic, thickened and fissured. These changes are generally confined to the area supplied by the nerves and are especially marked in paralysis of the median. An opposite condition is represented by "glossy skin," in which it is tender, smooth, shining and pink. Now this state is hardly ever confined to the domain of the damaged nerve. It extends, for instance, in an ulnar lesion, to the whole volar surface of the hand and often even to the other hand. Blisters are common within an analgesic area.

It is still doubtful whether special trophic nerve-fibres exist. For it is possible to account for neurogenic trophic disturbances as due to disorder of the known functions of the autonomic and cerebrospinal nerves: the altered blood-supply, the sensory disturbance and consequent inevitable traumata, and the altered mechanical conditions all contribute. Dumpert has recently stressed the importance of this mechanical factor, pointing out that "vasomotor trophic" disturbances, similar to those seen in limbs inactive through paralysis, can also be observed if their inactivity is due to local injuries or joint-changes. Tissue-cultures entirely separated from the nervous system can maintain a normal state of nutrition. Similarly the skin in an anæsthetic area may preserve its nutrition perfectly under certain circumstances. But this autonomy represents a regulation on a lower level. If greater calls were made on such nerve-isolated tissue, its local trophic regulatory capacity would no longer suffice; for that is just the function of the nervous system, to bind the individual organs into a co-operating union rendering possible their maximum achievement.

Pruritus. Mild degrees of itching are physiological: it becomes pathological if it is brought about by non-physiological stimuli or

when its intensity is so great that it leads to disturbance of conduct or sleep. Török's many experiments led him to the conclusion that itching arises through a special mode of activity of the pain-apparatus. This view has been strengthened by newer experiments of von Frey, Trotter and Pritchard. It is produced by subliminal stimulation of the nerve-endings for pain. If a certain threshold of intensity is exceeded, the specific character of the itching sensation ceases and the specific primitive sensations develop. Moreover, intense stimuli, which in normal skin would produce pain, evoke from skin with reduced pain-sensitiveness only itching. This is not to say that the itching *sensation* is the same as mild pain. One knows that the weakest painful sensation can be distinguished from itching. It has been widely held, therefore, that besides the weak stimulation of the pain-apparatus there must be other factors at work, outside the sensory organ, to bring about the peculiar colour of the itching sensation.

The idea that the *vegetative nervous system* takes part in the origin of itching depends essentially on two phenomena :—(1) that at the site of itching there are often local vegetative reactions, sometimes vasoconstriction and goose-skin and at other times vasodilatation with or without urticaria; (2) that pruritus and itching-dermatoses are often accompanied by general disturbances of the vegetative nervous balance, chiefly vagotonia (urticaria, anaphylactic shock, sensitisation-states). An effect upon itching can indeed be brought about by influencing this disturbed balance by means of adrenalin or atropine. But against the supposition that itching can arise through excitation of vegetative fibres alone, is the fact that afferent vegetative fibres in the skin, which could conduct the peripheral stimulus to consciousness, are not known. Moreover, vegetative nervous disturbances of the skin in themselves never cause itching (*e.g.*, amylnitrite redness, blushing, adrenalin anæmia, goose-skin, etc.). That stimulation of the sympathetic is responsible is really disposed of by the fact that adrenalin does not cause itching either when locally inoculated or when injected into the circulation. Conversely, neither vasoconstriction nor vasodilatation prevent it. Further, Ehrenwald's experiments with itching-powder,

(which is made from the hairs adhering to the pod of mucuna pruriens or cowhage), showed that in all areas of complete anæsthesia no itching can be produced. This excludes the possibility of conduction by perivascular sympathetic fibres. The vasomotor phenomena that may accompany pruritus are an autonomic reflex from the sensory stimulation; they are therefore not a cause but a result of the itching. Consequently vegetative reactions cannot, according to our present knowledge, be made responsible for the peculiar quality of the itching sensation.

Others have thought to explain its peculiar quality by the *character*, not only the intensity, of the *stimulus*. Thus Guttmann states that the stimulus must not only be subliminal but continue to act over a certain period. Pritchard found that to elicit superficial tickle the stimulus must be a moving or intermittent one. Increase of the tickle-response is, according to him, always associated with intensification of the response to painful stimuli. Loss of the response to tickling he found to be associated, in the case of damage to peripheral nerves, with loss of sensitivity to pressure: but in the case of damage to the spinal cord with diminished sensitivity to painful stimuli. So he argues that when a light hair is drawn across the skin so as to produce the sensation of tickling, it is the superficial pressure-receptors that are stimulated; afferent impulses from these pass along the peripheral neurons that convey those of a single touch; but entering the spinal cord they cross to the other side in the posterior commissure, pass up the cord and through the medulla near to the spino-thalamic tract, and are finally registered in the optic thalamus and not in the cerebral cortex. Except in the peripheral nerves this *pathway* is identical with the accepted course of all painful impulses.

Ehrenwald points out that whilst the sensations of sight, touch, temperature, taste and smell, that is to say, all specific senses, are related each to a well-defined physical, mechanical or chemical form of stimulus, itching or tickling can be evoked by various forms, which implies that various receptors are responsible. It therefore seemed to Ehrenwald and Königstein that the special

character of the sensation was conditioned by a particular course of the stimulatory process as regards space and time, and secondly by a characteristic *central* mode of reaction. This is opposed to the idea of von Frey that itching is a specific function of the pain-nerves, while tickling is a specific function of the tactile nerves.

Ehrenwald and Königstein made experiments (1) in pathological cases with dissociated sensory disturbances, and (2) by physiological investigation.

(1) In syringomyelia, in the absence of perception of pain and temperature, the itching evoked by itch-powder was somewhat weakened and qualitatively altered, but nevertheless in 2 out of 4 cases still preserved. In these instances, therefore, it seems to have been a function of the still intact touch-apparatus. Moreover, in a third case, where pain was preserved and touch was lost, it was absent. In a fourth, in spite of preserved touch, it could not be evoked. It was absent in all cases where pain, temperature and touch were all lost. As a result of these and many other investigations they concluded that for the development of the complete itching sensation it is necessary for the mechanisms of both pain and touch to be intact. It is not an additive sum, but a kind of amalgam of these components.

(2) The cornea and visceral organs are well known to register pain, but not touch. They are also unable to feel itching.

The receptive centres. They found that in pronounced thalamic disease, with severe central pains but diminution or complete loss of objective perception of pain, touch and temperature, that of itching was preserved. The pains disappeared a few seconds after the beginning of the itching and surged up again after its subsidence (pain-suppressing phenomenon). Cases of capsular hemiplegia behaved like peripheral paralyses, the itching failing or being diminished in the area of sensory disturbance. In cortical sensory disturbances itching was not at all or only slightly affected, even when pain, touch and temperature were markedly impaired. Central itching in the sense of itch-paræsthesia was observed in a case of spinal and of mid-brain damage. The pain-suppressing phenomenon is a direct reversal of the ordinary experience that itching can be suppressed by provoca-

tion of pain by scratching. The fact that this alternative relationship is only found in the case of central pain seems to point to the close connection of the thalamus in the origin of the itching sensation. This is to some extent further supported by the fact that cortical sensory disturbances hardly influence it at all. Scratching as the result of an itch-stimulus can be observed in sleep; so could it, too, in a case of mid-brain tumour during the stage of stupor.

Pharmacodynamic Effects. According to them, experimentally produced itching was not diminished by substances which act on the cortex, such as paraldehyde and bromide. Bromide only lengthened the latent period. Strychnine produced shortening of latent period, strengthening of intensity and sometimes lengthening of duration. Luminal lengthened the latent period, shortened duration, and perhaps lowered intensity. Clinical experience similarly showed that a therapeutic decrease was not achieved by the usual cortical sedatives nor by moderate doses of morphine. It was, however, attained by small doses of Luminal and by "Nautisan," a remedy whose point of attack has been shown by Pick's school to be the brain-stem and mid-brain.

Conjugated or Secondary Sensations. These may occur in addition to the itching set up at the site of the stimulus, and at a considerable distance from it. The phenomenon is observed both in the domain of itching and also of pain. The secondary sensation is lightning-like and occurs mostly at the same time as the primary, but is sometimes delayed. It is nearly always on the same side of the body and generally higher up. Sometimes there seem to be constant relationships between secondary and primary points. The study of this phenomenon is important for the elucidation of the pathology of itching and the question of reflex itching and reflex eczema. According to Goldscheider the sensory cells in the spinal cord can transfer their impulses not only to the motor cells but also further centripetally to other sensory cells. Without doubt these secondary sensations can give rise to scratch-effects far away from the primary lesion. Whether, in addition to these sensations which are transferred from skin to skin by way of the central nervous system, there also

exists a reflex itching projected from within, is not known for certain. Segmentary itching occurs in tabes. In a small proportion of asthmatics Balyeat found a segmentary itching zone corresponding to C.3 to C.5; this is supposed to represent a reflex zone of the bronchial mucous membrane. Müller (1927) noted disappearance of perception of tickling in segments showing reflex hyperalgesia in acute diseases of internal organs.

General Ætiology and Pathology. *Pathological Increase of Itch-Sensitiveness.* One commonly talks about itching eruptions with the idea that certain visible cutaneous changes (*e.g.*, urticaria, prurigo nodules, eczema blisters, lichen papules, etc.) cause itching. That this is not the case can be easily shown, at least as regards wheals. If these are produced by some external irritant (insect-bite, nettle, morphia, mechanical stimulus in urticaria factitia, etc.) itching nearly always starts earlier than the visible changes (Kreibich). By the time the wheal has reached its maximum the itching has long passed its own or even disappeared. Wheals caused endogenously by chemicals behave similarly (A. Walzer and M. Walzer, 1928). Factitious urticaria is often hardly pruritic at all. That the mere pressure of the exudate of a wheal or other lesion is not responsible follows from the fact that the injection of large quantities of indifferent fluid into the cutis produces no itching. Prurigo nodules are also frequently, if not always, preceded by itching. In acute eczema, too, the itching is most intense during the development of the blisters and abates while the œdema of the epidermis is at its height. Lichen planus may be accompanied by or free from itching, which sometimes precedes the eruption.

It is true that clinically demonstrable changes can considerably raise the itch-excitability of the affected areas, which is of great importance. It can be proved that on eczematous skin an itch-stimulus produces a much more intense, longer and more widespread itching than on normal skin; and, further, that inadequate stimuli, such as the weakest needle-prick, subliminal touch-stimuli (alteration of pressure, light rubbing) or change of temperature, produce itching. Moreover, the non-itchy sensations assume on eczematous skin an itchy character, in consequence of

their radiation and continuance after the stimulus has ceased. In other words, ordinary stimuli, which are almost constantly working on the skin and which normally are unnoticed or hardly analysed, can cause itching on eczematous skin. The same is true of a portion of skin affected by urticaria, but in this case it is quite independent of the wheal-formation. Though a wheal may have disappeared within a few hours, the itch-excitability is often raised for many days: the consequent scratching may or may not produce a new wheal. There is no itching dermatosis and no form of pathological itching, in which this phenomenon, called "mnémodermie" by Jacquet, cannot be demonstrated. Often the mnémodermie may be intensified by psychical influence; but the strictly fixed localisation of the raised excitability makes it probable that it has a somatic peripheral basis. In my own forearm the site of an experimental intracutaneous injection has sometimes come up in a pruritic wheal about 1 cm. across at intervals of many months or even years. (In some cases such mnémodermie is an example of allergic flare-up, see p. 260.) So, according to Rothman, spontaneous itching in eczema, prurigo and urticaria, occurs only before and during the early development of fresh lesions, when substances are formed which irritate the nerve-endings. In fully developed lesions these substances are probably diluted by the œdema, and itching is now only induced by external stimuli because of the raised itch-excitability. In general, hyperæmia raises excitability and anæmia diminishes it. In the infective exanthemata itching varies and is not proportional to the visible inflammation. Lortat-Jacob (1929) described an epidemic of scarlet fever in which itching was unusually intense. That it is the noxa, and not the resulting skin-lesions, that produces the itching was also suggested by Török, who pointed out that many foods and drugs and intermediate metabolic products cause in some persons itching and inflammation, and in others itching alone.

Pathological Itch-stimuli. As regards mechanical and thermal stimuli, the essential factor is not the absolute intensity but its alteration, for example, change of pressure or change of temperature. Chemical pruritus, exogenous or endogenous, sometimes

depends on a sensitisation from repeated or prolonged exposure and is probably produced by the same mechanism as "allergic" erythemato-urticarial or eczematous eruptions. In fact, itching and raised itch-excitability are characteristic of allergic states. It would be conceivable that the change in the nerve-endings, which has been described as raised itch-excitability, is caused by locally formed products of sensitisation-reactions. But we can hardly ascribe pruritus to the setting-free of histamine, since a wheal caused by pricking-in histamine does not itch. Why should a flea-bite wheal itch if it is nothing more than an endogenous histamine urticaria?

Special Pathology and Ætiology of Itching. *Endogenous Noxæ.* Recently there has been some accumulation of evidence associating itching with *malignant disease* of internal organs. It is characteristically accompanied by pronounced flecked or diffuse pigmentation. Perhaps it is caused by the same agencies as acanthosis nigricans. But it is an interesting fact that in some cases the itching is localised and precedes the appearance at the same spot of non-itchy metastases; the itching and accompanying inflammation seem to be the expression of an early reaction between skin-tissue and tumour-cells. Perhaps a similar process accounts for the early itching in *mycosis fungoides* and *leucæmia.*

It is important to remember that local pruritus very often has a general cause. Fenwick (1925) described pruritus in chronic *appendicitis*, especially in women. It involves the lower part of the abdomen, is most intense about an hour after going to bed, and is often associated with glycosuria. Appendicectomy frequently brings to an end the pruritus and the glycosuria. I have observed very severe and persistent pruritus vulvæ with local œdema, uninfluenced by treatment, which disappeared completely after removal of an infected *gall-bladder.* Horder considers this the commonest infective focus responsible for pruritus, of which, however, he thinks the most frequent general cause is *gout.* "Senile" pruritus in the great majority of cases is apparently *not* due to renal insufficiency, for taking together the figures of Touraine and those of Sézary-Lefèvre and Paraf it emerges

that of 60 cases it was only in 10 that the blood-urea was higher than 50 mgms. per cent., the highest figure being only 77 mgms. per cent. There may, however, be increased non-protein nitrogen in the skin (see p. 175).

SCRATCHING AND SCRATCH-EFFECTS. Hartmann-Karplus has shown that the new-born manifest as early as the 6th hour of life distinct *general* reactions to itching. These increase up to the 6th month and then gradually diminish. On the other hand, the *specific* reaction of *scratching* is only slowly learnt. The eyelids are the first to be specifically excitable (2½ months), then follow the ears and nostrils, and finally the rest of the body (12–18 months). The motor reflex is independent of the higher centres. Scratching by no means runs parallel with the intensity of itching. But the degree is to some extent characteristic of the disease, *e.g.*, pediculosis vestimentorum always shows numerous scratch-effects, whilst in urticaria and lichen planus there are very few, though their subjective itching may be much worse. Perhaps the sensation in pediculosis is more specifically that of a foreign body. Where, in spite of itching, no excoriations are seen there has, however, probably been rubbing.

Mental Influences

The great difficulty experienced by dermatologists in keeping abreast of and understanding modern developments in psychology has led some of them, according to their personal proclivity, to attribute all kinds of disorders of the skin to psychological causes on the flimsiest evidence and others seriously to underestimate the influence of the mind on the skin. There has been in recent years such a substantial development in the knowledge of psychology, that it is our duty to face its bearing on our problems. The following section is largely based on the admirable study of the subject by Sack.

Normally the vegetative processes are not deliberately influenced by the conscious mind; but *conflicts*, if they are not made conscious and thus rationally disposed of, are repressed into the unconscious, and the energy there " bottled-up " may lead either

to abnormal manifestations in the mind (psychoneuroses) or affective disturbances in the body (Freud's "conversion"). A particular organ may be chosen for the affection, either because it is constitutionally inferior or because it has some association of idea with the original conflict, providing a symbolic equivalent. It is for such disturbances of bodily processes caused through conflict that the term "psychogenic" should be used.

Kraus and Zondek group together the vegetative nervous system, the hormonal apparatus and the shifting of electrolytes in the cells under the term "the vegetative system." Between these groups of functions there is such close reciprocity and mutual dependence that there is probably also a special case of transformation of one type of energy into another enabling them to act as substitutes for each other vicariously. It is further obvious that the affective (psychical) energies have the closest reciprocal connection both with the autonomic nervous system and with hormonal circulation. The affective sphere can therefore be included as a further partner in the vegetative system.

There are no psychogenic skin-diseases, *sui generis*, recognisable as such at sight. But that pathological cutaneous phenomena are conditioned by the psychical state, in their development, course and curability, is undeniable. One would expect this psychical influence on the skin to be at least as great as, if not greater than, upon any other organ of the body, since it is the one of which the mind is most conscious.

Even when skin-stimuli are subliminal they work on the autonomic synergism. The autonomic reactions and their functional consequences can secondarily become supraliminal and therefore perceived. But the mind may remain ignorant of the original point of entry (the skin).

Skin-sensations of the most varied kind have the property of acting as sexual stimulants. We therefore frequently find sensory neuroses in general sexual neuroses.

Cerebral Formication. It is difficult to find a sharp dividing line between paræsthesiæ caused by lesions of the peripheral or central sensory system and hallucinations of cutaneous sensibility. For instance, there are the "iterations"

described by Tschlenoff, perceptions after repeated stimulation, which are independent of any new stimulation. This phenomenon is observed in some nervous diseases but also in healthy persons. Such illusions support the view that even hallucinations always originate from irritation of the corresponding sensory centres or the paths of conduction from the sense-organ. Especially interesting are the sensory hallucinations so characteristic of addiction to cocaine, namely the presence in or under the skin and under the finger-nails of tiny living things, which are described as mites, worms or bacteria. Since cocaine has a peculiar affinity for sensory nerves, it is natural to look there for the cause of the sensory hallucinations of its addicts.

But though cerebral formication is characteristic of cocaine-poisoning it can also occur without it. It is difficult to decide whether the sensations are the result of toxic irritation and the optical perceptions only illusory mistakes in interpretation, or whether it is a question of combined genuine hallucination. In those cases where the patients do not present " tangible evidence " (in the form of dirt, threads, etc.), one may assume the latter. They are absolutely convinced of the presence of parasites and cannot be persuaded to consult a psychiatrist.

Relationship to Environment. We can gain no objective experiences of our bodies without coming up against the skin. Very small cosmetic defects may so distress the owners as to make them unable to face society. *Hirsuties* is especially liable to be associated in this way with mental disturbance. O'Donovan points out that the fact that the hair can be shaved and the skin powdered, so as to remove all obvious signs, is no consolation whatever to the sufferers. The mental derangement is in striking contrast to the lack of concern shown by patients with appalling deformities due to such diseases as lupus vulgaris. The former are neurotic, that is to say, persons who, on a basis of some special disposition (schizoid, cyclothymic, degenerative-psychopathic, hysteroid, etc.), have come in conflict with their surroundings and now attempt, by means of the mechanism of a neurosis, to end the conflict. Now, just as neurotic settlement of a conflict can take place within the mind or work itself out in a functional

effect on some specially appropriate organ, so, on the other hand, in chronic dermatoses the victim will often try to turn them to his advantage. Skin-lesions are especially amenable in that they can always be demonstrated and easily aggravated. O'Donovan gives some good examples of this mechanism in patients receiving or claiming compensation.

ARTEFACTS. Artefacts are actions of the will directed towards the environment. Disturbances of the will are the least understood parts of psychopathology; of these there are two main groups, hysteria and compulsion-neurosis. According to Kretschmer the modern tendency is to call only those symptoms *hysterical* in which tendentious or purposive components are apparent, either in an active craving or a passive attempt to save oneself by flight—by taking refuge in disease. Hysterical self-mutilation (mythomanie—Dupré) is sometimes misleadingly described under the title "multiple neurotic gangrene of the skin." But milder degrees also occur, down to a mere erythema. In eczematous patients with hysterical mentality relapses can occur from the same mechanism. The purpose may be the winning of interest, sympathy or compensation. That the chosen method of achieving this purpose is often a false one, that the self-produced illness is mostly quite out of proportion to the trifling advantage thereby gained, makes manifest the specific pathological nature of the hysterical reaction. In my experience men afflicted with industrial dermatitis only very rarely suffer from this mental disorder. Artefacts are most often met with in young females. According to O'Donovan there is generally no monetary inducement. Sometimes they are used by employees to enable them to change their situations or type of work without appearing to have thrown up their jobs.

It is generally useless to confront them with their misbehaviour. Many seem to have a dual personality and to be unaware of their abnormal actions. Even those who admit their guilt may return to the same physician with a fresh attack. It is therefore not surprising that MacCormac (1926), who investigated their after-histories, found that they often strenuously denied their previous skin-troubles. Rank, education, intelligence, devotion

to duty and in other respects the most exemplary character, none of them exclude the possibility of self-injury.

Compulsion-neuroses are less well understood and seem to have less relationship to the environment. They are referred to as "pathomimie" by Dieulafoy and are probably due to a much more primitive disorder of the will, perhaps associated with very early habits of playing with the body. Brocq's "acné excoriée des jeunes filles" should probably be included here (Eller and Claude). Janet describes an obsession of bodily shame. Bettmann refers to a similar idea as "skin unrest," in contradistinction to the feeling of well-being or "eudermia," and speaks of a compelling desire to make certain of the presence of feelable disturbing peculiarities of the skin and of a need for active response to a burdensome stimulus. The efforts to suppress such behaviour and the consciousness of failure only increase the original embarrassment. Certainly among these patients, mostly young girls, many are of the type called by Kretschmer "sensitive," which connotes the feeling of shame-producing insufficiency.

PHOBIAS. These are usually single symptoms of a general disturbance of behaviour towards the environment. The motive is, as a rule, relatively easy to make manifest by analysis. Eller divides them into the following eight groups:—(1) acarophobia; (2) syphilophobia; (3) bromidrosiphobia (the fear of giving off bad odour); (4) rhypophobia (the fear of dirt); (5) parasitophobia; (6) cancerophobia; (7) peladophobia (fear of baldness); (8) erythrophobia. The only common factor is a depressive anxiety-affect, which in some form or other is connected with the patient's body. Rhypophobia is closely related to the compulsion to wash, a very common symptom of systematised compulsion-neuroses. Erythrophobia is called "reddening psychosis" by Türck. It is the most striking example of a psychically caused skin-reaction and belongs to the typical expectation-neuroses. The monosymptomatic manias and phobias no longer hold in the modern system of psychiatry an independent position, and should therefore also disappear as disease-entities from dermatology.

Pruritus as a Sensory Neurosis. Reactive scratching may

represent either the purpose of a hysteric or a true compulsion.

That pruritus itself can be purely psychogenic and independent of the specific excitement of peripheral end-organs is shown by an experiment of Sack's. He made the right forefinger anæsthetic by local infiltration, and in hypnosis suggested intense itching. This suggestion was realised just as vividly in the anæsthetic part as in the opposite untreated forefinger.

If one lies with eyes shut in a state of maximum physical relaxation and directs attention to one's own normal skin, Sack describes how at first certain localised sensations of tension are noticed, which he interprets as a projection of the tension of concentration. Then there develop quite fine isolated punctiform sensations like very weak electric stimuli. These are clearly signs from the receptors which have been stimulated by some internal or external cause. These infinitesimal sensations can, with corresponding increase of attention, be retained. They then rapidly increase in intensity, change their quality, spread and become pruriginous. If that does not happen spontaneously, the slightest extraneous disturbances, such as change of temperature, movements of the air, pressure of clothes, or emotional waves, may be enough to intensify them. We see, therefore, that the stage is already prepared for pruriginous stimuli. On the other hand, the degree of attention available for them is generally so slight that they pass unnoticed and they need to be greatly intensified in order to enter consciousness. This relationship is under certain circumstances reversed; that is to say, it is not the sensations that are intensified but the attention. Often it is a kind of contrarious reaction; for instance, when one has to stand still on parade or in a photographic studio, one begins to be conscious of itching places, such as, owing to their unimportance under ordinary circumstances, had hitherto passed unnoticed. A rather similar state of affairs is brought about by boredom and fatigue. As soon as the skin is pathologically altered (erythematous, eczematous, lichenoid or urticarial), or if the pruriginous mechanism has by repetition become ingrained, then these slight pruritic states, which normally could be abolished by conscious opposing impulses without scratching, grow into genuine radiating

itching-attacks. Such an attack so easily evoked is sometimes used to dull the emotion produced by a conflict—an example of the hysterical mechanism.

Pruritus is a very common symptom in the endogenous and reactive *depressions*, especially those of senescence ; these may be fatigue-states. Psychogenic pruritus vulvæ sometimes follows actual irritation. Such paræsthesiæ as itching and burning often start from a fear of disease or infection, or anxiety about some dangerous situation such as childbirth.

Sexual Neuroses with Pruriginous Mechanism. There is hardly any sensation of the skin that cannot under certain circumstances be erogenous. An acute itching-attack has great resemblance to the sexual orgasm. Modern studies of the neuroses have shown what farfetched and apparently quite irrelevant equivalents neurotics choose for their repressed desires. It is therefore natural that itching, which is so closely related to the sexual voluptuous sensation, should especially readily be drawn upon for this purpose. In the case of pruritus vulvæ et ani, these two excitations may be inseparably intermingled. Sometimes, it serves as substitute for unsatisfying or absent coitus.

Stokes describes 3 cases in which masochism or other sexual complexes seem clearly to be the basis respectively of pruritus and secondary eczematisation, relapsing generalised dermatitis on an allergic basis and an extremely exaggerated lichen Vidal.

Vegetative Correlations and Psycho-physical Mechanisms of the Skin. Up till now we have not been considering cutaneous symptoms directly produced by psychical disturbance, but only those of a purposive character brought about by cerebrospinal mechanism in psychopathic individuals.

The first extensive investigation of the vegetative behaviour of the skin in certain dermatoses was that of Brill (1926). In eczema and neurodermatitis he noted a marked predominance of vagotonia, which may account for the frequent effectiveness of ephedrine and adrenalin. He found that, especially in eczematics, the mind was a leading factor of great lability within the vegetative nervous system and recognised the frequent

dependence of fluctuations in blood-distribution on psychical conditions. Brack records the case of a woman who had pruritus vulvæ and then an eruption of firm, itching nodules on the limbs, face and neck, and widespread lichenified patches; aggravation of her cutaneous symptoms together with hæmoclasic crises followed psychical alterations, such as fright, anger and anxiety. He says psychical stimuli have a double significance. First, in the presence of an abnormal functional state of the autonomic system they can determine a reaction just as can the drinking of milk, coffee or wine. Secondly, if persistent or continually repeated they can, just as continuous intoxication with alcohol or coffee, directly bring about an abnormal functional state.

Lewis and Török have shown that inflammation *can* occur without a direct connection with the central nervous system, and Török proceeds to deny that urticaria, for instance, can ever have a direct neurogenic or psychogenic origin. But it may nevertheless be possible on the basis of the vasodilating action of sensory nerves (see pp. 13, 15). Kuré has brought forward evidence that these "antidromic" impulses are really conducted by efferent parasympathetic fibres. The actual vasodilatation is, according to Lewis, produced probably by histamine; Dale suspects acetylcholine. The latter idea would support Kuré's observation, since the parasympathetic is known to set free acetylcholine at the periphery. (I find it difficult to accept the acetylcholine theory, as it is given therapeutically by the subcutaneous method without producing any local physical signs or discomfort.)

Hæmorrhages. Schindler calls spontaneous ecchymosis one of the commonest vasomotor symptoms of the hysterical psychopathic constitution. They occur in the cutis or less often in the subcutis. Their size is generally about 1½ cm. in diameter, but it may reach about 5 cm. Pressure or other trauma in the immediate neighbourhood of the ecchymoses does not produce further hæmorrhage. E. Jacobi (1929) also reports cases of psychopathic individuals with spontaneous hæmorrhages.

Diehl and Heinichen (1931) were able, in hypnosis, to increase or diminish by appropriate suggestion allergic urticarial *wheals*

produced experimentally. Sack thinks that the "antidromic" impulse provides the mechanism which, by a co-ordination of the various systems, allows emotional impulses to be conducted directly to the skin and there set up redness, wheals, blisters or necroses.

ALLERGIC REACTIONS. The following explanation is given of their psychogenic causation. In an anaphylactic or allergic reaction the antigen-antibody interaction sets free histamine. This local reaction is, through its own effect or by chance, associated with a certain emotional general reaction. Through a single or repeated coincidence of the local allergic and the emotional general reaction, there develops a *conditioned reflex*. As a result of this, the specific physiological event, in this case the setting-free of histamine, still occurs even if the specific stimulus, the allergen, is replaced by the conditioned "signal" symptom (subordinate emotion). After a time even these emotional stimuli may lose their specific character, so that any strong impression can evoke the allergic mechanism. Hansen has shown that, in certain cases of asthma, allergen only produces the typical response when the individual is in certain psychical states. There are two conceivable explanations:—(*a*) the psychical influence leads to a change in excitability of the autonomic nervous system, so that subliminal organic stimuli acquire excitation-value; or (*b*) it acts through the blood-vessel innervation, changing the blood-supply of the peripheral tissues, so that pathogenic substances that normally do not penetrate to the cells are now absorbed and lead to antigen-antibody interaction.

Stokes has also been working on the connection between psychogenic and allergic factors. He thinks that the allergic reaction is in most cases due to the actual presence of allergen, but that the allergen itself only acts in certain emotional states. This corresponds with Hansen's observations in asthma, and Török and Jadassohn hold similar views. Stokes thinks that psychical influences also act very frequently through the gastro-intestinal mechanism. As the result of emotional or nervous stress, depression or fatigue there follows a diminution of secretion of hydrochloric acid in the stomach, resulting in a rise in *p*H in the

gastro-intestinal tract. This leads to an increase of Welch bacilli in the intestine, the activity of which produces a histamine-like substance. This, if absorbed in adequate quantity, can bring about the triple response. At the same time the hypochlorhydria impairs the local cutaneous defence-mechanism by diminishing calcium-absorption from the food. Further, the reduction of proteolysing power by emotionally induced insufficiency of pancreatic and intestinal secretion predisposes to the absorption of abnormal protein split-products. The subject may thus become sensitised to food and perhaps bacterial proteins. This would be further favoured by reduced motility, a common result of the same emotions. Thus an eruption which originates from a train of emotional influences may assume the semblance of a purely allergic phenomenon.

Relationships of the Skin to the Total Personality. PHENOMENA PRODUCED BY SUGGESTION. It is believed that it is possible by hypnotic suggestion to produce a blister on an apparently healthy skin at a particular spot. While under hypnosis the patient is given the idea of a definite circumscribed shape. This is traced by a pointed object at the desired spot, so lightly that it cannot be considered a mechanical or chemical stimulus. In fact, the experiment can succeed without actually touching the skin. It seems, then, that the presentation to consciousness of an idea brought from outside acts as a stimulus, to which the organism responds with the biological mechanism at its disposal. It is able to achieve a functional realisation at the part of the skin suggested. This is a model of the ideoplastic capacity of the organism.

We have to estimate the psychophysical personality as a self-contained unit, in which every process, quite apart from its physiological significance, has a meaning in connection with the total inner and outer personality. This meaning is either a purposive or an expressive activity. The purposive activity of the skin and its psychological conditions have been dealt with; now we consider the skin as an organ of expression. "Organs" are present in the individual's mind as functional, not as anatomical, units. Several observers have

claimed to have produced hyperæmia and wheals and even necroses under hypnosis. But Schindler has carried out such experiments with all possible controls. In women with severe hysteria it was possible to bring about by hypnotic suggestion spontaneous ecchymoses in the shape and size desired. *Case I.* In deep hypnosis a spot was marked on the inner side of the right lower leg: at the same time the suggestion was given that at that spot an ecchymosis would occur. Both legs were now encased in firm plaster of Paris bandages in the presence of Neubauer and Adler. After 2 days the bandages were removed in the presence of Neubauer. At the prescribed spot and in the prescribed shape an ecchymosis had occurred. A new ecchymosis then continued to appear every day for months; but a single hypnosis was enough to bring this to an end. *Case II.* The patient had suffered for many years from bleeding in the cutis and subcutis and swelling of the joints, that is to say, "purpura rheumatica." In hypnosis ecchymoses were produced by suggestion at prescribed spots. The same controls were used as in Case I. On one occasion, as the result of a suggestion that it would burn severely, there ensued, without the intention of the hypnotiser, a flat blister. Every day after this, without suggestion, spontaneous blisters appeared at various spots on the body. It was soon possible to evoke a blister exactly at a prescribed time under the eyes of the doctor. It took 5 minutes to develop fully. As the result of prolonged hypnosis and alteration of her domestic milieu the patient was cured and 6 years later was still well.

Skin-Diseases with Symbolic Character. We have seen that the mind can realise plastically on the skin conceptions suggested to it from outside. But it can also similarly realise its own ideas, arising more or less consciously in the personality itself. These realisations have symbolic character. The representation is, of course, imperfect, being limited by the physiological mechanism: it will require interpretation. This interpretation can naturally never satisfy a demand for exactitude or universal applicability; it will always be relative, conditioned by the personality and disputable. One has to try and trace some

significant connection between the appearance and its site, because the personality projects its symbol where it will show its meaning most impressively. The mind only causes the body to produce such manifestations as it already knows.

Bunnemann describes a number of instances. One was a man who, after a prolonged period in the trenches in which he was appalled by the appearance of dead bodies and their decomposing skin, had suffered from psoriasis. This disappeared when, in hypnosis, the picture of the dead bodies was brought back to his memory and he was told that his disgust no longer had any basis and the skin-trouble would disappear. The psoriasis returned when, again in hypnosis, the picture was brought back before him and he was told that the eruption would recur.

Kronfeld (1925) describes a case in a girl of 21, who periodically developed blisters on the back of the hands and between the fingers, resembling scabies, treatment for which had several times been unsuccessful. The eruption was accompanied by a strong pleasurable sensation. From time to time she entered a state of raised expectation that such blisters would appear. She chose beforehand places on the hands where she felt she could most easily produce them. If she now concentrated her mind on these spots, blisters appeared. After their eruption she experienced intense itching, which gave her sensual pleasure, and she scratched till she bled. She was therefore herself fully aware of the psychical character of the production of these blisters. This process was observed by her doctors in an area of skin chosen by them ; it required only 3 minutes. Blisters were also produced by hypnotic suggestion. Psycho-analysis of this case revealed a complicated neurosis with sexual repressions.

The term " psychical infection " is given to cases where manifestations seem to arise by psychical induction from one individual to another. Thus Wohlstein (1930) reported a whole series of such cases, partly in married couples, partly in patients in hospital. The lesions were mainly urticarial or herpetic.

Stigmatisation means the spontaneous formation of wound-marks on the hands, feet, chest and forehead of religious ecstatics, corresponding to the wounds of the Crucifixion. These pheno-

mena are explainable by the same mechanism as Schindler's spontaneous hæmorrhages. Such a case has been closely observed and reported by Ewald (1927).

We now have to consider a few typical clinical dermatoses suspected of being closely related to the subjects of this chapter.

Urticaria. We have seen that in the triple response only the surrounding flare is dependent on nervous action. The way in which the mind can influence allergic reactions has been explained on p. 105. That urticaria may also have a more direct psychogenic origin is suggested by the following cases. Sack describes a case of severe urticaria in a young married woman. Analysis revealed an experience in childhood which led to an intense aversion to small children. This became identified with a fear of pregnancy. Her married life was therefore a cause of almost incessant anxiety and excitement. Soon after marriage urticaria broke out. After the appearance of each eagerly awaited menstruation the urticaria disappeared. She was instructed, without being given the reason, to refuse coitus till after the next two menstruations. During the whole of that period she remained free from the eruption. Psychotherapeutic efforts succeeded in resolving the complex and the urticaria disappeared. She became pregnant and regarded it in a perfectly normal manner. Drake tells of a woman who had suffered from recurring urticaria for many years. After resting for some days quietly in hospital, remaining free from her urticaria, she developed an attack under his eyes when he surprised her by coming suddenly from behind a screen. The attack was accompanied by flushing and sweating. Dufke reported attacks of urticaria in a woman whenever her skin came in contact with, or whenever she believed it was in contact with, silk.

Eczema. (See also p. 222.) If Kreibich's view of its mechanism is right, namely, that the primary change is irritation of the sensory nerve-endings, its potential dependence on psychogenic causes is apparent. Darier says the influence of the sympathetic nervous system is indisputable, and Milian holds the same view.

Kronfeld reported the case of a young girl who was kicked by a

horse on her forehead when a child. Since then every year at the time of the accident an eczematous eruption appeared at the same spot. At puberty it spread over a larger area of the skin, accompanied by severe reactive depression and sense of inferiority. Psychotherapy led to complete cure.

Whitfield tells of a woman in poor financial circumstances who developed weeping eczema on her fingers every time one of her sons was about to compete for a scholarship; it subsided after the result was known. This happened on three occasions. In the intervals her skin was perfectly normal.

Eczemas depending on disturbed sweat-secretion and pompholyx are often the expression of affective states of excitement (Sack). Goeckermann describes a typical "dyshidrotic" eczema (pompholyx), which had resisted every treatment, in a woman who was constantly worried by an obscure illness of her husband. She was told that her husband might be cured by an operation and that then her eczema would disappear. The operation was successful and she lost her eczema.

Pruritus vulvæ et ani. Gabriel groups his cases of pruritus ani according to the following causes:—(1) lack of cleanliness; (2) excessive sweating; (3) leakage of mucus or liquid paraffin; (4) abnormal anal moisture from local causes, such as fistulæ, ulcers, warts, vaginal discharge; (5) thread-worms. These may be diagnosed (*a*) by observing them at the anus by separating the anal margins; (*b*) by proctoscopy; (*c*) by giving an enema of 4 oz. of normal saline when the pruritus is active; after being retained for a few minutes this is returned into a clean, preferably black, receptacle.

Castellani (1925) thinks genital pruritus is often primarily *mycotic*, the commonest causal fungus being epidermophyton; monilia is also often responsible. Clinically there may be hardly anything to see except small, red, slightly raised spots. If there is severe eczematisation there is usually secondary infection with streptococci, B. proteus, B. coli, etc., which overrun the fungi and render them difficult to find. As regards local infections in pruritus ani Montague attaches some importance to B. coli and staphylococci but not to streptococcus fæcalis; but the

bacteriology of this area in normal persons has not been adequately studied.

Pruritus vulvæ can be produced exogenously not only by diabetic *urine* but also by urine altered by cystitis, pyelitis, abnormal quantities of uric acid salts or calcium oxalate, and by intestinal *worms*. It has also been attributed to *trichomonas* in the vagina and bladder.

Though Gabriel finds that 90% of his cases are due to one or other of the definite causes mentioned above, Rothman's experience is that "essential" or unexplained cases are in the majority. O'Donovan and probably most dermatologists hold the same view. Montague thinks pruritus ani without obvious local cause is sometimes a reflex from various diseases of the abdominal organs. (The relationship of pruritus vulvæ and *cholecystitis* is referred to on p. 96.) But in his explanation he wrongly assumes the existence of afferent sympathetic fibres. The general relationship of the *mind* and pruritus has been dealt with. Where a neurosis is of a sexual character the localisation is likely to be in these erogenous zones.

Neurodermatitis. Brocq first gave this name to Vidal's lichen simplex chronicus, because he thought that itching, that is to say a nervous disorder, was the primary change. The actual visible alterations, called by him and Jacquet "névrodermite chronique circonscrite" or "névrodermite diffuse à forme objective de lichénification pure," he ascribed to a special predisposition of the terrain of certain individuals to react in this way to the inevitable scratching. He also included under neurodermatitis Hebra's prurigo and the multiform eczemato-lichenoid eruption called by Besnier "prurigo diathésique."

Herxheimer has recently described, in addition to the chronic forms, an acute form. Little groups of the typical papules appear suddenly and disappear again rapidly under suitable treatment or even spontaneously.

Alexander has made a careful study of the *histology* of these reactions. Though he considers neurodermatitis clinically a disorder quite distinct from eczema, he has to admit that the histology reveals a very close resemblance. The only differences

are as follows. In neurodermatitis there is less interstitial œdema (spongeosis). The basal cells are deprived of pigment; this has not yet been described in eczema. In neurodermatitis Alexander found with some constancy a leucocytic invasion of the epidermis, but Leloir and Pautrier have described this in eczema too. All the changes found in neurodermatitis that are also characteristic of eczema reach in the former only a certain degree. Thus, whilst there is a rich supply of lymph leading to intracellular œdema, there is, on the other hand, such a strong coherence of the rete-cells and the horny layers that blisters and weeping do not occur. On the other hand, the histology serves to distinguish neuro-dermatitis with ease from lichen planus, which clinically it may resemble.

As to its "nervous" origin, Jadassohn pointed out that, although the eruption is generally preceded by itching, the latter may itself be the result of microscopical alterations taking place in the skin before clinical changes become evident. Moreover, there are rare instances of circumscribed neurodermatitis in which itching is absent. Sack thinks that nervous stigmata are the rule; by this he means acute or chronic conflicts in labile individuals, which are resolved by scratching. He instances a young girl with beginning neurodermatitis of the flexures. She had an anxiety depression-state with consequent building up of a compulsion-ritual before going to sleep. She declared spontaneously that when she scratched herself her anxiety abated. Cure was achieved only by psychotherapy. But Jadassohn has noticed it not only in "neurasthenics" but also in thoroughly strong peasants and their children. He, as well as Alexander and Dind, have carefully observed their patients for nervous stigmata, but could never find anything definite either in the history or present state.

Schneider tells of a woman who developed neurodermatitis with each of her four pregnancies. She was completely free in the intervals. I have noticed a rather large proportion in association with the menopause.

Brill's finding of the prevalent vagotonia in eczema and neurodermatitis has been referred to on p. 103.

Alexander concludes that the purely nervous theory does not

stand, though in certain cases it has to be admitted that it seems to play a strikingly important *rôle*. The *allergic* ætiology of neurodermatitis is considered on p. 235.

NEURODERMATITIS NODULARIS. This is a better term for what Lailler and Brocq described under the name "lichen ruber obtusus corneus" and which has also been known as "prurigo nodularis." Pautrier gives good clinical reasons for his view that it has nothing to do with lichen planus but is a rare (circumscribed nodular chronic) variety of lichenification. He has recently reported that histological sections prepared by Masson's technique (see p. 52) reveal in all the cases studied by him an extraordinary hyperplasia of nervous elements. But this "neuroma" can hardly be the cause of the ferocious itching. For the pruritus precedes the formation of the nodules and their occasional disappearance is heralded by its cessation. Moreover, in ordinary lichenification there is no nervous hyperplasia, while conversely in the neuromas of nævi there is no itching.

Lichen Planus. According to Guttmann modern work has failed to show any connection between the nervous system and lichen planus.

But that it can sometimes be determined by mental disturbance is the opinion among others of Ormsby, Pusey, MacLeod and O'Donovan. Ramel tells of a woman who, a few days after a severe mental trauma, developed lichen planus, which, having resisted all other treatment, yielded to psychoanalysis which brought to consciousness a typical Freudian complex. Eller reports that during a serious fall in the exchange he observed the outbreak of acute lichen planus with severe itching in a number of business-men who had had losses. The wife of one of these was similarly affected.

The following case makes me doubt the importance of psychogenic influence. A girl, D. B., aged sixteen years, was treated by me for a very severe profuse acute lichen planus, which, however, cleared up rather rapidly but left deep pigmentation. She complained at the time and subsequently of depression and nightmares. While in hospital she became very friendly with a nurse. Three years later this nurse died, causing in D. B. a nervous

breakdown, for which she had to remain in a Home for some months. A few years later she consulted me on account of extreme self-consciousness, caused by the pigmentation. On examination I could hardly find a trace of pigmentation. In spite of the severity of her original attack, the nervous breakdown associated with a friendship made at the time and a persistent morbid self-consciousness directed to her skin, she has never had the slightest sign of a relapse of the lichen planus.

Recently Gougerot described lichen planus of the oral mucosa accompanied by widespread itching but no eruption on the skin. It is therefore important in general pruritus to examine the mouth.

Psoriasis. An example in which psoriasis appeared to represent a symbolic neurosis is described on p. 108. MacLeod thinks that depressing influences can determine attacks. A young man, who had been under my observation in hospital for many weeks with a fractured femur, developed a profuse eruption of psoriasis just before he was to have an operation for sequestrectomy.

Alopecia Areata. The results of investigations into its relationship with endocrine disturbances are very conflicting; often the most exact investigations fail to reveal any association. Among 25 cases, Lévy-Franckel and Juster found the basal metabolism raised in 18 and lowered in 5. According to this, thyroid treatment would in most cases be contraindicated and, in fact, it is generally ineffective. Nishimura examined the lipoid content of the blood in 50 cases of the disease compared with 25 controls. During the stage of fall, the fatty acid content proved to be very high and the cholesterol low. When the fall of hair ceased these two figures gradually approached normal; during the stage of regeneration there was a hypercholesterolæmia, whilst the fatty acid and lecithin figures had decreased nearly to the normal average.

Its relationship to the vegetative nervous system is also obscure. Joseph and Mibelli cut the posterior branch of the second cervical nerve of a cat, distal to the ganglion, and recorded the development of alopecia over the area of distribution. But

Wright repeated Joseph's experiment not only in animals but in man, and absolutely without effect on the hair-growth. Moreover, Fay, in order to relieve pain in incurable cancer of the face and head, cut completely the sensory and sympathetic supply to the hairy parts of the head, and in no instance was the hair-growth affected. This would not, however, exclude the possibility that it may be influenced by abnormal or excessive impulses passing along the sympathetic or somatic sensory nerves. Cases in which alopecia is preceded or accompanied by neuralgia or sensory disturbances are not very uncommon and do suggest the associated irritability of the nerves concerned. Thomas records the absence or marked diminution of the pilomotor reflex in alopecia patches, and an exaggerated and sustained vasomotor response. In the cases investigated by Brown there was little evidence of disturbance of the central or vegetative nervous or endocrine systems. Several were tested by him for their blood-sugar reaction to adrenalin. Though the curves varied considerably there was one point common to all, namely, the curve was less sustained, returning to normal distinctly earlier than in the controls. This he thinks suggests that they are all somewhat vagotonic. Fujiwara found that tests with adrenalin, atropine and pilocarpine only showed trifling variations from the normal in a small percentage of cases and concluded that alopecia areata cannot be due entirely to disease of the vegetative nervous system.

Roxburgh investigated the behaviour of the blood-vessels in alopecia patches by comparing their response to stroking, histamine, etc., with that of the surrounding unaffected skin. He found that in most cases the response to a heavy stroke was substantially the same on the patch as on the adjoining normal scalp, though in some the wheal and flare were rather more pronounced on the bald patch. Tests with histamine gave similar results. This suggests that the tone of the vessels responsible for skin-colour, namely, the subpapillary venous plexus, and also that of the arterioles responsible for the flare is somewhat less well maintained in the bald areas than in the normal. The response to pricking-in adrenalin was in all cases the same on bald and unaffected areas, which also points to the small vessels in the bald

patches not being in a more contracted state. Lévy-Franckel, Guillaume and Juster maintain that in alopecia areata patches the capillary loops are constricted as compared with the normal. This is not necessarily inconsistent with Roxburgh's results; for, as Lewis points out, the capillary loops make only a small contribution to the colour of the skin, because they are viewed end on. Nevertheless, it is rather surprising that the capillary loops should be contracted and the underlying venous plexus normal or even more easily dilatable than normal. In any case, I must point out that the hair-papillæ, mostly situated in the subcutaneous tissue, do not depend for their blood-supply on the capillary loops in the papillæ of the rete or even on the subpapillary venous plexus. But Roxburgh's observation that even the flare is slightly increased in the bald areas shows that the arterioles, too, are, if anything, more dilatable than normal. One must therefore admit that it is very improbable that alopecia areata is due to diminished blood-supply.

The evidence as to its dependence on psychological disturbances is most unconvincing, though the idea is supported by many authors, including Jordan, O'Donovan and McKenna. Bonjour's rather glib explanation that it is due to psychically induced contraction of the blood-vessels of the affected areas is negatived by Roxburgh's experiments. It is a common clinical experience that the therapeutic production of a prolonged erythema often fails to make the hair grow.

Sclerodermia. In sclerodermia Kuré found that the number of parasympathetic cells in the spinal cord and of parasympathetic fibres in the posterior roots was strikingly small. In the skin of the affected areas he found severe degeneration of the small medullated fibres, thought by him to be parasympathetic. In Barber's case of sclerodermia with atrophy of subcutaneous tissue and muscle, extensive investigations of the nerve-supply were made by Rogerson. The temperature of the affected shoulder was constantly 0·5°–1° C. lower than the opposite normal shoulder. Otherwise all tests were negative, and it was concluded that no anomaly of sympathetic function had been demonstrated. Nevertheless, if it is admitted that the parasympathetic causes a

vasodilatation, this constant difference of temperature would be in harmony with the findings of Kuré.

Pemphigus. Kreibich had in 1910 already described certain changes in the spinal ganglia. Buschke and Ollendorf (1925) in 2 cases examined the central nervous system very thoroughly and found in both brains severe arteriosclerosis with gross changes in the nerve-substance—an " état lacunaire ou criblé " in the region of the brain-stem. They lay particular stress on changes in the nucleus paraventricularis, *i.e.*, in one of those nuclei which have recently become known as regulatory stations of the vegetative functions. Their findings were further investigated by Urbach and Uiberall with the help of experts in the histopathology of the central nervous system. They found a whole series of uncharacteristic and irregular alterations in the central nervous system ; but just in these vegetative centres they found no tangible pathological changes. Buschke and Ollendorf's theory can therefore not yet be accepted.

Herpes Simplex. Heilig and Hoff (1928) established that in certain patients unpleasant emotions were regularly accompanied by herpes labialis. Analysis of 3 cases, in which the presence of the specific virus was demonstrated by rabbit-inoculation, revealed a trauma coloured with intense emotion. Reconstruction of this trauma in hypnosis, together with suggestion of itching in the region of the lip, led in all to the appearance of herpes labialis. An equally detailed suggestion of the herpes but without touching on the emotional motive was without result. The authors attributed these phenomena to the lowering of the natural resistance of the body by the depressive emotion, whereby the virus becomes more effective. These observations may have a very important bearing on susceptibility to other infections too.

We have now studied the various ways in which the mind and the nervous system *can* influence the skin and its disorders. I have made an attempt to get some idea as to the frequency with which certain dermatoses are in fact attributable to their influence. Over a period of 7 years all the patients attending the West End Hospital for Nervous Diseases (which deals extensively with

psychological and functional nervous disorders as well as organic), that have had anything wrong with their skin have been referred to me, and the neurologist's diagnosis and my own have been recorded. Many of the skin-conditions were, of course, obviously incidental. None of them was found to be predominantly associated with any particular nervous or mental disorder, except perhaps neurodermatitis, of which half the cases were associated with menopausal disturbances. In order to determine whether certain dermatoses occurred with greater frequency among "nervous" patients than among the general population, I have compared their relative incidence in proportion to the total number of new patients attending the West End Nerve Hospital with their relative incidence in proportion to the total number of new patients attending a general one, *i.e.*, University College Hospital. The following have been chosen for this comparison:—psychogenic excoriations, lichen planus, neurodermatitis, pruritus, urticaria, psoriasis and alopecia areata. None of these proved to be relatively commoner among the nervous patients than the general hospital population, except *psychogenic excoriations*, of which there were altogether extremely few. These were not true artefacts, but rather scratch-effects which I attributed to psychological causes. But curiously in just these cases the neurologist had made no diagnosis of mental disorder. *Psoriasis* proved about equally common at the two hospitals: so did *neurodermatitis* and *pruritus*. With regard to the latter, it was very striking that at the Nerve Hospital in the whole 7 years there was only 1 case of pruritus vulvæ, the neurologist's diagnosis in that instance being ulnar paralysis. *Lichen planus* and *urticaria* were only half as common at the Nerve Hospital. The figures for urticaria may be a little misleading, as I gather that some cases in which it appeared to be part of a symptom-complex, including acute anxiety, lienteric diarrhœa, mucous colitis and easily dilatable pupils, were not referred to me. *Alopecia areata* was less common by a third than at the General Hospital. This is especially surprising in view of the fact that many subjects of it went direct to the West End Hospital because they themselves thought it was due to nerves. In its In-patient Department I never

saw any dermatosis which I could link up with the neuro- or psychological condition, except perhaps one case of rosacea in a depression-state.

This experience has certainly led me to the conclusion that, though we must keep in mind the possible effects of disturbances of the mind and nervous system on the skin, we must be careful not to exaggerate their importance at the expense of other factors. On the other hand, the psychologists might remind us that, "Conflicts, if they are not made conscious and thus rationally disposed of, are repressed into the unconscious and the energy there 'bottled-up' may lead *either* to abnormal manifestations in the mind (psychoneurosis) *or* affective disturbances in the body (Freud's conversion)." In other words, a skin-disturbance resulting from a mental conflict should not be expected to be accompanied by a psychoneurosis. But if we accept that, then we must attach little importance to the opposite argument that a skin-trouble is likely to be of mental origin if it *is* accompanied by a psychoneurosis. We cannot argue both ways.

Treatment

Hirsuties. The occasional efficacy of *adrenalectomy* has been referred to. In other cases showing virile type of hair-growth in women where there is no clear evidence of adrenal tumour, *ovarian follicular hormone* has sometimes achieved partial success. It may also be used to promote regrowth of scalp-hair in women showing the male type of baldness.

General Pruritus. Causal treatment must be dictated by the very varied ætiology already discussed. In addition to such rational procedures, or in cases where the ætiology is obscure, various empirical methods have been recently advocated.

Internal Treatment. Among drugs taken by mouth the usefulness of *Luminal* has been emphasised and explained by Ehrenwald. *Bromide* lessens the pathologically raised excitability of the central nervous system and especially diminishes unpleasant sensations and malaise. It is the more effective the greater the psychic component of the itching. It is sometimes especially

effective when combined with *phenazone*. In senile pruritus, if associated with arterio-sclerosis, *iodine* is often beneficial: the nutrition of the skin and consequent lessening of irritability is further aided by gently massaging with *olive* or *almond oil*.

A very large variety of substances, some protein and some not, have been recommended for injection. Sellei recommends *turpentine* in doses of 0·02–0·05 gm., and gives 5 injections within 2–3 weeks. Meyer and Gallerand had success in obstinate pruritus in women between the ages of 52 and 75 with injections of *testicular extract*. They could, on the contrary, produce no improvement if instead they injected sodium chloride, ovarian extract or distilled water. Some cases of severe general pruritus, especially with lichen planus, have been relieved by *pituitrin* 1 c.c. hypodermically every 2 or 3 days. Ravaut and Tomescu recommend *autohæmotherapy* in doses of 20–30 c.c. I have found it effective in many obscure cases in smaller doses, from 5 to 15 c.c. once a week.

EXTERNAL TREATMENT. *Local anæsthetics* generally cannot penetrate unbroken epidermis. In any case their effect is of short duration, and while it is passing off various unpleasant paræsthesias sometimes occur, when mild pain-stimuli produce itching. This applies to cocaine and all its substitutes. The insoluble anæsthetics, *e.g.*, *benzocaine*, can only act as antipruritics if the horny layer and part of the rete are lacking, and they may cause inflammation, especially as habituation necessitates increased strength. Winkler recommends *Bromocoll* 10–20%, *Heliobrom* 10% in spirit, and especially *Calmitol*, which was introduced by Jadassohn. This is a weakly iodised ether-alcoholic solution of camphoraldehyde with menthol and hyoscine oleate. It is in some cases strikingly superior to other remedies; it can also be used in ointment-form in concentrations of 1–10%. In my experience the most reliable antipruritics are still *calamine lotion with* 1% *phenol* and, especially, *crude coal tar* 3% *or* 4% *in zinc paste:* Martindale's ether-soluble tar paste is almost equally efficient and much cleaner.

RADIOTHERAPY. Apart from the direct X-radiation of itching areas, many workers have in recent years described the good

effects of *irradiation of the spine*. Cottenot appears to have been the first. In 1923 he reported success in pruritic eczema, in which direct X-rays had failed, by irradiating the spinal ganglia of the corresponding segments. Kriser and Schoenhof also succeeded in chronic intractable eczema and neurodermatitis by irradiating either the whole length of the spine or the appropriate segments. It was especially the pruritus which was benefited. Gouin and Bienvenue (1927) also recommend this procedure. Whilst their technique is intended to act upon the sympathetic, Pautrier's aims at the cord. In lichen planus it is often found that the itching is allayed without the eruption being objectively altered. Fuhs and Konrad have not been impressed by the results of spinal irradiation. Borak thinks that senile pruritus can be relieved by X-radiation of the hypophysis.

Pruritus Ani et Vulvæ. When a definite cause can be found this is treated accordingly. In cases due to threadworms MacArthur stresses the importance of washing the hands not only after defæcation and before meals, but also after touching any portion of the body or undergarments. *Mercurial ointment* should be smeared on the anus every morning and evening; *hydrochloric acid* must be given by mouth if there is a deficiency. *Saline* in a strength of 2 tablespoonfuls to the pint should be injected into the rectum when itching begins. *Santonin* gr. 2 and *calomel* gr. 1 may be given to an adult three nights in succession. For children Paterson recommends *Butolan* half a tablet 3 times daily for a week.

But in the majority of cases there is no apparent local cause to deal with. Bregmann, with the idea that genital pruritus of women is connected with the ovaries and these with the thyroid, gave *dried thyroid* 0·1 gm. daily to 3 women between the ages of 37 and 39. In 2 or 3 weeks the pruritus had disappeared: after stopping the treatment it relapsed, again to disappear on resuming it. Eventually a dose of 0·05 gm. daily was enough to keep it in abeyance. As a *topical application* Gabriel specially recommends:—phenol, gr. 15; zinc oxide, dr. ½; calamine, gr. 15; glycerine, dr. ½; rosewater, dr. 1; milk of magnesia, to ℥ 1. Milk of magnesia is also recommended as an aperient, whilst he con-

demns liquid paraffin (wrongly I believe) and magnesium and sodium sulphate. For fissures I find *Percainal* valuable.

INJECTION METHODS. There are two ideas. One is to obliterate connective tissue spaces thought to contain irritating fluid: for this purpose hydrochloric acid, alcohol and quinine-urea have been used. The other is to produce a definite anæsthetisation. Yeomans in 1927 recommended *Benacol*, a solution of equal parts of para-amino-ethyl benzoate and benzyl-alcohol in 90 parts of almond oil. Gabriel in 1929–30 introduced *Percain in oil* (Percain, 0·5%; benzyl-alcohol, 10%; phenol, 1% in sterile olive oil) and *A.B.A.* (Anæsthesin, 3%; benzyl-alcohol, 5%; ether, 10% in sterile olive oil). It is much more suitable for anal than vulval pruritus. He recommends a few large injections rather than a series of small ones. The principle is to obtain a maximum effect round the entire anal circumference as soon as possible. At the first treatment 10 c.c. are injected through 4 punctures all posterior to the anus, in order to act on the principal sensory distribution, namely, the inferior hæmorrhoidal nerves and the perineal branch of the 4th sacral. Two of the 4 points are about 2 inches lateral to the posterior end of the anus, and the second pair of points about 2 inches posterior and a little medial to the first pair. The needle must be inserted deeply so that no surface-swelling is noticeable at the conclusion. A second injection of 10 c.c. of A.B.A. or Percain in oil is given about 6 days later, 5 c.c. into the right anterior quadrant and 5 c.c. into the left, using two punctures for each. A third injection of 10 c.c. is given in severe cases a week later on each side of, and posterior to, the anus.

Gabriel states that in about two-thirds of his cases within 24 hours of the first injection a feeling of numbness develops and the irritation disappears; this lasts for about 3–6 weeks. The Percain in oil produces a more pronounced anæsthesia than the A.B.A., but it does not last any longer, possibly not so long.

X-RAYS. In most cases, as in other forms of localised pruritus, X-rays are extremely efficient. Sometimes, but unfortunately in the minority, the effect is permanent. O'Donovan states that patients are most grateful for a single treatment of a $\frac{1}{4}$ E.D.,

and seems to conclude from this that the relief is the result of suggestion. This does not tally with my experience. I generally give $\frac{1}{3}$ E.D. at intervals of a week, and nearly always find that it is only after the 2nd, 3rd or 4th exposure that marked relief is obtained. Winkler recommends a dosage of $\frac{1}{2}$–$\frac{3}{4}$ E.D. with $\frac{1}{2}$–1 mm. of aluminium every fortnight. X-rays must be used with special caution when there is marked maceration or scratching, which seem to favour the appearance of eventual radiodermatitis. Miescher avoids a total dose of more than $1\frac{1}{2}$–2 E.D.

NEUROTOMY. The objects of the operation are to divide (*a*) the sensory fibres contained in the inferior hæmorrhoidal nerve, and (*b*) the superficial sensory branches of the perineal nerve. It is indicated for those severe cases of pruritus ani in which the above measures have failed. The nerves are identified and dissected out in the ischiorectal fossa. The motor branches are detected by faradic stimulation and left alone. Division of the internal pudic nerves was introduced for vaginism by Simpson in 1861 and first used for pruritus vulvæ by Tavel in 1902. It has recently been revived by Wertheimer and Michon and recommended for pruritus vulvæ, vaginism, kraurosis vulvæ and painful conditions of the urethra. The sensory distribution of the perineal or inferior branch of the internal pudic nerve includes the skin of the inferior part of the perineum, the scrotum or vulva, and part of the urethral mucosa; its superior branch furnishes numerous twigs to the corpora cavernosa and the glans penis or clitoris.

Neurodermatitis. Ehrmann, who found that there was generally a gastric hypochlorhydria, gave *dilute hydrochloric acid* and *pepsin*. Nobl recommends the intravenous injection of *Eczebrol*, which is a 20% solution of grape-sugar, containing in each 10 c.c. 1 gm. of strontium bromide. Up to 15 injections, each of 10 c.c., are given intravenously every 2 days. For diffuse neurodermatitis Bisson and Desaux recommend *X-raying the spine*. The localised cases are particularly amenable to *direct X-rays*. Louste and Juster advise ionisation of obstinate patches with *aconitine nitrate*, 10 gm. in 250 c.c. of distilled water, attached to the positive pole.

Comparing the influence of *peptone*, *autohæmotherapy*, *pilocarpine*, *physostigmine* and *ergotamine* in "prurigo vulgaris," Brack found they all had an influence in the same direction, namely, depression of the sympathetic or stimulation of the parasympathetic or perhaps both. The clinical effects were disappearance of the itching and papules and in certain cases disappearance of the abnormal psychical irritability. These findings are at variance with those of Brill, who noted a predominant vagotonia in neurodermatitis and eczema.

In my experience the most reliable external measures are crude coal tar paste, Calmitol or X-rays. Internally, I have had some success, in cases which had defied autohæmotherapy, with *Yatren Casein* given intravenously once a week, starting with 0·2 c.c. of the weak solution and increasing the dose gradually whilst avoiding any marked general reaction.

Psychotherapy. The field for the rational use of psychotherapy has been sketched in the section on Mental Influences. It may in some cases be the method of choice, but it can also, through lack of a sense of responsibility or expert knowledge, do great harm. As a rule, psychically caused disturbances will be especially accessible to psychotherapeutic influence, but in many cases of apparent psychogenic disorder treatment by medicaments or by physical methods is preferable. Similarly, some organic disturbances are nevertheless dealt with more successfully by bringing psychic influence to bear on the whole system. The important observations of Heilig and Hoff in herpes labialis show the close connection between emotion and susceptibility to specific infections.

Warts. Whilst popular superstition in all countries accepts the infectiousness of warts as well as their curability by suggestion, the first doctor to introduce modern suggestion-therapy for them, Bonjour, denies their infective origin in spite of its experimental proof. As early as the end of last century he cured warts in hypnosis. He ascribes the cure to the lowering of raised blood-pressure. (Incidentally he reports numerous successes by suggestion in cases of eczema, and here, too, ascribes the improvement to lowering of raised blood-pressure.) He thinks that

warts are not only cured but caused psychogenetically, and claims to have produced them by suggestion. But his psychogenic and vascular theories have been almost universally rejected. Bloch (1927), as the result of statistical and experimental studies, came to regard *suggestion* as the method of choice in common and plane warts. His method is as follows. The patient is placed blindfolded before a pantostat with his hands resting upon it. The motor is turned on, but no current is conducted to the patient. The warts are now painted with some coloured fluid and an emphatic verbal suggestion is made that the warts will disappear. After the operation the patient is told not to touch or wash the warts as long as the colour remains. Dull-witted individuals are difficult to influence: children, especially with plane warts, respond relatively easily. Bloch's statistics showed that common warts responded in 44% of cases and juvenile in 88%. Of the latter, 60% yielded to the first sitting. Most of the cures took place within a month and nearly all the rest within the second month. Often, soon after the suggestion, there was noticed a swelling of the warts and occasionally slight hæmorrhages. Memmesheimer and Eisenlohr compared the number cured by suggestion with the number in which warts disappeared spontaneously. They found that within the first 2 months there was a marked preponderance of cures after suggestion, but that after the 3rd month the untreated cases were in the majority. It seemed that if suggestion did not cure within the first 2 months it might even delay spontaneous disappearance. Nevertheless, Bloch's total of 55% cures after suggestion is about twice as good as Memmesheimer and Eisenlohr's total of treated and untreated cases.

Bloch thinks that suggestion provides a stimulus to the vegetative centres, which is conducted by the vegetative nerve-channels to the warts. The epidermis is so rich in nerve-fibrils, that there is no great difficulty in accepting the possibility that in this direct way nervous impulses may cause biological changes of a chemico-physical nature, which damage the virus. Many authorities have noted that the stronger the suggestion the better the result. Some doctors are naturally more successful

than others. The effect must be the result of psychically induced alteration of the terrain. The method probably depends on the bringing about of anxiety, fright, or, in the case of the popular methods, disgust. In this state of emotion attention is linked to the warts. Apart from lesions caused psychogenetically it is only unstable structures like warts, which already have a tendency to spontaneous regression, that are susceptible to psychogenic influence. It appears to me probable that the therapeutic effect is the result of the general *emotion* produced, and is not dependent on the specific suggestion. Heilig and Hoff's important observations on herpes labialis (also caused by a filter-passing virus) point in this direction.

If the possibility of curing warts by suggestion is a fact, no doubt some of the successes of other methods, such as X-rays, may also be by virtue of suggestion. It would be going much too far to say that they always depend on the mental effect. Moreover, in my experience, it is very rare for painful treatments, such as the galvano-cautery or CO_2 snow, fraught with considerable dread of the next session, to have the happy result of banishing the other (untreated) warts. Conversely, one must not forget that some of the apparent spontaneous remissions may be the result of emotional experiences.

Bibliography

ALEXANDER, A. "Neurodermitis," *Jadassohn's Handbuch der Haut u. Geschlechtskr.*, 1927, **6/1**, 371.

BALYEAT, R. M. "Reflex Itching in Asthma," *Journ. Amer. Med. Assoc.*, 1929, **92**, 873 (*cit.* Rothman).

BARBER, H. W. "Scleroderma with Atrophy of Subcutaneous Tissue and Muscle," *Brit. Journ. Derm. and Syph.*, 1932, **44**, 492.

BLOCH, B. "Über die Heilung der Warzen durch Suggestion," *Klin. Woch.*, 1927, **6**, 2271.

BLOCH, B., and STAUFFER, H. "Skin Diseases of Endocrine Origin," *Arch. of Derm. and Syph.*, 1929, **19**, 22.

BORAK, J. "Über eine neue Behandlungsmöglichkeit des Pruritus senilis," *Strahlenther.*, 1928, **29**, 245 (*cit.* Rothman).

BRACK, W. "Experiments in Treated Cases of Prurigo Vulgaris," *Ztschr. für des ges. exper. Med.*, 1926, **51**, 525.

BROSTER, L. R., and VINES, H. W. C. "The Adrenal Cortex," Lewis, London, 1933 (*cit. Brit. Med. Journ.*, 1933, 880).

BROWN, W. H. "On the Ætiology of Alopecia Areata and its relationship to Vitiligo and possibly Sclerodermia," *Brit. Journ. Derm. and Syph.*, **1929, 41,** 299.

COTTENOT, P. "Traitement par les rayons X des prurits et des dermatoses prurigineuses," *Journ. de méd. de Paris*, 1923, **42,** 795.

CUSHING, H. "The Basophil Adenomas of the Pituitary Body and their Clinical Manifestations (Pituitary Basophilism)," *Johns Hopkins Hosp. Bull.*, 1932, **50,** 137.

DRAKE, J. A. "Urticaria Evoked by Emotion," *Brit. Journ. Derm. and Syph.*, 1931, **43,** 184.

EHRENWALD, H. "Zur Pathologie und Klinik des Juckgefühls," *Zbl. f. d. ges. Neur.*, 1931, **132,** 502.

EHRENWALD, H., and KÖNIGSTEIN, H. "Klinische und experimentelle Untersuchungen über das Juckgefühl," *Wien. klin. Woch.*, 1929, **42 2,** 1397.

ELLER, J. J. "Neurogenic and Psychogenic Disorders of the Skin," *Med. Journ. and Rec.*, 1929, **129,** 675 (*cit.* Sack).

EWALD, G. "Die Stigmatisierte von Konnersreuth," *Munch. med. Woch.*, 1927, **74,** 1981 (*cit.* Sack).

FENWICK, W. S. "Glycosuria and Pruritus, dependent upon Latent Disease of the Appendix," *Lancet*, 1925, **1,** 279 (*cit.* Winkler).

v. FREY, M. "Über den Kitzel," *Zbl. ärztl. Fortbild.*, 1925, **22,** 81 (*cit.* Rothman).

FRIEDMANN, M. "A Case of Impetigo Herpetiformis," *Arch. für Derm. und Syph.*, 1932, **165,** 457.

GABRIEL, W. B. "The Principles and Practice of Rectal Surgery," Lewis, London, 1932.

GOUIN, J., and BIENVENUE, A. "De la radiothérapie du sympathique dans les dermatoses," *Journ. de Radiol. et d'Electrol.*, 1927, **11,** 129 (*cit.* Rothman).

GUTTMANN, E. "Haut und Nervensystem," *Jadassohn's Handbuch der Haut u. Geschlechtskr.*, 1933, **4 2,** 1222.

HALDIN-DAVIS, H. "Sclerodermia and Thyroid Tumour," *Brit. Journ. Derm. and Syph.*, 1932, **44,** 29.

HARTMANN-KARPLUS, D. "Untersuchungen über Juckempfindung, Kratzen und Pilomotorenreflex im Säuglingsalter," *Jb. Kinderheilk.*, 1931, **132,** 140 (*cit.* Guttmann).

HEILIG, R., and HOFF, H. "Über psychogene Entstehung des Herpes labialis," *Med. Klin.*, 1928, **24,** 1472 (*cit.* Sack).

HORDER. "Pruritus," Prosser White Oration, St. John's Hosp. Derm. Soc., 1935.

INGRAM, J. T. "Circumscribed Myxœdema associated with Hyperthyroidism," *Brit. Journ. Derm. and Syph.*, 1933, **45,** 19.

JORDAN, P. "Tastkörperartige Bildungen in einem zelligen Naevus der behaarten Kopfhaut," *Arch. für Derm. und Syph.*, 1933, **169,** 105.

KURÉ, K. "Spinalparasympathicus," Basel, 1929 (*cit.* Guttmann).

KURÉ, K., YAMAGATA, K., and KANEKO, Y. "Pathogenese der Sklerodermie und Spinalparasympathicus," *Klin. Woch.*, 1932, **11,** 1415 (*cit.* Guttmann).

LOUSTE and JUSTER, E. "Le traitement des prurits circonscrits (névrodermites) par l'ionisation à l'aconitine," *Bull. Soc. franç. de Derm.*, 1926, **33,** 78 (*cit.* Alexander).

MACARTHUR, W. P. "Pruritus Ani," *Brit. Med. Journ.*, 1931, **2,** 334.

MCMENEMEY, W. H. "Circumscribed Myxœdema associated with Graves' Disease," *Brit. Journ. Derm. and Syph.*, 1933, **45,** 350.

MEYER, J., and GALLERAND. "Traitement de certains prurits chez la femme,

par des injections d'extraits orchitiques," *Bull. Soc. franç. de Derm.*, 1926, **33**, 710 (*cit.* Winkler).

MÜLLER, E. F. "Über die Beziehungen der Haut und des autonomen Nervensystems zum qualitativen Blutbild," *Münch. med. Woch.*, 1924, **71**, 202 (*cit.* Guttmann).

NISHIMURA, E. "On the Lipoid Content of Blood in cases of Alopecia Areata," *Japan. Journ. Derm. and Urol.*, 1932, **32**, 11. (Abstr., *Brit. Journ. Derm. and Syph.*, 1933, **45**, 75.)

O'DONOVAN, W. J. "Dermatological Neuroses," Kegan Paul, London, 1927.

O'LEARY, P. A. "Localised Solid Œdema of the Extremities in association with Exophthalmic Goitre," *Arch. of Derm. and Syph.*, 1930, **21**, 57 (*cit.* Ingram).

PAUTRIER, L. M. (*a*) "Le traitement du lichen plan par la radiothérapie médullaire," *Bull. Soc. franc. Derm.*, 1927, **7**, 602 (*cit.* Rothman). (*b*) "Le névrome de la lichenification circonscrite nodulaire chronique (Lichen Ruber Obtusus Corné, Prurigo Nodularis)," *Ann. de Derm.*, 1934, 5, 897.

PILLSBURY, D. M., and STOKES, J. H. "Circumscribed Myxœdema of Skin," *Arch. of Derm. and Syph.*, 1931, **24**, 255 (*cit.* Ingram).

PRITCHARD, E. A. B. "The Clinical Significance of Variations in Tickle Sensibility," *Proc. Roy. Soc. Med.*, 1933, **26**, 697.

ROTHMAN, S. "Das Jucken und die juckenden Hautkrankheiten," *Jadassohn's Handbuch der Haut u. Geschlechtskr.*, 1930, **14**/**1**, 664.

ROXBURGH, A. C. "The Ætiology of Alopecia Areata and its relation to Vitiligo and Sclerodermia," *Brit. Journ. Derm. and Syph.*, 1929, **41**, 351.

SACK, W. T. "Psyche und Haut," *Jadassohn's Handbuch der Haut u. Geschlechtskr.*, 1933, **4**/**2**, 1302.

SCHILLING, E. "Die Sensibilisierung des vegetativen Systems durch Intracutaninjektion," *Med. klin.*, 1932, **28**, 1027 (*cit.* Guttmann).

SCHINDLER, R. "Nervensystem und spontane Blutungen," Berlin, Karger, 1927 (*cit.* Sack).

STOKES, J. H. "The Effect on the Skin of Emotional and Nervous States: II. Masochism and other Sex Complexes in the Background of Neurogenous Dermatitis," *Archives of Derm. and Syph.*, 1930, **22**, 803.

STOKES, J. H., and PILLSBURY, D. M. "The Effect on the Skin of Emotional and Nervous States. III. Theoretical and Practical Consideration of a Gastro-intestinal Mechanism." *Arch. of Derm. and Syph.*, 1930, **22**, 962.

STRANDBERG, J. "Haut und innere Sekretion," *Jadassohn's Handbuch der Haut u. Geschlechtskr.*, 1929, **3**, 166.

TOURAINE, A. "Prurit sénile et azotémie," *Bull. Soc. franç. Derm.*, 1935, **42**, 342. (*Abst. Zbl. Hautkrank.*, 1935, **51**, 204.

WEBER, F. P. (*a*) "A Note on the Nature of Cutis Verticis Gyrata (Bulldog Scalp) and Cutis Striata or Cutis Sulcata, and particularly on their Occurrence in Acromegaly," *Brit. Journ. Derm. and Syph.*, 1928, **40**, 1. (*b*) "Basophilic Hyperpituitarism (Cushing's Endocrine Pituitary Syndrome) and ? Basophilic Hypopituitarism," *Brit. Med. Journ.*, 1932, **1**, 935. (*c*) "Remarks on Endocrine Tumours, especially those of the Suprarenal and Pituitary Glands," *Med. Press. and Circ.*, 1933, **136**, 500.

WERTHEIMER, P., and MICHON, L. "Neurotomy of the Internal Pudic Nerve," *Journ. de Chirurgie*, 1928, **31**, 497.

WHITFIELD, A. "Some Points on the Ætiology of Skin Diseases," *Lancet*, 1921, **2**, 168.

WINKLER, M. "Prurigo, Strophulus, Pruritus," *Jadassohn's Handbuch der Haut u. Geschlechtskr.*, 1927, **6**/**1**, 301.

WOHLSTEIN, E. "Kasuistischer Beitrag zur psychogene Entstehung von Dermatosen mit hypothetischen Deutungsmöglichkeiten," 8th Internat. Derm. Cong., 1930, 840.

WRIGHT, C. S. "Ætiology of Alopecia Areata with special reference to Effect of Experimental Nerve Injuries," *Arch. of Derm. and Syph.*, 1929, **19**, 365 (*cit.* Brown).

CHAPTER V

THE RETICULO-ENDOTHELIAL SYSTEM

In modern discussions on the pathological processes underlying many disorders of the skin the reticulo-endothelium is so often mentioned, that I feel it will be useful to review briefly what is known of it, especially in its relation to the skin.

On the ground of various functional tests, Aschoff picked out parts of the active mesenchyme and separated them into one system. There is, however, no morphological unity among the cells composing it, the systematisation of the various cell-groups depending on their physiological properties. It cannot be said that there is complete agreement either as to what cell-groups do belong to the system or as to its function. Earlier workers had recognised the occurrence of cells in the organs, connective tissue and blood, which had phagocytic properties, as well as some relationship to blood-formation and blood-destruction, and which were also able to take up and store dissolved colouring matter, such as carmine and pyrrhol blue. In 1913 Aschoff decided to group these cells, so widespread in the organism, into one system, the reticulo-endothelial system (R.E.S.). They are found sometimes isolated and sometimes in a syncytium, and have special powers of phagocytosis and of storing. Kiyono was able to show a certain regularity about the granular appearance of stored carmine under normal and pathological conditions. The intravital storing of carmine formed thereafter the starting-point of further methods of investigation. The resulting granulation enables these cells to be distinguished from most parenchymal cells, from the ordinary blood-cells as well as the myeloic and lymphatic series, from lymphocytes of lymph-glands and from plasma-cells and mast-cells. The granulation is by no means uniform : in some groups of cells it is fine and in others coarse. On the basis of this observa-

tion, Aschoff arranged the groups of mesenchymal elements in an ascending series :—

(1) *The endothelial cells of the blood- and lymph-vessels.* These only store in the presence of very intense staining and only in the form of very fine granules.

(2) *The fibrocytes or the ordinary connective tissue cells.* These store in the presence of adequately strong staining in varying degrees in the form of fairly fine granules.

(3) *The reticular cells of the splenic pulp and Malpighian corpuscles, of the medullary fasciculi of the lymph-nodes and finally of the rest of the lymphatic tissue.* These store relatively easily.

(4) *The reticulo-endothelial cells of the sinuses of the lymph-glands, of the blood-sinus of the spleen, and of the capillaries of the hepatic lobules (Kupffer's stellate cells), bone-marrow, adrenal cortex and hypophysis.*

(5) *The histiocytes :* the name given to the mobile inhabitants of connective tissue (the clasmatocytes of Ranvier), as distinguished from the cells that build connective tissue—the fibroblasts and fibrocytes.

(6) *The splenocytes and dye-storing monocytes* (endothelial-leucocytes, blood-histiocytes), which are derived from the histiocytes (Group V.) and the reticulo-endothelial cells (Group IV.).

As Groups I. and II. stain very feebly and are also otherwise functionally different, Aschoff excludes them altogether from his system. Groups III. and IV., on account of their similar function, are included under the conception " reticulo-endothelial system in the stricter sense " ; whilst the histiocytes of the connective tissue and the blood-histiocytes (monocytes) are reckoned as " reticulo-endothelial system in the wider sense."

By the term " storing " is meant the granular intracellular deposition of acid or electro-negative substances, following their intravital administration. It is dependent on the properties of the dyestuffs, on their degree of dispersity, on the manner in which they are introduced and on the functional state of the storing cells at the time. It does not depend so much on the chemical reactions of the substances as on their electro-polarity : they must be electro-negative. To this class belong especially the dyes ordinarily

called acid, *e.g.*, pyrrhol blue, lithium carmine, colloidal metal hydrosols, colloidal products of intermediate metabolism (*e.g.*, lipoids, dissolved hæmoglobin, various serum-proteins), bacteria and protozoa. In the case of highly dispersed stuffs, such as carmine or pyrrhol blue, the site of their introduction is immaterial. But if the substances are in coarse dispersion they remain more or less at the site of injection, are there precipitated and are taken up by the local histiocytes. Only later may they become more widely distributed by means of the wandering cells. But if such coarsely dispersed substances are injected directly into the blood-stream they are taken up by the whole of the R.E.S. The variable storing capacity of the cells themselves is not quite so well understood. Wallbach and Wolff say it is impossible to make a sharp morphological definition of the R.E.S. on the basis of the behaviour of the cells towards the so-called vital staining. Siegmund says that local or general heightening of metabolic activity increases the number of different cell-elements that readily store and thereby widens the circle of cells admissible under Aschoff's R.E.S. It is generally admitted that the R.E.S. can be stimulated. This results not only in an increase of phagocytic power but also in a raised secretory activity (ferment-production).

According to Aschoff, cells of the R.E.S. have the power under certain conditions of leaving their cellular network and entering the blood-stream as regular components of it. The relationship of the histiocytes to the monocytes of the blood is still disputed. Whilst Schilling thinks that these are all derived from the histiocytes, Naegeli thinks that histiocytes seldom enter the blood. Quite recently Lang has reached the conclusion that the monocytes are preponderantly derived from lymphocytes.

Blood-catabolism. Red and white corpuscles and platelets are phagocytosed by the endothelium of the spleen, liver and bone-marrow, and by the splenocytes. But it is probable that the blood corpuscles are phagocytosed and intracellularly disintegrated in other parts, too, of the R.E.S. Intracellular disintegration of hæmoglobin sets free iron, cholesterol and bilirubin to return to the blood in order to be used afresh for the building-up of new blood-pigment in the blood-forming stations. But blood-corpuscles

are less often dealt with inside cells than dissolved outside. Nevertheless, all possible stages of the dissolution of blood-corpuscles can be found in reticulo-endothelial cells; and this taking-up of the products of hæmolysis, if not its initiation, by the R.E.S. is of the greatest importance in metabolism. The active part played by the R.E.S. in the formation of bile was shown by McNee.

With regard to the *metabolism of fat and lipoid* in the R.E.S., that of cholesterol is of special interest. With increasing destruction of erythrocytes there are larger quantities of cholesterol set free. But the quantity of blood-cholesterol does not depend alone on blood-destruction. In all conditions in which the amount of cholesterol in the blood is raised one generally finds conspicuous storing of it in the R.E.S. Other organs, too, participate in cholesterol metabolism, such as the adrenals, parenchyma of liver and testes, but not to the same extent as the R.E.S. In xanthelasma separate districts of the R.E.S. are involved, in which to a special degree cholesterol esters are deposited in the histiocytes. This is discussed fully in the following chapter. But Wallbach and Wolff consider that the present-day estimate of the importance of the R.E.S. in lipoid metabolism is lower, since one has recognised more clearly the participation of other cells, especially epithelial liver-cells. Further, they stress that the storing of lipoid under pathological conditions must not be confounded with normal metabolic performance.

The phagocytic property of the R.E.S., which is exerted not only against dyestuffs but also against bacteria and toxins, is of great importance in *infections*. Bound up with this function is the relationship of the R.E.S. to the production of immune bodies, to cellular reactions, and, in fact, to the whole process of immunity. Its activity can be stimulated by various measures, and the good effect of "irritation-treatment" by foreign proteins has been attributed to stimulation of R.E.S. in the sense of increased antibody-formation.

In tubercles, that is to say heightened tissue-reactions to the tubercle-bacillus, the so-called epithelioid cells are now thought to be derived from histiocytes, and, in the liver, from Kupffer cells.

Vital staining shows that all the elements of a tubercle, with the exception of the lymphoid cells, store dyestuff (Goldmann). The same applies, of course, to other granulomas. Infectious diseases commonly accompanied by a high-grade monocytosis include monocytic angina, endocarditis, variola, varicella, scarlatina, typhoid, pneumonia and purpura.

According to Schilling *monocytic leucæmia* represents a peculiar disease of the R.E.S. Letterer described the case of a child of 6 months who showed symptoms of an acute infective purpura. There was found to be disease of the whole lymphatic apparatus except in the small intestine and mesenteric lymph-glands, and there was great enlargement of the spleen. Histologically all the affected organs, including the skin, presented massive proliferation of large cells, rich in protoplasm, whose connection with reticular fibres was demonstrable. [In 1933 I described a case of primary leucosarcoma of the skin associated with lymphatic leucæmia, in which paper the nature of monocytes is discussed at length.]

Relationship to Skin-Diseases

There is still some doubt as to which cells in the skin are part of the R.E.S. The ordinary mesenchymal cells, mainly fibrocytes and endothelial cells, are not reckoned by Aschoff as strictly belonging to it. The relationship of histiocytes to fibrocytes has been mentioned. It is still uncertain whether they are genetically different or whether histiocytes can be formed from fibroblasts. Does the skin contain any other special structures which may belong to the R.E.S.? In particular what are the "lattice-fibres" (Gitterfasern), and what are the dendritic cells of the epidermis?

The name "lattice-fibres" is given to an especially dense felt-work of fibres at the border between epidermis and corium. They are most conspicuously demonstrated by Bielschowsky's silver method and are especially well seen if the skin is œdematous. Often they are arranged like a palisade or brush at right angles to the line of demarcation between the two layers of skin. They are

only about 7–10 μ long. They never penetrate far between the epithelial cells, but towards the deeper tissue they seem to link up with the connective tissue fibres. In the deeper layers of the corium, too, this method reveals copious, fine, black fibres between the collagen fibres, arranged as rings round the sweat-gland coils and as a feltwork between them. Further, the arterial walls contain thick radial lattice-fibres bound together by thinner fibres, making a dense network. According to Homma about a third of the arterial wall is composed of lattice-fibres. It is naturally difficult to distinguish them with certainty from elastic tissue, and one view is that they are precursors of collagen. But they are generally regarded as representing a third system of fibres in addition to the elastic and collagen. Hudelo and Cailleau regard them as the fibrillar part of the R.E.S. It is an interesting observation that they are increased in inflammatory granulation-processes (Way and Klövekorn).

With regard to the dendritic cells, the question of their identity with Langerhans cells or with basal cells has been discussed in Chapter III. Masson and Pautrier, who identify the dendritic with the Langerhans cells, call them "cellules amboceptrices." They think that they are in connection on one side with the epidermal cells and on the other with the reticulo-endothelial apparatus of the cutis, and so with the endothelium of the blood-vessels and the circulating blood. They look upon the system as a metabolic exchange-apparatus between the blood and the epidermis, forming a cutaneous peripheral portion of the R.E.S.

Saxl and Donath think that the R.E.S. is intimately connected with the *water-economy* of the body, and the investigations of Sakata led him to conclude that of all organs only the skin has the disposal of a large depôt of water, which can be shifted about as required and made use of by other tissues, especially by the blood; whilst the other organs, even if they are richer in water than the skin, need all they contain for their own purposes. For this capacity of storing water, as also salt, the skin is indebted to the fact that it possesses the greatest total quantity of connective tissue.

Xanthomatosis is discussed in the next chapter.

In connection with the systemic endothelial or monocytic disease mentioned above, one sometimes sees in the skin not only hæmorrhages but also other macular and papular changes. Necropsy in all such cases reveals proliferation of the reticulo-endothelial tissue in the blood-building organs. Bykowa (1933) described an interesting case, in which there were scattered over the body single and confluent brown-red or blue-red lumps, reaching the size of walnuts. Histologically they showed proliferation of large cells with long processes. Of a total of 5,600 white blood-cells monocytes formed 78%. The blood-forming organs were found to have a high degree of atrophy of the parenchyma and proliferation of the large reticulo-endothelial cells. The case is summarised as a "subleucæmic reticulo-endotheliosis with involvement of the skin."

The R.E.S. also takes part in *acute inflammatory reactions*. The activeness of this participation is, however, dependent on the general state of the body, especially on that of the R.E.S. apparatus as a whole. Kauffmann took this as a basis for his investigations, in which he tried to correlate the local inflammatory reactivity of the skin with the general reactivity of the body, the skin being used as a test-organ. Of course, for *specific* purposes it had long been so used, as, for instance, in tuberculin, luetin or trichophytin reactions and also for non-infective allergic disorders. But Kauffmann showed that by examining local skin-reactions one could also draw conclusions as to the functional state of the R.E.S. in general. He examined systematically in pneumonia the kinds and numbers of the cells in cantharides blisters. He found a regular parallelism between the percentage of reticulo-endothelial elements and the contemporary state of illness of the patient. Schreiner and Wendlberger (1933 and 1934) have carried out similar investigations in dermatological conditions. They found a clear relationship between the percentage of histiocytes and the state of reactivity of the body. Thus, an unfavourable course of the disease was accompanied by a low percentage and *vice versâ*. A very conspicuous example is afforded by extensive and serious burns.

This method of investigation also gives us an insight into the action of various *therapeutic* measures, especially X-rays. The effect of X-rays on the R.E.S. had already been studied by means of vital staining in animals, but vital staining is not suitable for human studies. Using Kauffmann's method Schreiner and Wendlberger came to the conclusion that it does not make much difference which organ is irradiated, whether spleen, thymus or hypophysis, but that X-rays, at whatever spot they enter the body, act as a stimulus to the R.E.S. If this is so, it would be wrong to use X-rays where there is already excessive proliferation of R.E.S. elements. They also found from their cantharides blisters that there is a raised activity of the R.E.S. after the use of ultra-violet rays and substances which irritate the skin: this is especially the case if the body responds readily to the particular method of treatment. It has been said that the R.E.S. is implicated in the therapeutic mechanism of salvarsan and of bismuth, which is chiefly stored in its cells. But this is hardly borne out by Kolmer and Schamberg's experiments on rats and rabbits, at any rate as regards salvarsan. They found that partial blockade of the R.E.S. with Indian ink had no appreciable effect upon the trypanocidal and spirochæticidal activity of arsphenamine and neoarsphenamine. Splenectomy did profoundly influence the chemo-therapeutic action of these compounds. But whereas in rats infected with trypanosoma equiperdum splenectomy reduced the trypanocidal activity of arsphenamine, in rabbits infected with spirochæta pallida splenectomy actually increased its spirochæticidal power.

Bibliography

KOLMER, J. A., and SCHAMBERG, J. F. "The Influences of Reticulo-Endothelial Blockade and Splenectomy upon Experimental Trypanosomiasis and Syphilis," *Amer. Journ. of Syph.*, 1933, **17**, 176 (Abstr. *Brit. Journ. Derm.*, 1934, **46**, 109).

SCHREINER, K., and WENDLBERGER, J. "On the Reticulo-Endothelial System," *Zbl. der Hautkrank.*, 1934, **47**, 369.

CHAPTER VI

DISORDERS OF METABOLISM

Amyloidosis

General Amyloidosis. Amyloid is now considered a protein body, and its appearance in the tissues is no longer ascribed to degeneration but to infiltration as the result of a flooding of the body with protein substances that cannot be catabolised. The process particularly affects the spleen, liver, adrenals, intestine and kidneys, and it was formerly thought that connective tissue organs, such as the skin, dura mater and fasciæ were always spared.

The ordinary cases of amyloidosis occur in diseases known specially to favour it, such as chronic suppuration, tuberculosis and syphilis. But in addition to these there are certain atypical amyloidoses, which Lubarsch in 1929 described as "systematised amyloidoses." This group has four peculiarities:—(1) copious infiltration of unusual organs, such as lungs, muscles, alimentary system or skin, together with sparing of the usual sites; (2) deposit in the form of nodules; (3) a certain irregularity in the staining reactions; (4) absence of the predisposing illnesses. Many of this group show a marked systemic distribution, selecting, for instance, the muscles (Shields, 1930). All the reported cases in which there was a widespread infiltration of the skin, especially when this caused clinical manifestations, belong to this systematised group. On the other hand, in a large proportion of ordinary cases of general amyloidosis there is a certain amount of involvement of the skin, though usually slight and not clinically apparent.

General Histology. The amyloid appears in the form of columns, layers or cylinders, or takes the shape of collagen or muscle-fibres by filling up empty spaces left by tissue-disappear-

ance. It may be amorphous or crystalline. The process primarily attacks the vasculo-connective tissue apparatus, especially where the small arteries pass over into capillaries. A homogeneous ring is seen to take the place of muscle in the media and gradually to widen till it involves the intima and adventitia. In the supporting areolar tissue amyloid is deposited in the lymph-spaces and does not involve the supporting fibres except by pressure. The elastic fibres present considerable resistance, and rings of elastin in a mass of amyloid often mark the site of destroyed blood-vessels.

STAINING. In sections stained with gentian or methyl-violet amyloid appears bright red in contrast to the blue of the rest of the tissue.

Amyloid has a great affinity for Congo-red. Griessbach noticed that Congo-red can be injected intravenously in man without danger. In a normal subject the plasma has become uniformly dyed about 4 minutes after an injection of 10 c.c. of a 1% solution. Decolorisation begins after 10 minutes and is complete in 24 hours. Bennhold (1922) used this procedure to detect disturbed function of certain organs, examining the serum colorimetrically 4 minutes and 60 minutes after the injection. Now in amyloidosis the Congo-red leaves the circulation, passing through the damaged capillary endothelium, and becomes fixed in the neighbouring amyloid substance. The affected organs seem to act like a filter on the circulating dyed plasma. This power of binding the stain is in such a degree peculiar to amyloid that it can be used diagnostically. If, in the above method of investigation, the serum is more than 60% decolorised within the first hour after the injection (without large quantities of the colour appearing in the urine) the presence of amyloid is indicated. Congo-red also escapes rapidly from the circulation in nephroses, but in these it appears in the urine. Amyloid is the only substance that can be stained during life by Congo-red and trypan blue. Of course, small quantities of amyloid cannot be detected by this test.

Congo-red is also made use of for differential histological staining. The sections are placed for a short time in 1% Congo-red, dipped in lithium carbonate and differentiated in 80% alcohol. Alcohol is the best fixative.

CHEMISTRY AND PATHOGENESIS. Amyloid is one of the great group of hyalines, transparent homogeneous proteins. It has an especially high content of tyrosin. Chondroitin sulphuric acid,

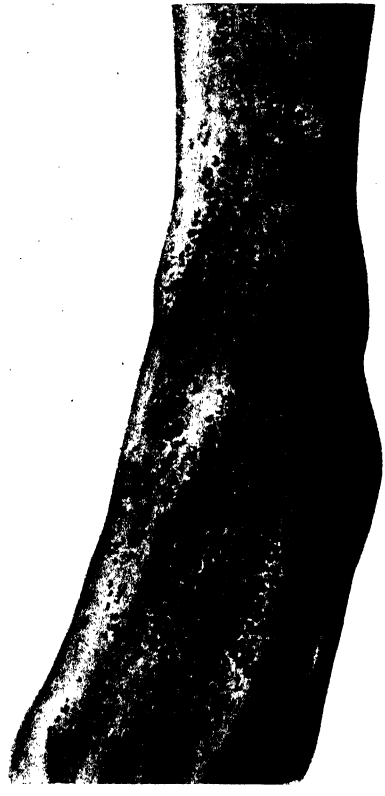


FIG. 8.– General amyloidosis. Dorsum of the foot. In addition to the skin-papules there are seen in the lower part of the leg swellings caused by massive infiltration of the fascia. (H. Königstein, *Jadassohn's Handbuch*, IV/3, p. 285.)

though not necessarily present in amyloid, is generally found in increased quantities in tissues infiltrated by it. Leupold thinks that it plays a part in causing the precipitation. This acid is excreted in increased quantities in the urine in patients with

PLATE IV.



General amyloidosis. Chest: wrinkling of the skin, transparent nodules, hæmorrhages and scars. (H. Königstein, *Jadassohn*'s *Handbuch*, IV/3, p. 274.)

[*To face p.* 141.

severe tuberculosis, which points to a raised protein catabolism. Some shifting in the protein metabolism is probably essential for amyloidosis. Schmidt's view, which is widely accepted, is that it results from transudation of a protein and its precipitation in the tissues. Some part is played in this precipitation by a ferment and possibly by chondroitin sulphuric acid. But as the amyloid protein molecule is too large to pass the vessel-wall (Schmiedeberg) Schmidt's hypothesis has been modified by the idea that outside the vessel a metamorphosis of the transuded protein from the sol- to the gel-state takes place under the influence of the reticulo-endothelium. A further reason for thinking that amyloid does not occur as such in the circulating blood is the fact that one can produce antibodies against it by sensitising rabbits. Animal and human amyloid behave identically with respect to such a specific antiserum.

Clinical Features. By the participation of the skin in general amyloidosis there arises an *exanthem*, the frequency of which is uncertain, as it has been neglected by general physicians. It is, nevertheless, so characteristic that sometimes an examination of the skin can give a clue to the diagnosis of the internal disease. The most characteristic lesions are hard, translucent, rather shiny nodules, varying in size from a pinhead to a bean, and only slightly coloured. They are sometimes rendered more conspicuous by the intervening skin being pigmented. They are seldom single, being mostly strewn over large areas of the body, but they may be collected into clusters (see Fig. 8). The smaller nodules are always free of pigment and cause a peculiar glistening of the skin. Sometimes there are little atrophic areas, and in some cases there is an alteration of consistency resembling sclerodermia (see Plate IV.). How far the sclerodermia-like state is a result of the amyloid deposit and whether it is the initial stage of the atrophy is not yet clear. L. Pick calls the condition "pseudo-sclerodermia amyloides." Gottron (1932) was the first to make a clinical diagnosis of systematised skin and muscle amyloidosis with the picture of sclerodermia amyloidosa and to substantiate it histologically. A characteristic of such cases is a macroglossia, depending on amyloid infiltration of the muscles of the tongue, with

hardening of the oral mucosa and pharynx. The skeletal muscles feel hard and appear hypertrophic but are weak and easily fatigued. There is loss of peristalsis of the alimentary canal and the colon is distended. Bennhold's Congo-red test is positive, and the histology characteristic. Therefore, in obscure diseases of the muscular and alimentary systems, histological examination of the skin may be of great diagnostic value.

HISTOLOGY OF SKIN-INFILTRATIONS. There may be considerable histological involvement of the skin without clinical manifestations. The amyloid forms subepidermal islands, tending to press up the epidermis, since the connective fibres deep to it offer a greater resistance. In the deeper layers of the skin it is especially associated with the hair-follicles and glands, and here, too, is deposited close to the epithelium. It is laid down in the lymph-spaces and in the small vessels. The subcutaneous fat is also a favoured site; here it takes origin from the capillaries. Its extent in the subcutaneous fat and in the cutis have no regular relationship. There is a general thinning of the epidermis, even where it is not stretched by underlying amyloid. There is no sign of tissue-reaction.

Now, as opposed to general amyloidosis, there are instances where the process is only local, affecting a single organ or part of one. The distinction between local and general amyloidosis is not only quantitative. Whereas the latter generally leads through cachexia to death, local amyloidosis runs, as a rule, a harmless course, though if situated in vital spots, such as in the heart, it may assume graver significance. Its commonest sites are the conjunctiva and then the respiratory tract.

Local Amyloidosis of the Skin. *Group I.* The amyloid accumulations are quite similar to those occurring in general or systematised amyloidosis, involving the vasculo-connective tissue and affecting all layers of the cutis. There is no doubt that amyloid can be precipitated in previously normal skin. This group, considered pathogenetically, really belongs to general amyloidosis. Itching, which is characteristic of the next group, does not occur at all in Group I. or in the generalised form.



FIG. 9. – Lichen amyloidosus: verrucose form. (A. M. H. Gray's case.)

Group II. includes the conditions which have been named by Gutmann "*amyloidosis localis cutis nodularis et disseminata*," and by Freudenthal "*lichen amyloidosus*." Most of the reported cases

belong in this group. In some of them the exclusive involvement of the skin was confirmed by necropsy, the other organs of the body being thoroughly examined histologically and found free from amyloid.

Clinical Features. The primary lesions are little transparent *nodules*, similar to those which occur in the general form. They are usually isolated, but occasionally they coalesce to form little tumours. In addition there is a variable degree of pigmentation and hyperkeratosis. The *hyperkeratosis* sometimes forms masses shaped like a convex lens, which are embedded in the underlying compressed epidermis. The disease especially affects the front of the legs. *Itching* is a constant association and may be so intense as to lead to deep excoriations. It may precede the eruption by many years ; but in this pre-eruptive stage amyloid can be found histologically. Nevertheless, there is no evidence that the pruritus is the direct result of deposit of amyloid, for it is not present in general amyloidosis nor in the local forms of Group I.

The clinical appearance may have a close resemblance to lichen ruber planus, the nodules having at times a polygonal outline, shiny surface and gyrate arrangement. It may also resemble prurigo, lichen Vidal and especially lichen verrucosus. But it is distinguished from them, quite apart from the histology, by its usually unchanging character, the translucency of the single nodules and its failure to respond even temporarily to treatment. Fig. 9 illustrates a case of Gray's, originally diagnosed as lichen verrucosus, which has been proved by Freudenthal to be amyloidosis. Gutmann stresses the clinical resemblance in many points to Pautrier's " lichénification chronique nodulaire." But certain cases have been described which do not resemble any other clinical picture (Freudenthal and Gutmann). In these, instead of tumour-formation, the predominant feature consists in *macular discoloration*.

Freudenthal has occasionally observed clinical regression, sometimes without scar-formation and sometimes leaving round, livid, slightly atrophic areas. But skin-amyloid is a substance of great durability, which obstinately withstands mechanical attacks and inflammatory processes and is therefore resorbed



Lichen amyloidosus verrucosus. The amyloid is stained red metachromatically by methyl violet (for simplicity of reproduction the blue component of the stain is represented as grey). (*a*) Two amyloid lumps escaping through the epidermis; (*b*) amyloid deposits around a hair-follicle and hair-muscles. (Semi-diagrammatic from material of W. Freudenthal.)

[*To face p.* 145.

with difficulty. Freudenthal has demonstrated in lichen amyloidosus the occasional elimination of clumps of amyloid through the epidermis.

Histology. In Group II., instead of thinning of the epidermis, there is acanthosis and hyperkeratosis. The histological structure of the nodules in the various clinical forms of lichen amyloidosus is very constant. The amyloid is almost confined to the papillæ; the blood-vessels are only slightly involved; the elastic tissue is almost completely destroyed in the amyloid areas; there is a moderate lymphocytic reaction (see Plate V.). In all these points the process differs from that in general amyloidosis and Group I. A further difference is found in the staining reactions. Whilst in general amyloidosis the substance is especially readily stained by Congo-red, in the lichenoid forms it is only electively stained by it in a modification worked out by Freudenthal, who found he could demonstrate it with more certainty by means of methyl-violet. From the papillæ the infiltrations spread laterally so as to obliterate the rete-pegs (Königstein). Hyperpigmentation is generally arranged around the hyperkeratosis covering a papilla full of amyloid.

But such amyloid infiltrations do not necessarily lead to the characteristic clinical transparent nodules and have often been found by Freudenthal, both in the lichenoid and in the macular types, in apparently normal skin far away from the eruption, for example, over the temple.

Pathogenesis. It might be objected that the lichenoid and verrucose forms are really lichen ruber, prurigo or lichen Vidal, in which the amyloid infiltration is only secondary. If that were so, one would expect to find quite a number of typical nodules which had not yet undergone that change; but examination of very large numbers showed the characteristic amyloid in all. In one case of Freudenthal's there developed on both legs a squamous epithelioma in areas involved by lichen amyloidosus. One of these epitheliomas was found to contain amyloid. Now it is not so very rare for epithelioma to contain amyloid; on the other hand, it is extremely rare for epithelioma to develop on ordinary lichen Vidal. This case is

especially significant in view of the epitheliomatous change occurring on both legs. Further, we have seen that not only in generalised but also in the localised forms of amyloidosis the substance can be deposited in apparently normal skin. Just as in the case of the itching and the formation of the characteristic nodules, it is uncertain whether the acanthosis and hyperkeratosis can be attributed directly to the amyloid deposit. Freudenthal and Königstein think that they all depend on a disturbance of protein metabolism leading to the development of a special kind of "prurigo diathèsique."

Senile Amyloid (Freudenthal): Secondary Deposit of Amyloid in already Diseased Skin. Freudenthal examined 3,000 biopsies from about 2,500 individuals for the presence of amyloid. The condition which was found to contain it most frequently was keratoma senile—32%—whilst verruca senilis only contained it in 20%. Of epitheliomas about 8% contained amyloid. The most common type to be affected was the metatypical, then the basal and least often the prickle-celled. In the case of epithelioma, as opposed to other conditions, amyloid is present even in specimens from covered parts of the body. It was also found occasionally in cylindroma, lentigo maligna, verruca vulgaris and nævus sebaceus. All these lesions are characterised by circumscribed epithelial proliferation. With few exceptions all the amyloid-containing specimens were from the face and in old people. The occurrence of amyloid in old people and on exposed parts, where the elastic tissue degenerates relatively early, together with the fact that in local amyloidosis the elastic tissue in the neighbourhood of the infiltrates is nearly always destroyed, suggest a direct connection between the amyloid and the elastic tissue. Possibly local amyloidosis is really a degenerative process of the supporting structures. Another possibility is that the degenerating elastin produces chondroitin sulphuric acid, which determines the precipitation of amyloid. But amyloid is not a regular constituent of senile skin, and there is no direct anatomical or histological evidence that it is a direct product of elastin or collagen.

Treatment of Amyloid. So far no satisfactory method of treatment has been worked out. It would be rational to give a

low protein diet, and in Gray's case it seemed to have a good effect. Arsenic has been tried, but with doubtful success. Local lesions can be destroyed with *high frequency fulguration*. In evaluating any method of treatment it is important to remember that occasionally, though rarely, spontaneous regressions take place.

Lipoid Disturbances

Till recent years only one lipoid disturbance of the skin was known, namely, that of cholesterol metabolism giving rise to xanthelasma or xanthoma. To-day we know a series of lipoid metabolic disturbances, which can be divided according to their chemistry into disturbances of cholesterol, phosphatide, cerasin or lipoid-protein. They can be further subdivided into general or local lipoidoses.

Xanthelasma, Xantheloid and Xanthoma. As regards nomenclature, "xanthoma" is a bad name for the disease generally so described, since it is not a blastoma. So-called "xanthoma cells" are not tumour-cells but lipoid-containing phagocytes and should either be called "foam-cells," from their appearance, or "lipoid cells." Urbach reserves the name "xanthoma" for the few true xanthomatous neoplasms, if indeed such really exist. Various tumours which may contain lipoid, such as fibroma xanthelasmaticum or lipoidicum and sarcoma xanthelasmaticum, he includes under the name "xantheloid." He uses "xanthelasma" to embrace all those lesions which have no autonomic growth but represent a local cellular reaction to cholesterol. In rare instances this reaction may take the form of large tumours; nevertheless, these are not neoplasms and can disappear again when their cause is removed. Urbach's nomenclature, which I adopt, is therefore as follows:—

I. Xanthelasma.
  (*a*) Infiltration xanthelasma (generally with hypercholesterolemia).
    (1) Xanthelasma palpebrarum.
    (2) Symptomatic xanthelasma.
    (3) Essential xanthelasma.

(*b*) Resorption xanthelasma (resulting from locally increased cholesterol supply. This corresponds to what was formerly called "pseudo-xanthoma").

II. Xantheloid.

III. Xanthoma (= xantho-blastoma).

XANTHELASMA. *Clinical Features.* The skin-manifestations may be localised, as in xanthelasma palpebrarum and some tumour-like forms, or perhaps more commonly they are disseminated. Any part of the skin may be involved. There is a rare diffuse type infiltrating extensive areas or even the whole integument. In generalised cases there is also involvement of mucous and serous membranes and internal organs. Morphologically one distinguishes xanthelasma planum, x.papulosum or tuberosum, x. tumoriforme and finally cholesterodermia. The first three can occur side by side. By cholestero- or xanthodermia one means diffuse yellow coloration of the skin depending on cholesterol infiltration of the cutaneous lymph-vessels. It may be difficult to distinguish clinically from xanthodermia lipochromica caused by excessive carotin or xanthophyll. The lesions of x.tumoriforme can reach the size of a mandarin, but in colour and consistency they resemble the tuberose form. Xanthelasmas are not always yellow: young lesions may be red and are sometimes surrounded by an inflammatory zone. The tuberose form may be soft, firm or fibrous, and vary in colour from straw-yellow or salmon-pink to violet or brown-red; hæmorrhages may even make them black. Glass-pressure will sometimes serve to bring out the yellow tint. Urbach states that in the tumour-like form the epidermis is always intact. But I have observed a case in a baby in which one group of tumours ulcerated and assumed a fungating aspect. They subsequently involuted spontaneously.

As regards time of onset one generally distinguishes congenital and juvenile from adult and pre-senile forms. But actual congenital cases are very rare, there being usually at least a few weeks before its appearance. The typical juvenile xanthelasmas generally appear within the first 12 years, taking the form of tumours with special preference for the extensor aspect of the

limbs. The nodules are often not yellow but red. In this stage the diagnosis may not be able to be clinched either clinically or histologically; later the central part pales and becomes yellow. They sometimes disappear spontaneously.

Though there is no essential difference between so-called symptomatic and essential xanthelasma it is characteristic for the lesions in diabetics to have an inflamed red or violet base, whilst their tips are yellow. There is sometimes a surrounding erythematous zone. The eruption tends to appear rather acutely, extend rapidly and often set up a moderate itching.

Urbach separates a group which he calls the "*resorption xanthelasmas*," in which there is resorption of local lipoid liberated as a result of local processes. Such processes are of an inflammatory or degenerative nature, such as scars, atrophic skin, nævi or fibromas. But even here it seems likely that there must be some general cholesterol disturbance, otherwise xanthelasmatic changes in these conditions would be commoner.

Histology. All forms of xanthelasma have fundamentally the same histology, the chief feature of which is the foam-cell, which Touton describes as follows: —a cell with distinct membrane, finely granular cytoplasm and large round or oval nucleus; it is packed with fat (more correctly lipoid) droplets; its size varies from that of an epithelial cell to the largest giant-cell; the number of nuclei varies between one and thirty. Nevertheless, the foam-cells are in no sense an essential or pathognomonic sign of xanthelasma; they represent, rather, a certain state of cellular elements of heterogeneous origin, which, as the result of cholesterol infiltration, assume the same honeycomb or foamy appearance (Corten). In studying the development of the smallest xanthelasma nodules, Arzt found that they begin with collections of fibroblasts. In a new-born baby he found only connective tissue proliferation and inflammatory changes. Only later, together with the development of the yellow colour in the formerly red nodules, could he find vacuolation of the protoplasm and the formation of typical foam-cells. In Whitehouse's case it seemed that the foam-cells arose from epithelioid cells. Kyrle has also described an epithelioid origin. Localised xanthelasma usually

begins immediately around the subpapillary blood-vessels with the development of cells of peculiar structure from the adventitial connective tissue cells. They are oval or round, rather larger than endothelial cells, and possess, when fixed by alcohol and stained by hæmatoxylin and eosin, finely honeycombed or foamy protoplasm with a darkly staining eccentric nucleus. Staining for fat reveals them to be filled with very fine granules.

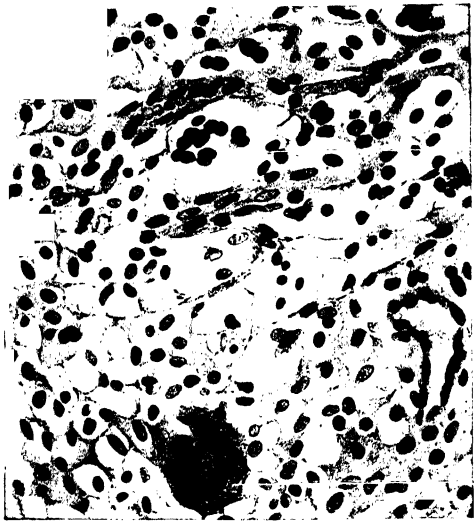


FIG. 10.—Xanthelasma giant cells: the upper one is the Langhans type and the lower one is the Touton type. (Arzt, *Jadassohn's Handbuch*, XII/2, p. 281.)

Thence the process spreads throughout the cutis. In addition to the foam-cells there are giant cells twice or many times their size (see Fig. 10). They have numerous peripheral nuclei, which form an uninterrupted circle (Touton's type), whilst giant cells of the Langhans type with half-moon-shaped arrangement of nuclei are rare. A further peculiarity of the Touton giant cells is that when fixed by alcohol they are seen to have a honeycomb structure, a conspicuous chromatin framework of the nuclei and commonly, according to Smith, giant

centrospheres. Rowland (1929) says that they are derived through coalescence and that he has never seen mitoses in foam-cells. There are also giant cells of the foreign body type. In most lesions one can see all transitional stages from the simple connective tissue cells up to the large polygonal foam and giant cells. Xanthelasmatic infiltration may become so massive that the cells lose their individual outline and elastic and connective tissue fibres are destroyed. In older nodes the foam-cells are much less conspicuous in comparison with connective tissue, so that one gets the impression of a fibroma in which a few lipoid cells are embedded. In the centre there may be a collection of doubly refractive particles which no longer have any obvious connection with cells; these are cholesterol crystals. If they have fallen out, their former presence can be detected from the whetstone-like shape of the empty spaces.

Histo-chemistry. The xanthelasmatic process consists essentially in the fact that lipoids, chiefly cholesterol fatty acid esters from the blood, are taken up by various types of cells, especially endothelial and fibroblasts, which they infiltrate and transform to foam-cells. But lymph-spaces (Johnson) and collagen bundles

	Nile Blue Sulphate.	Sudan III.	* Double Refraction.
Cholesterol ester.	Dark blue.	Brown-red.	Positive: disappears on warming, reappears on cooling.
Cholesterol ester fatty acid mixtures.	Dark blue.	Brown-red.	Positive only in presence of large proportion of cholesterol.
Lipoid substances.	Transition tints between red and blue.	Red.	Sometimes positive: disappears on warming, does not reappear on cooling.
Neutral fats.	Red.	Bright red.	Negative.
Fatty acids.	Dark blue.	Yellow.	Negative.

* The double refraction is preserved in Nile blue stain but is lost in the Sudan-stained sections. In fixation part of the anisotropic drops of cholesterol fatty acid esters turn into crystals which retain double refraction but do not take up the stain, whilst the rest of the drops stain specifically though they have lost their double refraction. As regards neutral fats and fatty acids Harrison states that though local fat is isotropic the crystals of neutral fats and fatty acids are invariably anisotropic, *i.e.*, doubly refractive.

can also, as an indication of lipoid infiltration, contain cholesterol crystals. Occasionally lipoid is diffusely spread in the tissue. Fresh or formalin sections examined in the polarisation microscope show the anisotropic substance, partly in the form of needles within and without the foam-cells and partly in amorphous masses; the latter disappear on warming the sections and reappear on cooling in the form of Maltese crosses, that is, round figures divided into four shining white quadrants by a dark cross. Sudan III. stains the foam-cells partly brownish-red and partly orange-red, the engulfed droplets showing the latter colour. The table on p. 151 shows some of the staining reactions and the anisotropism of the various fatty substances which have to be differentiated. The staining methods are not absolutely reliable, and cholesterol can sometimes still be demonstrated chemically when histological methods have failed to reveal it.

XANTHELOID. This name is applied to various tumours having the tendency to accumulate doubly refractive substances; the individual varieties might well be described in such terms as "fibroma xanthelasmaticum or lipoidicum." Typical foam-cells may be present or absent, and most of the tumours contain giant cells. The tumours generally consist of not very nuclear fibrillar tissue, which at first sight gives the impression of a fibroma or sarcoma. On closer examination one sees between the fibrils spindle-shaped elements which stain brown-red with Sudan III. and are doubly refractive. Nearly always there is, in addition, a pale yellow, finely granular, partly intra- and partly extra-cellular pigment: this is a blood-pigment and its irregularly sized granules are mostly much larger than those of melanin. Krogius (1923), who showed that neither the foam-cells nor the giant cells were constant, thinks that in no case is the cholesterol deposit the primary cause of the growths, but that it is a secondary manifestation, to which sarcomas are specially disposed. On the other hand, Wustmann (1925) considers at least the giant cell xanthelasmatic growths to be granulomas, provoked by the irritating action of cholesterol, which is being formed in excess in the body. According to Kirsch (1924) xantheloids are regularly accompanied by hypercholesterolemia, to which he attributes them, though he admits

that some local mechanism plays a part. It is, therefore, still a matter of dispute as to whether this class of tumour is blastomatous or granulomatous. Herxheimer suggests the expression "granuloma sarcoides xanthomatosum."

XANTHOMA. Is xanthoma an independent type of tumour? The majority of authors, including Pinkus and Pick, Lubarsch and Arzt, think not, as in recent years blastomas of the most varied origin have been found to have undergone xanthomatous alteration, and, secondly, the occurrence of foam-cells with doubly refractive lipoid has been recognised as a secondary process.

PATHO-CHEMISTRY AND ÆTIOLOGY. One now considers that both the so-called "essential" and the symptomatic xanthelasmas represent a cutaneous expression of the same metabolic disorder, possibly brought about by different causes, and that all forms, including xanthelasma, xantheloid and xanthoma, arise on a basis of a disturbed cholesterol metabolism. But the precise nature of this disturbance is still very baffling. Is cholesterol accumulated in the tissues because too much is being formed in the body? That there is a frequent association with hypercholesterolemia there is no doubt. Bloch found that of 136 cases of xanthelasma (in the wider sense used in this chapter) 71·33% had increased cholesterol in the blood, 19·85% a normal quantity, and 8·82% less than normal. Its long-recognised association with diabetes is also probably connected with the lipoidemia, so often a feature of it. But it is clear that hypercholesterolemia alone cannot cause xanthelasma. For a high blood-cholesterol occurs during pregnancy, the puerperium and menstruation and in many common disorders of the liver, pancreas and kidneys, reaching its highest figures in Bright's disease and obstructive jaundice. Yet it is only in a very small proportion of these common conditions that xanthelasma is found. Attempts to produce it in man by an artificial hypercholesterolemia have never succeeded.

Conversely we are confronted with the cases of xanthelasma in which the amount of cholesterol in the blood is normal or even below normal. But this does not necessarily mean either that there is no excess being produced or that there is no failure in excretion, for we know from general pathology that the blood

tends to keep its content of all substances as constant as possible, whilst the tissue, and in a special degree the connective tissue of the skin, acts as a depot for non-excreted metabolic products. An examination of the blood only gives a momentary picture of the process of transportation, and it is necessary to carry out *analyses of the tissue* to get a right idea of the degree of accumulation in the skin. These have recently shown that its connective tissue can accumulate cholesterol even up to twenty times the amount in the blood. The relationship of blood-cholesterol to tissue-cholesterol is illustrated by the experiment of Wacker and Hueck. After feeding rabbits for some months with cholesterol, there resulted an accumulation of it in the organs. When the feeding was stopped the blood-cholesterol rapidly fell to normal, but any physical exertion again raised it to an abnormal figure. So it appears that cholesterol is not stored in the blood but in certain depots from which, when necessary, it is again mobilised.

Recently Wile, Eckstein and Curtis, as the result of chemical examinations of xanthelasma tumours, have stated that cholesterol forms the smallest component of all lipoids and undergoes the least increase. In fact, they found that in xanthelasma there is no greater quantity of cholesterol in comparison to total lipoid than in the normal epidermis. They therefore doubted the importance of cholesterol and thought the cause of xanthelasma to be a pathological fat-metabolism. It is, however, unfair to compare the percentage of cholesterol in a subcutaneous or cutaneous xanthelasma with its percentage in the epidermis, where it is always relatively high. If a comparison is to be made between tumour and normal tissue, it should be normal dermis or subcutaneous connective tissue. Such estimations have been made by Nathan and Hermann, who found that whilst a xanthelasma contains 0·55% of cholesterol esters and 2·6% of cholesterol, the normal skin from the environment only holds 0·54% of cholesterol.

Bloch points out that unless we study the *laws of precipitation* we cannot make inferences, from a determination of the composition of xanthomatous lesions, as to the amount in the blood of the

individual constituents of the total lipids. Moreover, we do not know whether xanthomatous lesions cannot greatly change their composition in course of time, so that the analysis only gives a momentary picture. He emphasises the necessity of considering the physiology of the whole lipid system before we can evaluate any departure from the normal. The blood contains a whole series of lipid constituents, namely :—(1) the sterols (cholesterol), 0·11–0·15%, of which 70% are cholesterol esters and 30% free cholesterol ; (2) the phosphatides (such as lecithin, cephalin, etc.), 0·2–0·25% ; (3) neutral fats, fatty acids and soaps, about 0·4%. They exist in the form of a finely dispersed stable emulsion. It is necessary that this physical state, *i.e.*, the normal proportion of all the lipid constituents, should be maintained in the blood in order that the named substances (cholesterol, lecithin, etc.), contained in every living cell and essential to life, should be able rightly to fulfil their functions. If this proportion is considerably changed in any direction, there ensues a disturbance of the stable aqueous lipid emulsion, a coarsening of the lipid particles and, in favourable conditions, *e.g.*, in the tissue, a precipitation of one or all of the individual constituents, *i.e.*, there results a xanthelasma. If an animal or human being is given pure oil free from cholesterol, not only does the fat-content of the blood increase, but also the cholesterol content, and *vice versâ* ; the two changes occur side by side in order to avoid an upset of the lipid proportions. The body must, therefore, possess one or more mechanisms for regulating the lipid-content of the blood and tissues. So the estimation of only one constituent of the entire lipid complex in the blood is of little value : all the components must be estimated quantitatively. The relative values are of more importance than the absolute. It is essential to know the ratio of free to bound cholesterol. If possible, a dietary test, corresponding to the sugar-tolerance test, should be carried out. Five grammes of cholesterol in 100 c.c. of olive oil are given in the morning on an empty stomach and the free and bound cholesterol in the blood are determined after 4, 8 and 24 hours. In all the cases completely investigated by Bloch disturbance of the lipid metabolism was demonstrated in one or another direction :—(*a*) In the cholesterol

fraction : the total cholesterol-content in 1 case was increased by about 200% ; in 4 cases it was reduced, in 2 it was normal ; the quotient of free to bound cholesterol in 3 cases was abnormal. Only in 1 case were the quotient and the total quantity of cholesterol normal. The lack of hypercholesterolemia consequently does not exclude a disturbance in the cholesterol metabolism. (*b*) In the phosphatide fraction : in none of the cases was it normal. (*c*) In the neutral fat and fatty acid fraction : in 2 a great increase. (*d*) In the results of the dietary test : this was done twice and in both cases was pathological (once with reference to the cholesterol and once with reference to the phosphatide fraction). But Urbach warns against drawing too confident conclusions from the tolerance-tests, as the figures vary so much in individuals with apparently normal metabolism and liver.

The solubility or physico-chemical state of cholesterol is also influenced by the amount of *bile-acid* present with it (Schaaf). A diminution of bile-acid would impair the solubility of cholesterol, making it less easy for it to permeate the tissues without precipitation.

But if the cause is a general metabolic disorder why is it that in the same subject the various local lesions, such as xanthelasma tuberosum of the skin, xanthelasma palpebrarum, arcus senilis of the cornea, white plaques in the retina and atheroma in the arteries, so seldom co-exist ? And why does xanthelasma occur in such a small proportion of conditions associated with hypercholesterolemia ? There must clearly be some *local factors*. The frequent localisation of the tuberous form on the knees and elbows suggests a traumatic factor. Similarly xanthelasma has been observed to pick out scratch-marks and the sites of injections. In animals (though not in man) experimental xanthelasma has been produced by feeding with cholesterol, and its deposition at any particular site has been found to be favoured by the occurrence there of some inflammatory process. But in human subjects already suffering from xanthelasma all attempts to induce new lesions by means of chronic irritation, such as by the insertion of sterile silk threads, injections of lamp-black, etc., have failed. Circulatory, especially lymph, stasis has also been

blamed, but Arning found that the experimental subjection of xanthelasma nodules to Bier's congestion led to no increase in their size. Moreover, an examination of the majority of lesions does not give evidence of the constant occurrence of any inflammatory or other disorder prior to the infiltrative process. Chester concludes that the process is inflammatory, but that the first change is brought about by the harmful properties of the lipoid itself: the phagocytosis of the lipoids and the cellular exudation are responses to it and connective tissue proliferation completes the healing.

To answer many of the problems one seems forced to hypothecate some kind of "cholesterophilia" of the cells (Siemens). Why, for instance, do we find the deposit of cholesterol esters chiefly in the cutis, and so seldom in the internal organs? Why is just the skin of the eyelids so especially favoured? The cholesterol seems to have a special affinity for cells which, according to the work of Anitschkow, also readily take vital staining, the cells, in fact, which constitute Aschoff's *reticulo-endothelium* (see Chapter V.). Anitschkow was the first to show by staining with trypan blue the identity of the xanthophores (lipoid cells) with the macrophagic histiocytes. Masson showed that in palpebral xanthelasma the cells in the cutis together with the Langerhans cells of the epidermis (see p. 43) are infiltrated with lipoid and take the vital stain. Pautrier, Lévy and Diss, by injection of Sudanophil foreign bodies, also observed what they considered a cell-reticulum of trophic function between the vasculo-endothelium and the Langerhans cells. The stained particles were seen in the endothelium of the vessels, in the perithelial and connective tissue cells, which had become xanthelasmatic, as well as in the Langerhans cells of the overlying epidermis. Arzt and Rowland think that the cause of xanthelasma is a disturbance in the function of the reticulo-endothelial apparatus, especially that part of it situated in the skin. Kyrle's view is that there is a disorder of the whole reticulo-endothelial system, either congenital or acquired, leading to irregularity of cholesterol catabolism. In a minority of cases, according to his idea, only the cutaneous portion is damaged, explaining the absence of hypercholesterolemia

which would occur if the reticulo-endothelial apparatus of the liver were also involved. In certain cases, on the other hand, the latter may be affected, especially as a sequel of disease of the hepatic parenchyma, without the cutaneous reticulo-endothelium being damaged : in such cases there would be hypercholesterolemia without xanthelasma. That the foam-cells originate from reticulo-endothelial cells is supported by the tissue-culture experiments of Biedermann and Höfer (1930). They were able to grow cells from xanthelasmatic tissue removed during life which, in their morphology and movements, resembled reticulum-cells, but at the same time contained copious doubly refractive lipoid. The cholesterol esters, though brought in the blood and lymph in a dissolved state, appear in the tissue in the form of granules or crystals. Possibly they are changed by a specific metabolic action of the cells. It is even probable that the cells do not take up cholesterol esters or even cholesterol as such, but as some precursor substance (Thannhauser and Beumer). This would also explain those cases where no excess of cholesterol is found in the blood. But even if it is a fact that the reticulo-endothelial system plays an important part, it remains true that in generalised xanthelasmatosis other cells, smooth muscle fibres for instance, can also contain the lipoids.

One has long recognised a connection between *endocrine* organs, especially the sex-glands and adrenals, and the regulation of cholesterol metabolism. A greatly raised blood-cholesterol in xanthelasmatosis falls almost to normal during menstruation (E. Schmidt). Xanthelasma is relatively frequent at the climacteric. In a girl aged 15 years with extensive xanthelasma Schmidt observed this customary fall of blood-cholesterol to normal during menstruation, but at the same time the xanthelasma tumours became large and painful. He concluded that during menstruation an increased infiltration of the skin-lesions with cholesterol from the blood occurred. Berberich and Löwenthal observed doubling of the blood-cholesterol after removal of the ovaries. A similar effect was shown by Landau and McNee to follow extirpation of the adrenals. Nevertheless, it is only in a small fraction of cases of xanthelasma that one can find clear evidence of ovarian or other endocrine disturbance.

Parkes Weber was the first to draw attention to the *familial* factor. He, and after him, Pautrier, Lévy and others, found that in parents, brothers and sisters, and children of xanthelasmatic patients there is often a raised blood-cholesterol, atheroma of the aorta, cholelithiasis or other signs of a diathetic cholesterol disturbance. As regards the time of onset, Arzt distinguishes juvenile xanthelasma from other forms on the ground of its appearance before puberty and the absence of general disease. But Fasold found 9 cases of hereditary xanthelasma with liver-disorder and, on the other hand, familial xanthelasma which only appeared after puberty.

The cause of the *yellow colour* itself is uncertain, cholesterol and its esters not being yellow. Histo-chemical analysis of the anisotropic fat-substances has shown the presence of a body, not soluble in the usual fat-solvents, which is possibly the same as lipofuscin. Klinge and Wacker, after experimental feeding of mice with cholesterol, found in the connective tissue of the skin an alcohol-insoluble pigment, which stained red with Sudan and dark blue with Nile blue.

On the whole it is widely held that the primary disorder is a functional disturbance of the liver, which plays an important part in cholesterol metabolism, and is also the organ mainly responsible for its excretion. But xanthelasma may precede by many years the appearance of jaundice, and in generalised xanthelasmatosis chemical analysis shows no increase of cholesterol in the liver (Chiari), facts which appear to me to be against a primary hepatic origin.

Treatment. This must be directed in the first place to any associated diseases, such as diabetes, syphilis or liver-disease. A sugar-tolerance test should be done in all cases. As regards diabetes, Templeton and Chouret (1931) found that xanthelasma is more closely bound up with the disturbance of fat-metabolism, a secondary phenomenon, than with the diabetes itself. For they found in their case that a considerable improvement of the skin-manifestations followed the lowering of the cholesterol and total lipid content of the blood by means of a *fat-poor diet*, though the blood-sugar remained high. The xanthelasma disappeared

altogether after a course of *insulin*, which still further lowered the cholesterol and total lipid figure, whilst the blood-sugar still remained unchanged (294 mgm. per cent.). Occasionally a dietary cure of glycosuria may be followed by an actual increase of xanthelasma, especially if the diet is rich in fat. But even restriction of alimentary cholesterol does not always influence the xanthelasmas favourably, just as feeding large quantities does not necessarily aggravate it. In certain cases where the trouble seems to be due to disease of the liver Chalatow recommends giving *sunflower-oil* (boldoa frageans) 100–150 gm. per day. He ascribes the good effect to a specific stimulating effect on liver-function, favouring a destruction of the cholesterol and fat deposited in it, heightening fat-metabolism and leading to more rapid excretion of cholesterol through the bile. On the other hand, many other authors have reported success by means of a diet poor in cholesterol and fat, forbidding milk and milk-products, eggs, meat, fat and glandular organs. Wile, Eckstein and Curtis report the good effect of a *calorie-poor* diet such as is given for obesity.

Insulin also seems to act by way of influencing the fat and cholesterol content of the tissues and blood. Depancreatised dogs always have hypercholesterolemia. It was shown in 1924 that if they were at the same time kept on insulin such a hypercholesterolemia and hyperlipemia did not arise (Nitzescu and co-workers). This effect of insulin is only found in severe diabetes, and not in cases with normal blood-cholesterol. Insulin causes a much greater diminution of neutral fat in the blood than of lipoid in general and cholesterol in particular. Chauffard and Brodin suppose that insulin not only acts on the lipoid in the circulation, but also loosens that fixed in the tissues; they recommend it for non-diabetic cases also. Generally 30–50 units a day are enough.

Rothman (1927) in a case of diabetic xanthelasma with a high degree of lipemia, which did not improve on a diabetic diet, succeeded by means of *ultra-violet irradiation* in producing a substantial lowering of the blood-cholesterol and regression of the xanthelasma. The blood-sugar also dropped and the sugar-tolerance increased. Even xanthelasmatic areas not directly irradiated underwent involution, though more slowly. Rothman

thinks that light has a specific action on the cholesterol, altering it physico-chemically, so that it becomes more diffusible and more easily resorbed. Peyri has also had success with general ultra-violet irradiation.

Extra-cellular Cholesterolosis. In 1930 Kerl showed a case under the title "multiple formation of nodes containing copious lipoid." Urbach, as the result of the examination of 15 separate specimens of skin from lesions varying in their duration from two days to two years, drew attention to the fact that the cholesterol was never inside cells and that there were no foam-cells.

Clinical Features. The essential lesions started as lentil-sized, hard, translucent nodules, sometimes with a central blister. After one or two days they became blue-violet, generally with a yellow centre, and later still reddish-brown. They grew peripherally and tended to coalesce: there was some fine lamellar scaling. In the course of two years there was a very large number of outcrops of these nodules. Sometimes at the beginning the eruptions resembled erythema multiforme. The distribution was very extensive, including the mucous membrane of the nose and soft and hard palate. The skin of the chest, arms and thighs had a striking violet tint, as the result of numerous ill-defined little macules. The spleen was enlarged and hard. The nodules had a certain resemblance to Kaposi's "idiopathic sarcoma," but the localisation and histology were quite different. Some of the lesions disappeared spontaneously after a few days, and even nodes of many months' duration regressed considerably under X-rays.

Histology. Both the clinically normal skin and also the various stages of the nodes showed essentially similar changes, namely, vascularity of the cutis with severe damage to the vasculo-endothelium, an infiltration of round and spindle-cells, extensive cellular and nuclear disintegration and hæmorrhages, and infiltration of partly doubly-refractive lipoids, first round the vessels and later in the whole cutis. In none of the preparations was there the slightest indication of foam-cell formation. The lipoid was entirely extra-cellular and histo-chemically gave the reactions for cholesterol or cholesterol esters.

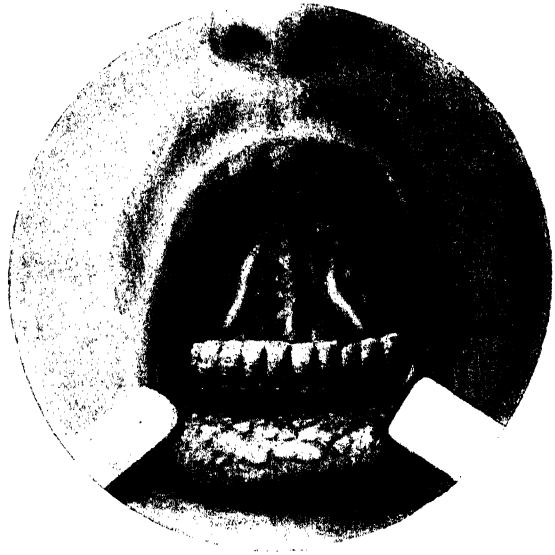
Metabolic Investigations. (1) The carbohydrate meta-

bolism was normal. (2) The results of a cholesterol-oil meal and the galactose test suggested disorder of the liver. (3) There was disturbance of the lipoid or cholesterol metabolism :—(*a*) portions of clinically unaltered skin contained twice as much cholesterol as that of normal controls, and the nodes contained five times as much ; (*b*) reversal of the cholesterol : cholesterol-ester quotient ; in this case it was 3·1 : 1, whereas in xanthelasma it is 1 : 3·6–5·1 ; (*c*) hypocholesterolemia : (*d*) absence of hypercholesterolemia even after cholesterol-oil feeding.

PATHOGENESIS. Urbach favours the view that the primary disorder is that of the lipoid or cholesterol metabolism and that free cholesterol is the aggressive agent which damages the endothelium. For in nodules less than 24 hours old, as also in clinically unaltered skin, there was evidence of primary damage to the endothelium of the vessels, the rest of the cutaneous tissue being quite normal. Further, nearly all the capillaries contained in their walls deposits staining brown-red with Sudan III, and not yet doubly refractive. On the patient being given 5 gm. of cholesterol in olive oil, there followed a macroscopically visible accumulation of cholesterol at the limbus, together with marked dilatation of the capillary loops at the corneo-sclerotic junction. He explains absence of hypercholesterolemia by the constant pouring-out of cholesterol into the tissues.

Lipoid Proteinosis. The mucous membrane lesions of this disease were first described by Wiethe in 1924. He thought it was a local deposit of hyaline in the upper air-passages. In 1928 Urbach, on the ground of histo-chemical and metabolic investigations, concluded that the disease was a constitutional process, characterised by general and local disturbance of fat-metabolism. He recognised the deposits as lipoids of the group of acetone-soluble phosphatides, bound by adsorption to protein. In 1929 he and Wiethe described 9 cases of the disease coming from 4 families. Since then several more have been reported by other observers. That the disease depends on inherited factors is suggested by the repeated finding of consanguinity of parents, familial incidence, congenital hoarseness and absence of the two upper incisor teeth.

PLATE VI.



Lipoid proteinosis. Yellowish-white infiltrations in the mucous membrane. (E. Urbach, *Jadassohn's Handbuch*, XII 2, p. 338.)

[*To face p.* 163.

CLINICAL FEATURES. The chief clinical manifestation of the mucous membrane involvement is a severe *hoarseness*. This is a constant symptom and appears generally in the first months of life and never later than the second year. In the developed disease all cases present fairly hard, yellowish-white infiltrations of the inner surface of the lips, soft palate, fauces, uvula or under-

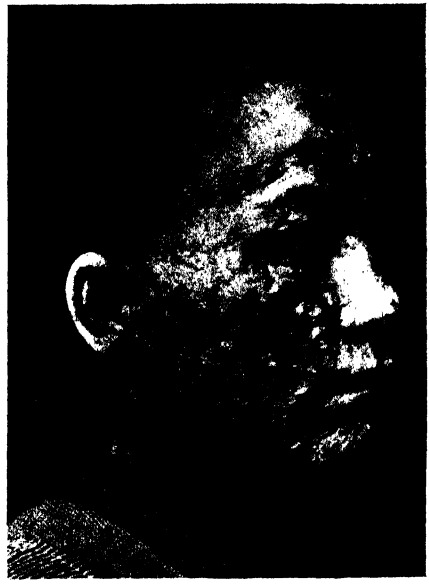


FIG. 11.—Lipoid proteinosis. (E. Hoffmann, *Jadassohn's Handbuch*, XII, 2, p. 336.)

surface of the tongue (see Plate VI.). There are also some scar-like depressions. The tongue is "wooden" and moves with difficulty. The larynx is similarly and severely involved. The cutaneous changes only develop much later and include two varieties. (*a*) *Nodular*. On the face are seen yellowish nodules mingled with varioliform scars and extensive sepia discoloration (see Fig. 11). The lid-margins present a row of white nodules and almost complete loss of lashes. Nodules in the scalp lead to

sparseness of hair. On the elbows are brown-violet or yellowish-white, firm, elastic nodules built up from many single papules. (*b*) *Hyperkeratotic.* On the fingers, especially the dorsum and sides and over the proximal interphalangeal joints, are numerous pin-head sized lesions grouped in mulberry-like, warty clusters



FIG. 12.—Lipoid proteinosis: wart-like growths. (E. Urbach's case.)

(see Fig. 12). The hyperkeratosis masks the nodular formation. Hyperkeratotic lesions also occur on the elbows and knees.

HISTOLOGY. The main points are:—(1) constant involvement of the vessel-walls; (2) histo-chemical demonstration of lipoid deposit in vessel-walls and areolar tissue; (3) vacuolation of the infiltrating masses in paraffin sections. The hyperkeratotic lesions show an especially great dilatation and thickening of the capillaries. The connective tissue largely loses its fibrillar struc-

ture, presenting horizontal bands of homogeneous, intensely acidophil substance.

HISTO-CHEMISTRY. The vacuoles are found by frozen sections stained by Sudan III. to contain a dark orange substance, which is also seen in stripes between the collagen fibres and round the vessels and hair-sheaths. Even in apparently normal skin, though in much slighter degree, typical lipoid mantles are found round the vessels. In one section, showing otherwise very little, lipoid was seen within the capillaries bounded by somewhat proliferated endothelial cells. This seemed to be the earliest stage. Various histo-chemical and micro-chemical tests prove this substance to be lipoid, but exclude cholesterol, fatty acids and neutral fats. The lipoid is soluble in boiling acetone, which distinguishes it from that composing the infiltrate in xanthelasma; reactions for phosphatide are positive. Urbach therefore assigns the substance to the group of acetone-soluble phosphatides. But as only a small part of the homogeneous masses can be removed by hot alcohol or boiling acetone it is thought that the lipoid must be bound to protein.

METABOLIC INVESTIGATIONS. In the majority there is a raised fasting blood-sugar or a pathological sugar-tolerance curve. The lipoids in the blood are increased, the cholesterol portion only to a slight extent. Chemical examination of the skin shows an actual diminution of ether-soluble lipoids, including lecithin and cholesterol.

PROGNOSIS AND TREATMENT. The disease is serious and not uncommonly dangerous to life. Children are in especial peril, owing to the possible complication of diphtheria or whooping cough. In general, its course is slowly progressive, though regressions are possible. In a case of Urbach's disappearance of the lesions followed the first pregnancy. Laryngotomy or tracheotomy is sometimes required. For the yellow nodules on the face Kromayer's electric punch is recommended. Causal treatment has not yet been evolved.

Necrobiosis Lipoidica Diabeticorum (Oppenheim—Urbach). Urbach in 1932 described under the title "multiple degenerative tissue-damage of the skin with extracellular lipoid deposits in a

case of severe diabetes " or " necrobiosis lipoidica seu diabetica " what he considered a new local lipoid metabolic disease depending on diabetes. Oppenheim recognised it as the same condition as he had observed in a diabetic woman in 1929 and which he called " dermatitis atrophicans maculosa lipoides diabetica."

CLINICAL FEATURES. In Urbach's case there was a history of gout and diabetes on the mother's side. The patient, who had diabetes, had been receiving for 3 years a diet rich in fat and poor in carbohydrates. There then appeared on the left calf a slowly growing red spot, followed by many similar ones, all on the lower extremities. According to Urbach there are no subjective symptoms, but in a case described by Klaber in 1933 each fresh lesion was preceded by itching. The lesions begin with an intensely red, hard, lentil-sized, peripherally growing raised papule. Later the centre sinks in, assumes a sclerodermia-like consistency and becomes sulphur-yellow. Round the periphery is a 2–3 mm. broad, violet-red zone. The yellow part is flecked with dark spots and traversed by numerous telangiectases. Sometimes there is a little scaling (Plate VII.). Balbi, in 1933, reported a case in a diabetic aged 55, which was characterised by numerous, ulcerated, necrotic lesions on the body and limbs. In Klaber's patient there were nodules, chiefly on the legs, which passed through several phases. They first appeared as small fawn-coloured papules, increased in size and became violaceous. There then developed a firm yellow plaque in the centre ; at this stage the nodules greatly resembled inflamed nodular xanthelasma. The firm yellow plaques softened and sometimes ulcerated, leading to a scanty thick discharge. The lesions continued to extend in area for a few weeks, at the same time flattening out. In their final stage they appeared as yellow-white atrophic patches surrounded by an irregular, scaly, red or violaceous, infiltrated zone with some marginal pigmentation. In a case of my own (1934) the clinical lesions tallied exactly with Urbach's description. She had a pronounced family-history of tuberculosis and a strongly positive tuberculin-reaction, and had previously had erythema nodosum in the same leg.

HISTOLOGY AND HISTO-CHEMISTRY. Urbach describes severe



"Necrobiosis Lipoidica. (Author's Case)."

[*To face p.* 166.

tissue-damage leading to necrosis in the cutis, associated with a conspicuous vascular alteration. The necrotic masses are infiltrated by a fat-like substance and also contain calcium phosphate and carbonate. In the neighbourhood of the necrotic tissue there appear, later, foreign-body giant cells and also foam-cells, resulting from the taking-up of locally deposited lipoid. The blood-vessels are dilated and thickened, and Balbi attributes the necrobiosis to vascular thrombosis. Klaber did not observe any marked vascular changes. In my case there was a very conspicuous and extensive necrosis of the collagen in the upper layers of the cutis and large numbers of droplets staining with Sudan III. in the necrotic zones. The droplets were all extracellular.

Pathogenesis. All the cases described have been frank diabetics except Klaber's and my own patients. But on investigation Klaber's patient was found to have a fasting blood-sugar of 300 mgm. per cent. and a typically diabetic sugar-tolerance curve. Her blood-cholesterol was within normal limits. In my case the blood-sugar curve was normal, as well as the blood-cholesterol. Balbi's patient had a marked hyperlipemia, hypercholesterolemia and hyperphosphatidemia. Urbach thinks it most probable that the seat of primary damage is in the blood-vessel walls and that it is caused by a toxin associated with the diabetes. This leads to necrobiosis in the connective tissue of the cutis, shown by loss of cell-outline and deposit of calcium salts. The lipoid seems to be secondarily imbibed from the blood. In Urbach and Balbi's cases the lipoid was isotropic (not doubly refractive), but Urbach predicted that it would be equally possible in other cases to find anisotropic cholesterol, according to whether there was a hypercholesterolemia or some other variety of hyperlipoidemia. Klaber did, in fact, find a few doubly refractive crystals in the centre of fatty foci.

Differential Diagnosis. Apart from nodular xanthelasma, there may be clinical resemblance to erythema induratum, Darier-Roussy sarcoid or dermatitis atrophicans. Urbach states that in erythema induratum and in sarcoids the central yellow coloration does not occur. This yellow central atrophy was, however, a

conspicuous feature of the case which I described in 1929 as "A Case of Clinical Morphœa with Tuberculous Histology". The lesions in this case, though more extensive, had a close clinical resemblance in all their features to those described by Urbach. The histology, however, was quite different, resembling that of tuberculosis, and the case is accepted by Volk as an instance of sclerodermia-like erythema induratum. It is to be noted that the late stages of necrobiosis may histologically resemble a granuloma. On the other hand, my case of necrobiosis, clinically and histologically unmistakable, had no diabetes but a strong tuberculous background. It is possible that sclerodermia-like erythema induratum and necrobiosis lipoidica are the same condition in different phases.

TREATMENT. Urbach found that improvement followed the administration of *insulin*, together with a relatively *fat-poor and carbohydrate-rich diet*. Klaber's patient was not benefited by X-rays. My patient is improving on *gold*.

Sclerema Neonatorum

The subject of certain indurative affections of the new-born has been clouded by a very confusing nomenclature. It has been greatly clarified by Gray, upon whose papers the following account is based.

CLINICAL FEATURES. This rather rare condition always occurs within the first few weeks of life and usually within the first few days. In a few recorded cases it has been present at birth. It consists of a gradually progressive hardening of the subcutaneous fat in sharply circumscribed areas. It particularly attacks, usually symmetrically, the calves of the legs, buttocks, scapular and deltoid regions and cheeks. It is not obviously associated with any other morbid condition. It can occur in either healthy or weakly infants, whose body-temperature may be normal, subnormal or even raised. In 1923 Gray and McNee described a case in which there developed a cystic swelling on one of the sclerema patches. It was found to contain broken-down fat and acicular crystals. Similar cysts were found in a subsequent case of Thursfield's.

HISTOLOGY. There is marked thickening of the subcutaneous trabeculæ, and from them masses of cells are seen invading the surrounding fat-lobules, penetrating and absorbing the septa between the fat-cells. Fibroblasts predominate, but there are also numerous foreign-body giant cells and a few lymphocytes and leucocytes. In ordinary stained sections numerous narrow clefts can be seen both in the fat-cells and in the surrounding cellular infiltrate. In sections cut in gum and stained with Sudan III. these clefts are found to contain acicular crystals, which are doubly refractive but do not take the Sudan stain; they are present in enormous numbers. In some parts, especially where there is no cellular infiltration, there is a considerable deposit of lime-salts. These histological appearances are found in all the cases of sclerema neonatorum that have been examined, whether the infant is of the healthy or unhealthy type.

CHEMISTRY. It used to be thought that the crystals were those of fatty acids, but in 1926 Channon and Harrison showed that they were composed of palmitin or stearin or both. The melting-point of sclerematous crystals, according to Harrison, is between 40° and 50° C., whilst that of crystals found in non-sclerematous fat (removed from infants at operations) is about 30° C. He attributes the higher melting-point to the presence of a higher percentage of palmitin. Now in sclerema fat, as compared with the subcutaneous fat of normal babies of the same age, this higher melting-point is associated with a lower iodine-value, which probably represents a decreased content of olein. This would, of course, result in a relatively increased proportion of palmitin.

Harrison found that saponification does not take place in the early stages of the disease; this has been confirmed by Kohnstam and Herbert and distinguishes the sclerema process from both pancreatic and traumatic fat-necrosis.

ÆTIOLOGY. The histology suggests that the earliest changes take place in the fat-cells and result in the formation of crystals in the fat-lobules. There follows a tissue-cell reaction, beginning in the trabeculæ, whereby the crystals are to some extent absorbed and the destroyed fat-cells replaced by connective tissue. The chemical investigations indicate that olein is gradually removed,

causing a rise in the melting-point, until the palmitin and possibly stearin crystallise out at body-temperature. It is unnecessary for the body-temperature to be lowered, as is so often supposed. In the four cases studied by Gray this was practically always up to 97° F. He found that in 50 healthy babies the temperature in 40% was only between 97° and 98° during the first 10 days. The cause of the removal of the olein is still unknown.

Differential Diagnosis. *Pre-agonic or cadaveric induration of the cellular adipose tissue.* This may appear not only in infants a few weeks old, but also later. It takes place during the ante-mortem agony in infants who have suffered from exhausting maladies, especially of the nature of athrepsia or infantile diarrhœa. It differs from sclerema in that it supervenes rapidly and involves diffusely the subcutaneous fatty tissue of the whole body. Histologically the changes seen in sclerema are absent, the fat appearing practically normal. Whilst fat affected by sclerema contains less olein than that of normal infants of the same age, it was shown many years ago by Langer that the fat of the new-born normally contains less olein than adult fat. This is not in itself enough to cause solidification *in vivo* at ordinary body-temperatures, but it is enough to do so if the body-temperature is much reduced, as in infants dying of wasting or dehydrating diseases. It also explains why it occurs in infants and not in adults, and why the induration occurs so suddenly and universally.

Œdema neonatorum. This is a condition of true œdema of the subcutaneous tissue, apparently due to a variety of causes not really dermatological. True *sclerodermia* has been met with in new-born infants, but differs in no way from the same disease in adults.

Carbohydrate Disturbances

As opposed to disorders of protein and of lipoid metabolism, carbohydrate disturbances are not known to give rise to any specific dermatoses. Moreover, their relationship to any disorder of the skin is very uncertain.

In most studies hyperglycæmia has been taken as the criterion

for a disturbed carbohydrate metabolism. Rost, in 1932, carried out careful sugar-tolerance estimations on 1,000 cases by means of intravenous injections of glucose by Wislicki's method. The essential points of this method are as follows. First the fasting-value is estimated after twelve hours' fasting. An intravenous injection is then given of 20 c.c. of 40% glucose. Blood-sugar estimations are made after 3, 5, 10, 15, 20, 30, 45, 50, 90 and 120 minutes by the microchemical method of Hagedorn-Jensen. The total examination therefore lasts two hours. He found that, though there may be no glycosuria or raised fasting-level in the blood, the curve may show a delayed drop. In many such cases diet and insulin treatment were successful in curing the dermatosis. Normal curves were obtained with regularity in *acne*, *seborrhœic eczema*, *furunculosis and other pyodermias*, *dermatitis toxica or venenata*, *carcinoma*, *tuberculosis and flexural pruritus* (*neuro-dermatitis*). As regards *eczema* the curve was normal except in a small group. There were two conditions in which pathological curves were often, though not always, found, namely, *dermatitis intertriginosa* and *psoriasis*. Of 84 cases of psoriasis only 58% had an absolutely normal curve. Tauber, in 1933, estimated the blood-sugar in 511 cases of skin-disease, comprising 254 cases of various affections and 257 cases of *furunculosis*, *pyodermia* and *ecthyma*. The method used was not so exhaustive and accurate as that of Rost. Tauber found that the blood-sugar in the former group averaged about 102·4 mgm. %, whilst in the furunculosis and pyodermia group the average figure was only 97·6 mgm. This prompted him to try giving these patients a high carbohydrate diet together with liver-extract and intravenous injections of 500 c.c. of 5% dextrose daily for six successive days. He reported rapid and beneficial results. Strickler and Adams investigated fluctuations of blood-sugar in 101 cases of *acne vulgaris*, and came to the same conclusion as Rost, namely, that there was no correlation.

Is hyperglycæmia itself harmful to the skin? Greenwood (1927) studied the dermatological conditions in 500 diabetic patients, and he concluded that diabetics have a higher incidence of skin-infection and other dermatoses than normal persons. As regards

fungous infections, the incidence is about the same, but the results tend to be more severe. The skin was moist in 74% and dry in 26%, but those with dry skin were twice as liable to infection. *Pruritus* appears to be more frequent in diabetics and to affect predominantly women. But these findings are not very reliable, as the non-diabetic controls were not examined by the same observer.

Milbradt (1931) applied modern functional tests of the liver and pancreas to a number of subjects of various skin-disorders. To test the function of the liver he used Althausen and Mancke's insulin-glucose-water test, which is thought to be specific for hepatic disturbances and probably to concern only its carbohydrate metabolism. The pancreatic function was tested by the Staub-Traugott method of two successive administrations of glucose. Normally the second dose causes a smaller rise in blood-sugar than the first, owing to the insulin which the first dose caused the pancreas to throw into the blood-stream. In insufficiency of the pancreas the second curve is not lower than the first. All controls gave negative results. He found an underaction of the pancreas in a large percentage of the cases of *pruritus* and follicular diseases (*furunculosis* and *folliculitis*) and in a smaller proportion of *psoriasis*. Hepatic disorder was found in a large percentage of *pruritus with lichenification* in contradistinction to pruritus without objective signs or with eczematisation. It was only occasionally found in chronic constitutional eczema. It was sometimes present in urticaria, toxicodermia, especially *salvarsan dermatitis*, lupus vulgaris, acne vulgaris, sclerodermia, dermatitis herpetiformis, pemphigus and rosacea. But the exact relationship is doubtful, and Milbradt thinks that only in a very small percentage are the cutaneous symptoms directly dependent on disorder of the liver and pancreas. He draws attention to Spiethoff's successful treatment of salvarsan and bismuth dermatitis with liver-extract. Pancreatic insufficiency is an indication for appropriate diet and insulin. Mu (1932) found that 8 out of 9 cases of arsphenamine dermatitis revealed a delayed blood-sugar curve and 4 had a high fasting blood-sugar content. The figures could be related to the extent and degree of the dermatitis. He thought that the blood-sugar changes were due to impaired

glycogen metabolism caused by the deleterious effect of arsphenamine on the liver, but admitted that the dermatitis itself might have been a causative factor in the hyperglycæmia.

Folin, Trimble and Newman (1927) found from animal experiments that the skin is an important outlet for sugar from the blood. It is not, however, a depot for glucose or glycogen, having no special capacity for holding and conserving carbohydrates; for in a fasting condition it contains practically no glycogen and only a trifle more sugar than skeletal muscle. But as a temporary receptacle in response to sugar-injections the importance of the skin seems very much greater than hitherto appreciated. The amount in the skin may, under certain circumstances, actually exceed that in the blood. The influx is the result of passive diffusion, and as the blood-sugar falls the skin-sugar flows back again into the blood.

Usher and Rabinowitch (1927) showed that dextrose is a normal constituent of sweat. They studied the rate of its excretion in subjects of eczema, both with and without an abnormal sugar-tolerance. The concentration was fairly constant in both groups. But they found that in all patients with diminished sugar-tolerance there was an increased *rate* of excretion after ingestion of dextrose, owing simply to an increased volume of sweat. There was, however, nothing in their observations to support their conclusion that the disturbance of carbohydrate metabolism had any relationship to the eczema. Moreover, they found that intradermal injections of dextrose 0·1–1 mgm. per c.c. produced no local reaction.

Somerford has made some interesting observations on the cause of hyperglycæmia in *eczematous* patients. For the purpose he divides them into four classes, according to the clinical stages, :—(1) erythema without abrasion accompanied by intense pruritus = *pruritic type;* (2) *vesicular type* with the formation of papules which later become vesicular and are still pruritic; (3) weeping eczema with diminution of the pruritus = *exudative type;* (4) *dry, non-pruritic type.* Taking the average sugar-curves of these groups he found that the vesicular gave the highest reading, then the pruritic, then the exudative (still above

normal), and finally the dry, non-pruritic, in which the figures were below the maximal normal. These figures suggest that in eczema there is a relationship between the pruritus and the hyperglycæmia. The hyperglycæmia appears to be highest while the epidermal exudate is retained in the tissue and presumably absorbed to some extent into the blood-stream. The blood-sugar falls as the exudate is voided externally. It is unlikely that the hyperglycæmia is the cause of the eczema, for in these cases the blood-sugar falls as the eczema gets better, and there is no subsequent development of diabetes. Moreover, in 10 such cases he found that the daily injection of insulin, though it reduced the blood-sugar and the pruritus, did not cure the eczema. If, on the other hand, the eczema causes the hyperglycæmia, it might do so by various mechanisms :—(1) stimulation of cutaneous nerves ; but the application of mustard till the skin was red and the patient complained of severe pruritus caused no alteration in the blood-sugar : (2) absorption of histamine or protein substances ; but injections of histamine large enough to cause marked general symptoms and intramuscular injections of sterile milk or whole blood failed to influence the blood-sugar : (3) hypothetical products of epidermal inflammation. In a series of cases of *dermatitis æstivalis* Somerford found a high hyperglycæmia. Now it was in this condition that Liebner concluded that products of actinic irritation are absorbed and carried to distant areas of the skin, which they sensitise. If this is so, it would seem likely that the accompanying hyperglycæmia might be due to the same absorbed products. If, therefore, the absorption is the cause of both autosensitisation-eczema (see p. 201) and hyperglycæmia, we should expect those suffering from autosensitisation-eczema from various causes to have hyperglycæmia. Somerford found that this is actually the case.

If, however, a disturbed carbohydrate metabolism in the sense of a hyperglycæmia is to be interpreted as a result of inflammation of the skin, it is remarkable that it occurs in so few types of dermatitis, at any rate according to Rost's results. It would appear that very specific substances must have to be elaborated from the skin to have this effect.

General Chemistry of the Skin

Urbach emphasises the importance of microchemical examination of freshly removed skin. The normal content of chlorides, non-protein nitrogen, sugar, uric acid, etc., is markedly different from that of the blood.

WATER. The water-content of the skin is high in infancy and old age and also in *obesity*, *sclerodermia*, *ichthyosis* and *eczema*. In eczema it is high even in apparently healthy areas, whereas in inflammatory conditions such as *erysipelas* normal values are obtained except in the affected part.

CHLORIDES. The skin is the chief storehouse of chlorides (von Frey). In all circumstances it is the tissue richest in chlorine, holding from a quarter to a third of the total body content. When chlorine is lost (from sweating, etc.) as much as 60–90% of the loss may be at the expense of the skin, although the weight of the skin is only 16% of the total weight of the body. In *pemphigus* and *dermatitis herpetiformis* there is an abnormal retention of chlorides in the skin. In some of the cases the fasting chloride value is normal, but it rises to a pathological figure after the intake of chloride.

NON-PROTEIN NITROGEN. In many cases associated with *pruritus* an increased non-protein nitrogen has been found in the skin, even in the absence of nephritis. In some the itching appears to be related to the presence of uric acid, the symptom being relieved by the administration of cinchophen. In this connection it is to be remembered that Schamberg and Brown (1923) found an increase of *blood* uric acid in 44% of cases comprising mainly *eczema* and *pruritus*. In 33% of the pruritus cases the blood uric acid was over 3·7 mgm. per cent. Barber has noted an increase of blood uric acid in certain cases of symmetrical palmar inflammation with hyperkeratosis (see Keratoderma Climactericum, p. 493). It is interesting to note that a prolonged protein-poor diet actually leads to an increase of uric acid in the skin (Urbach).

Calcium. Brookfield stresses the part played by calcium in the maintenance of correct ionic balance. The inter-digestive is the best period for absorption of calcium, as it is favoured by

an acid reaction of the upper intestinal tract and the presence therein of bile; it is hindered by excessive phosphorus in the diet and by alkalies. He himself showed that injection of a magnesium-salt causes a prompt lowering of the serum-calcium, and in rabbits he found a distinct inverse relation between the magnesium and calcium of the serum. Its availability to the tissues is favoured by the simultaneous exhibition of ammonium chloride. Of the various calcium-salts the *gluconate* and *lævulinate* have the advantage of solubility and freedom from irritant effects when given either orally or subcutaneously. It is necessary to give large doses. The usefulness of parathyroid is strictly limited, because, while it raises the serum-calcium, it does so at the expense of the calcium reserves in the skeleton. It probably drains calcium from other tissues too, including the skin. At any rate I have found that, in cases of pruritic exudative dermatoses in which calcium appeared to be doing good, the exhibition at the same time of parathyroid diminished its efficacy. Mole states that insulin causes a diminution of blood-phosphorus and a rise of blood-calcium.

In 1930 Schamberg and Brown introduced *calcium thiosulphate* for post-arsenobenzol complications, and in 1932 Schamberg and Wright quote Cannon as having employed it in cases of arsphenamine dermatitis with excellent results. It was especially effective in drying up surface-exudation. The dose recommended was ½ gm. daily for three days and subsequently two or three times a week. McLachlan describes 2 cases of "914" dermatitis and 2 cases of bismuth dermatitis treated with calcium thiosulphate intravenously with good results.

Calcinosis cutis. Maloney and Bloom distinguish (1) local: deposits in long-standing inflammatory lesions, such as old lupus nodules, and in certain tumours; (2) general: this is subdivided into (*a*) metastatic: associated with bone-destruction and presumably due to excessive amounts of calcium in the blood; (*b*) metabolic. Steinitz further subdivides the metabolic group into circumscribed and universal.

Calcinosis circumscripta is characterised by slowly growing circumscribed deposits of lime-salts, which begin as small hard

nodules and grow to about the size of a large pea. The overlying epidermis becomes thin and ruptures. The calcareous mass is extruded and healing rapidly ensues. The lesions are most commonly situated on the hands, in the neighbourhood of the small joints, and are usually multiple. The next most common sites are the extensor surfaces of other joints and rarely the trunk. Tate and Trumper (1933) described severe calcinosis confined to



FIG. 13.—Calcinosis circumscripta of the scrotum. (D. C. Tate and H. B. Trumper, *Brit. Journ. Derm. and Syph.*, 1933, p. 416.)

the scrotum in a patient aged 57 years. The scrotum was covered with small tumours varying in size from a pin's head to a large pea (see Fig. 13). The condition had been present since the age of 17 years. Histological examination revealed deposits in the connective tissue of the dermis, separated from one another by dense fibrous tissue. There was a little inflammatory reaction around the superficial parts, which were breaking down, but none around the deeper masses. The material was found to consist

chiefly of phosphate with a small amount of carbonate. Flame-tests showed sodium and calcium.

In *calcinosis universalis* the calcareous deposits occur as large plaques in the skin and subcutis and also in the connective tissue of fascia, nerve-sheaths and muscles. It may be widespread throughout the vascular system. There is often severe ulceration with secondary infection following the disintegration of the masses. The disease may end fatally. Histological examination shows the subcutaneous fat and deeper connective tissues to be infiltrated by large ill-defined masses of calcium-salts, which may be surrounded by slight inflammatory reactions. The deposits consist of a mixture of calcium phosphate and carbonate, the phosphate preponderating.

Weidman and Shaffer's case of *metastatic calcinosis cutis* differed widely from both these types. The calcium was deposited not only in the connective tissues but also in the sweat-glands and diffusely throughout the epidermis, where it was largely intracellular.

Ætiology. In the metastatic cases it is probable that the calcium comes from the bones *viâ* the blood-stream to the skin, where it is deposited, possibly as an attempted excretion. In the other cases it is suggested that it is due to some error in calcium-metabolism. In Tate and Trumper's case, in which a blood-examination was refused, it is difficult to conceive of so localised a condition of such long duration being due to a general disturbance of calcium-metabolism. Moreover, biochemical investigations in other cases do not lend support to that view. It seems more probable that it is caused by some primary local change. In a universal case reported by Bolam the histological picture suggested that the calcification followed some degenerative change in the fat-lobules. It is noteworthy that the lesions occur chiefly where the subcutaneous fat is either naturally scanty or diminished as the result of disease, as in sclerodermia. The association between calcinosis and sclerodermia has been emphasised by several writers; of 71 cases of circumscribed and 34 of universal calcinosis collected by Steinitz it was present in nearly a third. He also points out a definite association in certain cases between the onset of calcinosis

and puberty, childbirth or the menopause, and suggests a possible endocrine basis. Tate and Trumper's case began shortly after puberty.

Bibliography

BALBI, E. "Researches into the Pathogenesis of Necrobiosis Lipoidica Diabeticorum (Urbach-Oppenheim)," *Giorn. Ital. di Derm. e Siph.*, 1933, **74,** 14 (Abstr. *Brit. Journ. Derm. and Syph.*, 1934, **46,** 41).

BIEDERMANN, W., and HÖFER, K. "Ergebnisse der Züchtung von menschlichem Xanthomgewebe *in vitro*," *Arch. für exper. Zellforschg.*, 1930, **10,** 93 (*cit.* Urbach).

BLOCH, B. "Metabolism, Endocrine Glands and Skin Diseases, with special reference to Acne Vulgaris and Xanthoma," *Brit. Journ. Derm. and Syph.*, 1931, **43,** 61.

BOLAM, M. "Calcinosis," *Brit. Journ Derm. and Syph.*, 1935, **47,** 340.

BROOKFIELD, R. W. "Calcium," *Brit. Med. Journ.*, 1933, **1,** 542.

CHANNON, H. J., and HARRISON, G. A. "The Chemical Nature of the Subcutaneous Fat in the Normal and Sclerematous Infant," *Biochem. Journ.*, 1926, **20,** 84 (*cit.* Gray).

FREUDENTHAL, W. "Amyloid in der Haut," *Arch. für Derm. und Syph.*, 1930, **162,** 40 (*cit.* Königstein).

GOLDSMITH, W. N. (*a*) "A Case of Clinical Morphœa with Tuberculous Histology," *Brit. Journ. Derm. and Syph.*, 1929, **41,** 226. (*b*) "Necrobiosis Lipoidica in a Non-diabetic," *Proc. Roy. Soc. Med.*, 1935, **28,** 363.

GRAY, A. M. H. (*a*) "Sclerema Neonatorum," *Arch. of Derm. and Syph.*, 1926, **14,** 635. (*b*) "On the Identity of Adiponecrosis Subcutanea Neonatorum with Sclerema Neonatorum," *Brit. Journ. Derm. and Syph.*, 1933, **45,** 498.

GREENWOOD, A. M. "A Study of the Skin in Five Hundred Cases of Diabetes," *Journ. Amer. Med. Assoc.*, 1927, **89,** 774.

HARRISON, G. A. "Sclerema Neonatorum," *Arch. of Dis. in Childhood*, 1926, **1,** 63 (*cit.* Gray).

KLABER, R. "Necrobiosis Lipoidica Diabeticorum," *Proc. Roy. Soc. Med.*, 1934, **27,** 713.

KÖNIGSTEIN, H. "Amyloidosis," *Jadassohn's Handbuch der Haut u. Geschlechtskr.*, 1932, **4 3,** 254.

MCLACHLAN, A. E. W. "Calcium Thiosulphate in the Treatment of the Complications of '914' and Bismuth Administration in Syphilis," *Brit. Med. Journ.*, 1933, **1,** 916.

MALONEY, E. R., and BLOOM, D. "Cutaneous Calcinosis," *Arch. of Derm. and Syph.*, 1931, **23,** 245 (*cit.* Tate and Trumper).

MILBRADT, W. "Contribution to Carbohydrate Metabolism in Dermatoses on the basis of Modern Functional Tests of the Liver and Pancreas," *Arch. für Derm. u. Syph.*, 1931, **164,** 399.

MU, J.-W. "Blood Sugar in Arsphenamine Dermatitis," *Chinese Med. Journ.*, 1932, **46,** 449. (Abstr. *Brit. Journ. Derm.*, 1933, **45,** 40.)

PAUTRIER, L. M., LÉVY, G., and DISS, A. "Dermo-epidermic Interchanges as controlled by the study of Melanic Pigment, the Esters of Cholesterol (Xanthoma) and Hæmosiderin (Schamberg's disease)," *Arch. of Derm. and Syph.*, 1928, **17,** 1 (*cit.* Urbach).

ROST, G. A. "Hyperglycæmia and Skin Diseases," *Brit. Journ. Derm. and Syph.*, 1932, **44,** 57.

ROWLAND, R. S. "Xanthomatosis and the Reticulo-Edothelial System," *Arch. int. Med.*, 1928, **42**, 611 (*cit.* Urbach).

SCHMIDT, M. B. "Amyloidproblem," *Med. Welt*, 1932, **6**, 656 (*cit.* Königstein).

SOMERFORD, A. R. "The Cause of Hyperglycæmia in Eczematous Patients," *Brit. Journ. Derm. and Syph.*, 1932, **44**, 476.

STEINITZ, H. "Calcinosis Circumscripta and Calcinosis Universalis," *Klin. Woch.*, 1931, **10**, 1132 (*cit.* Tate and Trumper).

TATE, D. C., and TRUMPER, H. B. "Calcinosis Cutis," *Brit. Journ. Derm. and Syph.*, 1933, **45**, 413.

TAUBER, E. B. "Hyperglycæmia in Diseases of the Skin," *Arch. of Derm. and Syph.*, 1933, **27**, 198. (Abstr. *Brit. Journ. Derm. and Syph.*, 1933, **45**, 377).

TEMPLETON, H. J., and CHOURET, E. E. "Xanthoma Diabeticorum," *Arch. of Derm. and Syph.*, 1931, **24**, 604 (*cit.* Urbach).

URBACH, E. (*a*) "Die Bedeutung der gewebschemischen Untersuchungsmethodik für das Studium der Physiologie und Pathologie der Haut," *Münch. med. Woch.*, 1931, **78**, 89. (Abstr. *Brit. Med. Journ.*, 1931, **1**, 652). (*b*) "Lipoidstoffwechselerkrankungen der Haut," *Jadassohn's Handbuch der Haut u. Geschlechtskr.*, 1932, **12**/**2**, 238.

USHER, B., and RABINOWITCH, I. M. "Excretion of Sugar in Sweat: its relationship to Eczema," *Arch. of Derm. and Syph.*, 1927, **16**, 706.

WEBER, F. P. "Cutaneous Xanthomas and 'Xanthomatosis' of other Parts of the Body," London: Lewis, 1924 (*cit.* Urbach).

WILE, U. J., ECKSTEIN, H. C., and CURTIS, A. C. "Lipid Studies in Xanthoma," *Arch. of Derm. and Syph.*, 1929, **19**, 35 (*cit.* Urbach).

CHAPTER VII

ALLERGY

THIS subject is beset by a large number of confusing technical terms, such as "anaphylaxis," "allergy," "idiosyncrasy," "antigen," "antibody," "allergens," "atopy," "atopens" and "reagins." These represent different aspects, some clinical and some pathological, of the complex processes of immunobiology, which are susceptible of infinite addition and modification according to the extent and depth of our knowledge. It is therefore a mistake to attempt too rigid a definition of any of these terms, as that necessitates a continual invention of new ones. It is, however, an even greater mistake to use them in a totally wrong sense or in conditions where the processes they connote are in no way established. At the end of the chapter I have given what seems to me in the present state of our knowledge the most practical definition of the most important terms.

We are faced with certain clinical puzzles, which resolve themselves very broadly into the two questions:—(1) Why does an individual skin show conspicuous alterations in its reactivity to particular substances? (2) Why are some individuals so much more sensitive to certain substances than the great majority of their fellows? The first question is the problem of allergy, the second that of idiosyncrasy.

The name "allergy" was given by von Pirquet to a phenomenon studied by him from 1905 to 1910. He experimented with the "cuti-reaction," *i.e.*, the results of placing certain substances on a scarified area of the human skin. He studied many immunity-conferring diseases and especially vaccinia and tuberculosis. One was already aware of the difference between the effect of a first vaccination with cow-pox and that of a revaccination, according to the degree and duration of the "immunity" produced by the

first. In tuberculosis he discovered the apparently opposite phenomenon, namely, that subjects with an active or latent infection gave a positive reaction to Koch's tuberculin, whilst non-infected persons did not. In the last stages of miliary tuberculosis or under the influence of pathological states known to favour its dissemination, such as measles and typhoid fever, the cuti-reaction was found to be weaker. He interpreted this as a sign of the lowering of the body's power of resistance. Koch showed that a second local inoculation of tubercle-bacilli into the skin of a guinea-pig resulted in a lesion which took quite a different course from that following the first inoculation. It is just this change in reactivity to repeated administration of the same foreign substance that von Pirquet called "allergy." It is wrong to identify this term with over-reactivity. If we call the original reactivity "*normergy*," then allergy includes "*hyperergy*" (*increased reaction*), "*hypoergy*" (*diminished reaction*), and "*anergy*" (*absence of reaction*). The term also connotes specificity.

In 1909 Bloch and Massini showed that, just as tuberculous patients gave a positive reaction to tuberculin, so persons infected with trichophyton or favus gave a positive skin-test to the fungus-extract trichophytin.

Before going into the mechanism I will refer quite briefly to a few illustrative examples of various kinds of cutaneous allergy.

In *syphilis*, after the entry of the spirochætes, 3 to 4 weeks elapse during which nothing obvious happens. Then there appears at the site of inoculation a quite small inflammatory lesion teeming with spirochætes. If further inoculations of spirochætes take place during those first 3 weeks, similar primary lesions may appear after similar incubation-periods. In the meanwhile the organisms have spread to all parts of the body, and 3–4 weeks after the first appearance of a chancre general manifestations known as the "secondaries" appear. The beginning of this period represents a great change in the reaction of the whole body towards the spirochæte, and thereafter all chancres, in whatever stage they may be, involute, and a further inoculation of spirochætes no longer causes a local reaction of that type. That this pheno-

menon is due to allergy and not to a change in the spirochætes is shown by the fact that material from a secondary lesion inoculated into an uninfected subject gives rise as before to a chancre. In secondary lesions the spirochætes are numerous but not quite so numerous as in the chancre, though the degree of inflammation may be greater. In the tertiary period, though the lesions may involve enormous tissue-damage, it is extremely difficult to demonstrate the presence of any spirochætes. There appears to be a local sensitisation to such a degree that minimal numbers or perhaps even fractions of the infective agent are able to evoke an exaggerated response. Warthin has sought to show that the scarcity of spirochætes in the lesions of malignant syphilis and gummas and their destructive character are explained by their being essentially anæmic infarcts produced by obliterative endarteritis. But if this is so it seems to me difficult to explain the rapid healing which follows treatment with anti-syphilitic drugs.

The part played by allergy in tuberculosis and fungous infections is dealt with in the two following chapters. In this chapter we shall be chiefly concerned with the varieties of allergy represented by the following examples: -sensitisation to exogenous substances, such as plant-juices, insect-poisons and simple chemicals like phenylhydrazine, paraphenylenediamine or mercury and to endogenous substances, such as various foods, and chemicals like phenolphthalein and aspirin.

In trying to explain these specific changes of reactivity it is natural to suspect that the same mechanism may be at work as in the classical experimental sensitisation of animals known as "anaphylaxis," which represents a particular example or variety of allergy. In order to see how far its mechanism can be extended to other allergic manifestations, we must first consider rather carefully the essential features of anaphylaxis, especially in view of some modern additions to our knowledge of it.

Anaphylaxis

The essentials are as follows:—a preparatory injection of a substance of a certain class (generically referred to as the

" antigen ") in a sub-toxic dose produces in an animal after an interval of 10–20 days a modification, thanks to which, if one gives a second injection of the same substance, a reaction occurs known as " anaphylactic shock." Classical experimental anaphylaxis has generally been performed by sensitising the guinea-pig to horse-serum. Contrary to earlier views, the amount of serum required to produce sensitisation is extremely small, namely, about 0·000001 gm., whilst the amount required to cause anaphylactic shock in the sensitised animal is about 0·01–0·1 c.c. (Topley). This sensitive state can be transferred to another animal by injecting it with the serum of the anaphylactic animal. Even this passive sensitisation requires a short latent period. It is this possibility of passive transmission by means of the serum which forms the basis of the conception that new substances appear in it, called " antibodies," the interaction of which with the antigen is responsible for the anaphylactic symptoms. Many experiments, especially with Dale's technique, using the excised perfused uterus of a guinea-pig, seem to show that the antibody has to become fixed to tissue-cells before its interaction with antigen can produce anaphylactic symptoms. As a general rule, to produce " shock " the second injection has to be given intravenously, but this is not absolutely essential. Thus in a man sensitised to chloroplatinite of potassium Vallery-Radot and Blamoutier have described serious shock as a result of a skin-test with this salt.

Arthus demonstrated that in the same species of animal the symptoms produced by various non-toxic antigens are the same, but, on the other hand, that with different species and the same antigen the point of attack varies. From this it was argued that the symptoms are due in all cases to the same substance, possibly histamine set free from cells by the antigen-antibody interaction. If histamine is injected it produces pharmacological symptoms like those of anaphylaxis and the same variations according to the species of animal. If the test-injection is made subcutaneously instead of intravenously, a local inflammation known as " Arthus' phenomenon " arises.

The anaphylactic state can be abolished by introducing enough antigen parenterally to saturate (as is thought) the antibodies.

The majority of experiments on anaphylaxis have been performed on the guinea-pig. In man, anaphylactic shock, which is rare, has been stated by Richet and Widal to be accompanied by a group of humoral phenomena known as "hæmoclasia."

HÆMOCLASIA. This is said to comprise hypotension, leucopenia, diminution of erythrocytes, inversion of the leucocytic formula, rarefication of the platelets, hypo- or hypercoagulability of the blood, lowering of the refractive index and variations in the viscosity, surface-tension, electrical conductivity, *p*H, relationship of potassium to calcium, etc. Though many at any rate of these changes occur with some constancy in anaphylactic shock, they can also be produced by many other agencies and must be looked on as part of the symptomatology and not an essential expression of anaphylaxis.

In 1920 Widal described a new test for liver-function under the title "digestive hæmoclasis." From experiments on dogs he claimed to have proved that during protein-digestion the peptones absorbed from the intestines are normally arrested by the liver (proteopexic function) and do not reach the general circulation, and that a protein meal excites "digestion leucocytosis." On the other hand, intravenous injection of peptone into a fasting dog immediately provokes hæmoclasic crisis, namely, leucopenia with relative lymphocytosis, fall of blood-pressure, hypercoagulability and decrease of the refractometric index of the serum. These data he then applied as a test for hepatic insufficiency in man with the idea that in liver-disease there is impairment of the proteopexic function, allowing the peptones to reach the circulation and so cause hæmoclasia. Now Widal says that in practice all that is required for the test is a series of leucocytic counts.

But subsequent work, leaving aside the question of liver-function, has shown the leucocyte-count to be utterly unreliable as a sign of hæmoclasia. Shaw states that during physiological rest the number of white cells in the peripheral blood is subject to considerable and rapid fluctuations. He found no evidence that ingestion of milk, casein, butter, fat or distilled water or local application of cold had any influence on the leucocytic content of the peripheral capillary blood. He concluded that the phenomena

of "digestion-leucocytosis" and "digestion-leucopenia" are nothing more than physiological variations. Simpson has confirmed these findings. He has observed in a normal subject a variation between 2,800 and 11,200. He could trace no kind of constancy in these fluctuations. Even successive counts at intervals of a few minutes revealed only a capricious irregularity. I have drawn special attention to this matter for the following reason. Even in present-day literature a clinical phenomenon under debate is often attributed to an allergic (meaning anaphylactic) process because it is associated with hæmoclasia, and the presence of hæmoclasia is inferred from a fluctuation in the leucocyte-count. This whole argument is fallacious.

Antigens and Haptens. The *in vitro* reaction that enables us most easily to detect an antigen is its capacity for forming a precipitate when mixed with a serum containing the corresponding antibody. An antigen in the full sense has the power of inducing the formation of that antibody when injected into the tissues of a suitable animal. The majority of the known complete antigens in the above sense are proteins or have a protein component. But Landsteiner and others have shown that if certain chemical groups are combined with different proteins they confer on the latter their own specificity, even though the proteins themselves are immunologically distinct. To obtain actual precipitation Landsteiner found it necessary to use the complete antigen. For example, the serum prepared against a metanilic acid horse-serum antigen will give a precipitate, not only with this antigen, but also with a metanilic acid chicken-serum, but it will not give a precipitate with metanilic acid alone or with either of the uncompounded sera. On the other hand, he found that the relatively simple chemical groups would unite specifically with the antibody present in the antiserum so as to inhibit the precipitation by it of the complete antigen containing the same chemical group. He was led to formulate the conception of partial antigen, the "hapten" as he called it, namely, the part of the antigenic complex that carries the specific reacting group. These haptens, though they are not capable of giving rise to the formation of the corresponding antibodies, will combine specifically with

them when produced in response to the injection of the complete antigen.

There are many substances, particularly among the polysaccharides separated from bacterial cells, that behave as haptens but differ from the simple haptens of Landsteiner in that they form a precipitate when mixed in the test-tube with the corresponding antiserum. This capacity is probably a function of molecular size and complexity, and such substances are called "complex haptens." But Landsteiner and van der Scheer (1932) have shown that relatively simple substances, such as some azo-dyes, will give specific precipitation with the corresponding antisera without previous linkage to protein.

So, according to Landsteiner, who is followed by Topley, though a complex hapten can form a precipitate with its specific antibody *in vitro*, it is only the protein component of the complete antigen that has the power of stimulating the manufacture of antibody. But recent observations suggest that some substances, which generally behave as complex haptens, may under certain conditions act as complete antigens. Thus the polysaccharide fractions separated from various types of pneumococci when tested by the ordinary methods of inoculation have no antigenic action, but when injected in very small doses into the human skin may lead to the formation of specific antibodies (Francis and Tillett, 1930; Zozaya and Clark, 1932). Now it seems that the antigenicity of a substance, that is, its power of stimulating antibody-production, has something to do with its state of dispersion, for Zozaya and Clark (1933) reported that the injection into animals of polysaccharide adsorbed on to collodium-particles, charcoal, aluminium hydroxide or casein, may be followed by the appearance of specific antibodies in the blood. So perhaps in the usual antigens the protein which bears the specific hapten may act as a physical rather than a chemical agent, presenting the hapten to the tissues in a form which stimulates the antibody-producing mechanism.

A hapten, by combining with preformed specific antibody, is capable of causing shock-symptoms. Thus in animals passively sensitised with the serum of animals immunised against tubercle-

bacilli Enders (1929) induced acute shock by injecting the polysaccharide fraction of tubercle-bacilli.

Serum-Disease

This term is generally applied to those reactions which follow the injection of foreign serum after an incubation-period *but without a second injection.* The sera of different horses differ greatly in their tendency to produce serum-disease in man (Park). According to the experiments of Tuft and Ramsdell (1929) there are at least some horse-sera to which the great majority of persons will react. Serum-disease is composed of varying combinations of the following symptoms:—fever, urticarial eruption, œdema and joint- and nerve-pains. Hitherto the only attempt at an explanation has been that of von Pirquet and Schick, who attributed the symptoms to a reaction between the persisting foreign serum-proteins and the nascent antibodies. Coca has brought forward the following objections to this theory. (1) There is no practicable way of applying to this problem the method of passive transmission. Antibodies are not always demonstrable in serum-disease or always absent in those cases where such symptoms do not arise. Antibodies are not found in the blood-stream in any regular time-relationship to the appearance of the symptoms. (2) The typical incubation-period can also sometimes be observed in drug-allergies. Thus he has seen an eruption appear suddenly 8 days after a single subcutaneous injection of novocain. This difficulty, however, would disappear as soon as it could be shown that antibodies are formed as a result of the injection of chemicals such as salvarsan or novocain. We shall see later that there is already some evidence of this. (3) Typical serum-disease is sometimes seen in man following the injection of human serum. To this we may add the urticaria sometimes seen after extensive bruising, *i.e.*, extravasation of blood into the tissues. Probably in the course of breaking-down and absorption of these extravasates substances are formed which are foreign to the physiological system. (4) The symptoms of serum-disease are sometimes recurrent. Dale and Hartley explained these recurrences

as being successive reactions to several specifically different proteins in horse-serum. This idea is supported by Coca's observation that such recurrences are not observed in those cases of serum-disease that follow the injection of therapeutic horse-serum, which is chiefly pseudoglobulin. Similarly Hooker has described a series of three local urticarial reactions following a single intracutaneous injection of 1 in 10 horse-serum, appearing after 20 minutes, 5 hours and 12 hours respectively. He then tested the patient with three isolated horse-serum proteins and obtained single reactions to each, but after different intervals of time, namely, to pseudoglobulin after 1 hour, eu-globulin about 6 hours and albumen about 10 hours. Coca asks why the reactions require these different intervals if they all depend on the interaction between antigens and preformed antibodies. But the whole point of von Pirquet and Schick's hypothesis is that the antibodies are *not* preformed and there is no inherent improbability in one substance requiring longer to provoke the formation of its appropriate antibody than another.

Coca puts forward the alternative theory that the symptoms may be due to an altered reactivity of the protoplasm of some of the body-cells, without the mediation of antibodies. He adduces the following arguments. (1) Any evidence of the specificity of the reaction in serum-disease is only indirect. (2) He invokes the analogy of certain forms of sensitisation of the skin in which *apparently* antibodies play no part. Thus Straus's observation that he could sensitise 73% of infants by surface-application of concentrated extract of poison-ivy, whilst the subcutaneous injection of the same quantity usually failed, indicates that "skin-sensitivity to non-antigens originates in the epidermis." But we have seen that it is difficult to say that any particular substance *cannot* be an antigen. Further there is no reason why the antibodies to some of these antigens should not be formed in the epidermis. We shall also see that there is some evidence of antibody-formation in some instances of contact-dermatitis produced by chemicals. (3) The course of serum-disease, the incubation-period, symptoms and the shortening of the incubation-period on re-injection are paralleled by the results of injection of "non-

antigenic " drugs, and he goes so far as to say that in the latter mediation of antibodies is excluded. The same objections apply here as to his previous argument. He further suggests that his hypothetical *specific* alteration of reactivity of cellular protoplasm may take place even when the excitant is a true antigen and when antibodies are demonstrable. This is an important suggestion, though it cancels out his first argument about the specificity of serum-disease. Thus Coca's arguments against the antigen-antibody mechanism of serum-disease appear to me invalid. Nevertheless he does well to point out some of the difficulties of this theory even when antibodies *are* demonstrable. Some of these will be referred to later.

A local reaction following a single intracutaneous injection, but with a definite latent period, is generally referred to in the literature of cutaneous allergy as a " flare-up."

Whilst the general eruption in serum-disease follows about 10 days after the injection, it has been mentioned that in Hooker's experiments with intracutaneous injection of horse-serum proteins the latent periods were very much shorter, namely, from 20 minutes to 12 hours. In 1923 Biberstein and W. Jadassohn described " immediate reactions " taking place at the latest 10 minutes after the intracutaneous injection of certain sera in man. W. Jadassohn observed that rat- and goat-serum always produced an immediate reaction in man. A large proportion of positive results were obtained with guinea-pig and even human serum. In the case of rat- and goat-serum specimens from different individuals of the same kind of animal behaved similarly, but individual men reacted differently to the same serum. In the case of guinea-pig and human serum there were not only differences in the reaction of individual subjects to the same serum, but the results also varied with sera from different individuals of the same kind of animal. Following these observations similar immediate reactions were reported, especially by American authors, to pollen, animal-scales, foods, bacterial proteins and other substances in certain individuals who showed clinical symptoms of abnormal sensitiveness towards them. This brings us to the subject of idiosyncrasy.

Idiosyncrasy

Idiosyncrasy is a very old *clinical* conception, long preceding our knowledge of immunobiological processes such as anaphylaxis. It was used to describe any mental or physical behaviour that was peculiar to the individual, and hence it was applied to pathological reactions to a substance or influence which for the vast majority of people in the same quantity was quite harmless. The older medicine looked upon such behaviour as an inexplicable innate peculiarity. Darier and others restrict the term to a pathological response to a *first* contact with a substance harmless in that amount to most other people, attempting in this way to differentiate it from allergy. I shall try to show that this differentiation is impracticable. Doerr's latest definition is as follows:—"An abnormal state of increased and qualitatively altered reactivity occurring under natural conditions of life after contact with certain substances in the form of special pathological manifestations. The clinical type of the disturbance is independent of the chemical and physiological actions of the causative substances." By "abnormal" is meant that under natural conditions the disorders only occur in a small percentage of the population. There are two main factors which determine this percentage, namely, disposition and exposure. Predisposition is dealt with later. Idiosyncratic reactivity is very rarely present at or soon after birth, generally showing itself only after some years.

Importance of the Exposure-Factor. The few reported cases of idiosyncratic reaction to a first contact with a certain substance are unconvincing. Most such substances are complex mixtures or compounds, and, though it may be true that there has been no previous contact with them as such, there may have been previous contact with some responsible constituent or chemical group. Thus Mayer has shown that supersensitiveness to the fur-dye ursol depends on a body of quinone-structure, which is common to pellidol, certain photographic developers, etc. In 1912 Boycott demonstrated that persons who might reasonably be presumed never to have been bitten by rat-fleas gave no response at all to their first application, though they reacted violently to the human

flea. But after several feedings the rat-fleas too excited a vigorous response. He obtained the same result with sand-flies (*Phlebotomus papatasii*). These are not found in England and were obtained from abroad. No one reacted to the first experimental bite except one man who had been in the East. It is so difficult to be certain that a first contact really is a first contact that it is better not to make this an essential part, as Darier does, of the definition of such a common expression as "idiosyncrasy." Though such a state of inborn sensitiveness could be hypothetically explained as due to sensitisation *in utero* to substances reaching the fœtus through the placenta, or to passive sensitisation by the same route, it is doubtful whether in fact it exists.

On the other hand, there is no doubt that repeated contacts with certain substances, which at first are tolerated with impunity, lead in certain individuals to a specific idiosyncrasy, such as sensitiveness to primula in some gardeners, to ipecacuanha in some apothecaries and to drugs such as mercury or aspirin. The percentage of idiosyncratics in a population varies for each substance. Whereas fur-dyes or shellfish are now well known to produce sensitisation in a considerable number of persons, there are only solitary instances of sensitisation to camomile or celery, and to many other substances as yet no examples. But in the case of any one allergen (see definition on p. 259) the percentage is a question largely of the intensity and frequency of the exposure. In Zürich and its neighbourhood, where infestation with ascaris is common, W. Jadassohn found that 80% of the population between 2 and 40 years of age gave a positive cutaneous reaction; whilst children under 1 year all reacted negatively. Not all the 80% were so sensitive as to present clinical symptoms. Nevertheless, in a considerable number of individuals the sensitiveness reached so high a pitch that urticaria, asthma or hay-fever-like symptoms were provoked by exposure to extremely minute quantities of its vapour. Similarly, primula obconica under natural conditions affects a very small proportion of the population, whilst a few individuals react with violent eczema to the slightest contact of the leaves. But this supersensitiveness has been experimentally reproduced in "normal" persons by Low and

others by means of repeatedly rubbing primula into the skin. Low showed that this sensitiveness was specific, and that it extended to the whole of the skin, not only the part rubbed with primula. He found that only a certain proportion of persons were sensitisable and that these tended to be grouped in families. However, by using a concentrated ethereal extract of primula Bloch found that *everybody's* skin reacted, at first with a local blister, and that after the subsidence of the first, second or third reaction a supersensitiveness of the whole skin, indistinguishable from the natural (non-experimental) idiosyncrasy, developed and remained indefinitely. The responsible substance, primin, has been obtained in crystal form by Karrer, and is a relatively simple organic substance. So in this example of a typical idiosyncrasy it has been shown that the feature which essentially characterises an idiosyncrasy and has been thought to differentiate it from allergic or anaphylactic reactions, namely, its restriction to certain individuals, only marks a quantitative and not a fundamental difference between idiosyncratics and others. Similarly he succeeded by means of single or repeated inoculation in sensitising about 95% of guinea-pigs to the active principle of primula. This sensitisability of guinea-pigs to primula does not differ as far as the quantitative factor is concerned from that of the same animal to foreign protein in the classical anaphylaxis : in neither is the individual factor *quite* eliminated. We still have to explain the great variation in the ease with which individuals or families can be sensitised. This predisposition, considered more fully below, varies with the nature of the offending substance. Whilst nearly every guinea-pig can be sensitised to foreign serum and every man (though with varying facility) to primula, only a small proportion of human beings (as far as we now know) can develop sensitiveness to iodoform, egg-white or pollen. At what percentage can idiosyncrasy be said to end ? Idiosyncrasy cannot therefore be considered qualitatively distinct from other allergic processes.

In 1921 Doerr drew attention to the fact that idiosyncratic symptoms were to a considerable degree independent of the nature of the noxa ; and that therefore this analogy with anaphylaxis

necessitated extending to the idiosyncrasies the hypothesis that the noxæ did not act directly on the cells, but interacted with a specifically adjusted component or antibody in the cells in such a way as to irritate or damage them. In the same year idiosyncratic sensitiveness of the skin was passively transmitted to a non-sensitive person's skin by Prausnitz and Kuestner. Their original patient was sensitive to cooked fish. They injected the serum of this patient intracutaneously into a non-sensitive test-subject, and as a control they injected a similar quantity of the serum of a normal person. After 24 hours they injected into the same two sites an extract of fish. The place where the patient's serum had been introduced reacted with an urticarial wheal and red flush, whilst the site of the control-serum did not. This passive sensitisation was found to be specific. This test, which has played a most important part in all later work on the anaphylactic nature of idiosyncrasies, will be studied in detail on p. 204. It will be referred to as the "P.-K. test." It has been shown to be positive in, for instance, hay-fever, asthma caused by exogenous substances such as animal-dandruff, and in urticaria produced by certain foods. In practically all cases where the P.-K. test is positive the idiosyncratic patient's own skin gives a strong urticarial immediate reaction to inoculation with the offending substance, either if rubbed on to a scarified area or injected intracutaneously. But the P.-K. test has not been shown to be positive in by any means all instances of allergy nor for all allergens.

Allergens. This term applies to any substance (or influence) to which the skin (or other tissue) has become specifically sensitised. If in any particular instance of allergy the symptoms can be shown to depend on the mediation of antibody, then the particular allergen concerned is acting as a hapten. If it can further be shown that this same allergen was originally responsible for *bringing about* the sensitisation by stimulating specific antibody-production, then, and only then, may the allergen be called an antigen.

Now in making skin-tests with various allergens in already sensitised patients, in order to find out which is responsible for evoking the symptoms, we are testing their haptenic and not their

antigenic function. We have already seen that it is not essential even for a complete antigen to be protein. Very much less is this necessary for a hapten : indeed, it is unlikely for the specific reactive fraction to be protein. That non-protein substances can give positive skin-tests was shown many years ago by Low in a case of *codein* idiosyncrasy. In 1926 Zaruski and W. Jadassohn showed that in a man with an idiosyncrasy for *celery* the substance responsible for evoking the symptoms was present in a dialysate of the juice, in which all reactions for protein were negative. Still more interesting was the demonstration by W. Jadassohn in a boy who was supersensitive to *hen's egg* that reactions of equal intensity were obtained with (1) egg ; (2) a dialysate of egg in which all reactions for protein were negative ; and (3) the undialysable residue. The P.-K. test was positive whether egg itself was used or the dialysate. The haptenic substance was insoluble in ether and was, therefore, probably not a lipoid. In case it may be objected that such dialysates may nevertheless contain minute traces of protein, W. Jadassohn and Schaaf have shown that a dialysate of a solution of egg-white giving a positive P.-K. test certainly contains less protein than that dilution of egg-white which corresponds to it quantitatively in activity. These results are important not only in understanding the theory of allergy but also with regard to the question of the absorption of unaltered proteins through the intestinal wall. We know that in idiosyncratics certain foods cause urticaria, and we shall see that even the P.-K. test can be obtained by oral administration of the allergen. But the conclusion generally drawn from these facts that proteins, as such, must reach the circulation through the intestinal wall is, in the light of the dialysate experiments, no longer necessary. Similarly dialysates have given positive tests in idiosyncrasies to *ascaris*, *pollen* and other allergens.

But though dialysates can perform all the functions of haptens, it has not been found possible to produce an original sensitisation with them. W. Jadassohn suggests that this may be only a question of concentration, since the substances come through the membrane so slowly. But the very fact that these haptens are dialysable renders them most unlikely to be able to act as antigens.

for we have seen in the section on anaphylactic antigens that the power of a substance to stimulate antibody-formation appears to depend on its state of dispersion. But, as in the case of anaphylactic haptens, these dialysates can not only evoke symptoms but also desensitise.

In idiosyncrasy to *ascaris*, which was thoroughly studied by W. Jadassohn and proved to be passively transmissible, the allergen was shown to be heat-stable and not distillable with steam. Its activity is not impaired by mixing with ½% phenol, by prolonged autolysis or by peptic and tryptic digestion. It is dialysable. Its activity is, however, destroyed by boiling in 10% hydrochloric acid.

That the skin can become specifically sensitised to known and relatively simple chemicals has been proved by the following experiments. Frei, in 1928, succeeded by means of the intracutaneous injection of minimal quantities of *neosalvarsan* (0·13 mgm.) in sensitising the whole skin of a few persons not previously treated with it. In syphilitic patients in the middle of a course of neosalvarsan this phenomenon could not be brought about. In guinea-pigs he also achieved specific sensitisation of the whole skin in the same manner. As in the case of human beings, sensitisation was at first only successful in a small percentage of individuals. But after several weeks, during which injections were repeated, nearly all the animals became sensitised, though there were individual differences in degree. In some of those that early became highly sensitised intracordial injections of neosalvarsan produced morbilliform eruptions but not shock. Klauder, in 1922, observed asthma and eczematoid dermatitis develop in a person exposed to neoarsphenamine 8 months after an intracutaneous injection of the drug. Nathan and Mui k and also Frei collected clinical evidence to show that an allergic susceptibility to arsphenamine may be induced in man by its intradermal deposition. An intravenous injection at a later date produces an explosion of dermatitis. Bernstein (1932) succeeded in demonstrating specific antibodies by means of the P.-K. and Königstein-Urbach methods in a patient with arsphenamine dermatitis, whose skin was proved supersensitive to it. Nurses who for some

time have prepared neoarsphenamine for administration have developed asthma and gastrointestinal pains. Scratch-tests with the drug elicited big wheals and were followed by nausea and vomiting.

But that the addition of a minimal quantity of foreign protein can greatly aid the sensitising power of a chemical has recently been shown by Haxthausen. By adding 0·5 c.c. of an 11 in 1,000 dilution of horse-serum he was able to convert mercury perchloride, in the otherwise inactive dose of 1/20 mgm., into an allergen capable of inducing specific sensitiveness to mercury involving the whole skin.

In 3 cases of dermatitis following the instillation of *atropine* into the conjunctival sac, Biberstein, in 1928, succeeded in transmitting this sensitiveness by the P.-K. method. The test was also given by eumydrin and sometimes by apoatropine. Mayer made further observations which showed that the production of local manifestations of supersensitiveness to *atropine* depends on some as yet unknown characteristic of *atropine*, apoatropine, *homatropine* and *scopolamine*, but has nothing to do with the various chemical properties which give atropine its known pharmacological action.

Biberstein has also reported successful passive transmission of sensitiveness to *mercury oxycyanide*, *potassium iodide* and *salvarsan*. Valléry-Radot and Blamoutier described, in 1929, a very instructive case of extreme sensitisation to *chloroplatinite of potassium*. The patient was a man aged 45 years, who had previously suffered from eczema. He came in daily contact with the chemical with impunity for several years; then eczema and very severe asthma arose after every exposure. Skin-tests showed a high degree of specific sensitisation. A short time later a further cutaneous test produced within 3 minutes violent nausea, desire for defæcation, vertigo and intense precordial distress and after a few seconds an attack of asthma of unprecedented severity. There was very conspicuous horripilation over the whole skin-surface and intense pruritus. One hour after the beginning of the symptoms he was practically normal. Other men similarly exposed were entirely unaffected. Though in this case the symptoms of

sensitisation were not predominantly cutaneous, the case is of importance in showing that a chemical can cause extreme sensitisation independently of pharmacological toxicity. It also shows the danger of skin-tests (or injections intended to desensitise) in cases where the sensitisation extends to other organs.

Mayer, in 1931, experimentally sensitised guinea-pigs to *paraphenylenediamine*. He used crystallised, finely powdered paraphenylenediamine 10% in vaseline. This ointment was rubbed daily into the shaved skin for about 12 days, the total dose being about 1 gm. This was well borne. The uninjured skin so treated took on a blackish discoloration within 24 hours after the first inunction: thereafter ensued progressive discoloration and some thickening. If the skin was previously excoriated the reaction was much stronger and more painful. About 4 weeks after the beginning of this treatment the opposite flank was shaved and the ointment rubbed in. This revealed that some individuals had developed a general cutaneous sensitisation in that there appeared in from 12 to 24 hours a marked reddening, infiltration, occasional vesicles and gross lamellar desquamation. There was great individual variation. In the same litter some animals became highly sensitised, some moderately and some not at all. The fact of sensitisation could also be demonstrated by intradermal tests, but it was found impossible to *cause* sensitisation by intracutaneous injections, which indicates that the process of sensitisation to this allergen is a function of the epidermal cells. Toxicity-determinations by means of intracordial injections showed that the sensitised animals had the same tolerance as controls. Further, the uterus of animals with high-grade skin-sensitiveness did not react to paraphenylenediamine. The P.-K. test was negative, even if performed with skin-extract instead of serum. The sensitisation was, therefore, confined to the skin, perhaps even to the epidermis, and the presence of antibodies could not be demonstrated.

Secondary or Endogenous Allergens. There are many instances of symptoms strongly pointing to an allergic origin but in which no specific exogenous allergen can be traced. In such conditions as urticaria, angioneurotic œdema, asthma, Besnier's

prurigo and infantile eczema Oriel has isolated from the *urine* a complex nitrogenous substance corresponding for the most part in its chemical properties to a *proteose*. It is chemically similar to the specific part of the tubercle-bacillus isolated by Dudley and Laidlaw and of the pneumococcus isolated by Dochez and Avery. Although present in small quantity in the urine of persons apparently in normal health, it is found in relatively large amounts in acute and chronic microbial infections and admittedly allergic states and in various other unsuspected or manifest conditions of ill-health. Experimental and clinical observations have shown that in certain allergic diseases the proteose contains the specific haptenic substance responsible for the symptoms. When isolated and injected intracutaneously into such a patient it evokes a reaction similar to that seen on the injection of an allergen to which the patient is sensitised. Oriel showed that guinea-pigs can be specifically sensitised to this proteose both actively and passively. Specific passive sensitisation was also obtained by injecting a guinea-pig with the serum of an asthma-eczematous patient. This rendered the guinea-pig's uterus sensitive to the patient's proteose but not to that of another patient similarly affected. This shows that it is to his own proteose that an allergic patient is sensitised. The serum of a normal person cannot sensitise to proteose. Thus urinary proteose can act as antigen and sensitivity can be transferred by the injection of a sensitised patient's serum. In recurrent urticaria the amount of proteose excreted during a period of quiescence is very much less than during an attack, when it is also much more antigenic.

Perhaps in some cases and under certain conditions the proteose may itself be the sole primary allergen, but there is some evidence that it can also play an important part as a secondary allergen in patients sensitised to some exogenous substance. To demonstrate this connection, a guinea-pig was actively sensitised with proteose from an asthma-eczematous child who was milk-sensitive, the proteose being obtained while milk formed part of the diet. It was found that the uterus had thereby been sensitised to milk. Repeated application of milk ceased to cause contractions, but the uterus still responded, even more strongly, to the original

proteose. It follows that the proteose contained a certain quantity of milk-antigen and a greater quantity of some other antigen. Conversely, a guinea-pig injected with milk can be rendered sensitive to proteose from a milk-sensitive patient. Thus it seems that in sensitisation urinary proteose contains the antigen to which the patient is sensitised. The phenomenon of passive sensitisation to urinary allergen has been found in asthma, urticaria, migraine and rheumatoid arthritis.

The antigen to which the patient is finally sensitised may be neither the original primary exogenous substance nor his own proteose, but a new or secondary antigen formed by a combination of the two. Thus Oriel describes a patient who was aspirin-sensitive, responding to minute doses of aspirin with severe angioneurotic œdema. It was found (1) that when not taking aspirin he gave negative skin-tests with his proteose; (2) that he gave negative skin-tests to aspirin; (3) after the ingestion of aspirin his urinary proteose gave sharply positive skin-tests on his own skin and also on that of other aspirin-sensitive patients.

So far, however, Oriel's observations on proteose have not been widely confirmed. Freeman, even with Oriel's co-operation, was unable, at any rate as regards asthma and hay-fever, to confirm (*a*) the presence of proteose in any greater quantity in the urine of allergic patients than in controls; (*b*) that proteose prepared from the urine of asthma or hay-fever patients gave a specific reaction in their skin, whether taken during periods of quiescence or exacerbation. Murray-Lyon, Percival and Stewart did confirm Oriel to the extent that in cases of asthma-eczema and angioneurotic œdema they found proteose in larger quantity during attacks than in the intervals. But they obtained positive skin-reactions with it in a majority of subjects tested, whether normal or allergic, and entirely failed to confirm its specificity. In two instances proteose, isolated from the urine of cases of asthma-eczema, actually gave a negative reaction in the patients' own skin but positive in other individuals. Again, a patient with angioneurotic œdema reacted negatively to his own proteose (though this was present in remarkably large amount) but gave a positive reaction to proteose isolated from another person suffering

from urticaria. Burgess also confirmed Oriel and the above authors to the extent that in a case of angioneurotic œdema he found that only specimens of proteose obtained during an attack, when it was also more copious, gave a positive skin-reaction. But, from a study of 24-hour specimens of urine of sufferers from chronic urticaria, angioneurotic œdema, eczema of internal origin, Besnier's prurigo, asthma and psoriasis, he concluded that, although slight variations in amount of proteose are found in different persons and in the same person at different times, the average quantity excreted by allergic individuals and normal controls is the same. Comparing the intracutaneous reactions of patients with the above diseases and normal persons, using peptone as a control, he found that many allergic patients are more sensitive to injections not only of proteose but also of peptone than normal persons. Of normal controls 16% and of untreated skin-cases 67% reacted positively to their own proteose. Among 18 normal persons 4 were positive both to proteose and to peptone, 3 to peptone only, and none to proteose only. Among 50 untreated skin-cases none were positive to peptone only, 9 were positive to proteose only, and 22 positive to both.

The weakness in most of these studies is that the diseases chosen as representatives of allergy could not be shown in each individual instance to be in fact allergic in ætiology.

There is much evidence that the skin can become sensitised to *products of its own damaged cells*. Experiments of Sellei and Liebner some years ago in cases of prurigo æstivalis showed that after irradiation of other regions of the body-surface the characteristic eruption only developed at the sites of election, namely, extensors of the arms and the face. After irradiation of one upper arm exacerbation of symptoms occurred equally in both arms. They concluded that products of the damaged epithelium were transported by the blood and caused inflammation of cells at the sites of election, the special sensitiveness of these particular cells remaining unexplained. Passive transmission of sensitiveness failed. More recently Whitfield has drawn attention to the phenomenon of auto-sensitisation in eczema. He cites the case of an elderly man who had an acute vesicular eczema of both

legs. If the fluid from the eczematous vesicles was allowed to flow over an area of apparently healthy skin, there appeared, "first, a red streak, secondly, after a few minutes, a well-marked urticarial wheal and, lastly, a row of vesicles, at first minute and clinically indistinguishable from the primitive vesicles of eczema, but subsequently coalescing to form a linear bulla." On Whitfield's own skin, however, the fluid produced no reaction, thus proving that the patient was sensitive to the fluid containing his own tissue-products, but that it was innocuous to another person. Whitfield also points to the common experience of the development of a generalised eruption of papulo-vesicular eczema, sometimes urticate, after a chronic patch of lichenified eczema, as a rule on the leg, has been violently scratched; or when a varicose eczematous dermatitis has been irritated by unsuitable local applications. The generalised eruption is presumably due to auto-sensitisation having taken place to some tissue-product absorbed from the primary eczematous area, and, when the latter is treated by soothing applications, the former disappears spontaneously. Whitfield also remarks that he has met with many cases of nurses who have developed true eczematous lesions beginning on the hands, wrists and forearms, and spreading to other parts after the *prolonged* dressing of patients with exudative eczema. The culpability of antiseptic irritants having been excluded, it is suggested that the nurses had become sensitised by repeated contact to the patients' exudate. Finally, he explains the development of the generalised exfoliative dermatitis which occasionally results from treatment of eruptions such as psoriasis by irritants, *e.g.*, chrysarobin, as being due to auto-sensitisation to the patient's own tissue-products.

Bites of Insects and Mites. *Varying Intensity of Reaction.* Not uncommonly there is a complete absence of reaction. Kemper, in 1929, found that among 45 persons 8 were completely immune to bed-bug bites, though he showed that bed-bugs will attack everyone impartially. Individual immunity to body-lice has also been noticed. On the other hand, there may be excessively big reactions. Kemper mentions a case in which, 15 hours after three bug-bites, the hand, forearm and lower half of the arm

were red, hot and very swollen. Such reactions have also been observed to *Anopheles Maculipennis* and to midges. A bulla generally forms at the actual site of the bite. I myself and two members of my family react to the horse-fly with a local bulla and extreme œdema extending far beyond the bite and lasting more than a week.

Habituation. Hase in 1916, among 1,000 persons, found a considerable number who had lost their sensitiveness to lice. Pick (1929) says that habituation to body-lice develops sooner than to fleas and bugs. Experimentally Hase, by repeatedly exposing the same area of his leg to bed-bug bites, eventually achieved a local immunity. Kemper obtained the same result; but after a month's interval some bites again reacted, and this recovered reactivity thereafter persisted. On the other hand, some individuals retain full sensitiveness to lice (Hase), and Martini (1932) was unable to produce by repeated exposure any diminution of reaction to yellow-fever midges.

Intensification of Reactivity or Abolition of Non-reactivity. Boycott's experiments have already been mentioned, in which he showed that persons who had not previously been exposed to rat-fleas or rabbit-fleas gave no response at all to their first application though they reacted violently to the human flea, but that after several feedings the rat-fleas excited a vigorous response. He obtained the same result with sand-flies. When a positive reaction was obtained the sites of the previous bites also flared up, showing that in addition to the general sensitisation of the skin there was a still greater degree where the allergen had already been introduced. The interval required for sensitisation was approximately 8 days. It was found that some individuals were more easily sensitised to some insects and other individuals to others.

But it would be wrong to assume that the first contact with a noxious insect is always reactionless. Hecht has often observed reactions to first contacts with yellow-fever midges (*Aëdes Fasciatus*) in persons who have never been to the tropics.

Reactionless individuals cannot always be rendered sensitive. Hecht (1929) failed to sensitise himself to bed-bugs though they did actually bite, leaving red points. Kemper, within 25 months,

let about 10,000 bed-bugs bite a victim with "congenital immunity," without sensitising him.

In some individuals there is not so much a change in degree of reaction on repeated bites as a shortening of the latent period (Kemper). In one such case, which led eventually to immunity, the size of the wheal at first increased. It is perhaps of considerable significance that in this active immunisation-process there was at first this rise of reactive intensity. But the non-reactivity so obtained was only a temporary one, and Hecht considers that it was not a true antitoxic immunity but a kind of anti-anaphylaxis (temporary saturation of antibodies). A further continuation of repeated bites only reduced the duration of the wheal from 3 hours to 2 hours, while the size increased from $3\frac{1}{2}$ to 6 mm. The reaction remained an immediate one. Eventually, therefore, a sort of equilibrium is reached through the interplay of sensitisation and desensitisation processes.

Demonstration of Antibodies. Two persons non-sensitive to bed-bugs were passively rendered locally sensitive by the injection of the serum of a sensitive individual by the P.-K. method. The converse experiment, that is, local immunisation by injecting non-reactive serum into a reactive skin, failed to alter its response.

Focal Reactions. Flaring of the sites of former bites when the allergen is introduced elsewhere is probably due to the cells having meanwhile manufactured antibody which reacts with the fresh antigen.

Generally speaking, the reactions to insect-bites are zoologically specific. Occasionally there are group-sensitisations (cf. Bloch's group-immunity for the Hyphomycetes). But here, too, individuals or families may have a special aptitude for becoming sensitised to a number of different insects.

The Nature of the Antibodies. If the antibodies are really distinct substances it is a marvel how the body can produce such a huge number imbued with such specificity.

THE PRAUSNITZ-KUESTNER REACTION. Our knowledge of the behaviour of the antibodies of idiosyncrasies is based very largely on the study of the P.-K. reaction, which we must therefore consider now in greater detail. The test is generally performed by

making two parallel vertical rows of intracutaneous injections on the back of a normal test-subject, one row consisting of a series of dilutions of serum from the idiosyncratic patient and the other of corresponding dilutions of serum from a normal control. The allergen is introduced to all the sites 24 hours later, giving in positive cases immediate reactions in the former row and none in the latter. The test can be performed with citrated blood just as well as with serum.

W. Jadassohn found that, if the allergen is introduced not at the site of the serum-injections but into some distant part of the skin, the effect is nevertheless as before, namely, that wheals appear where the idiosyncratic serum has been injected and nowhere else. This is called the "distant reaction" (*Fernauslœsung*). It proves, first, that only very small quantities of allergen are needed, and, secondly, that the antibodies have remained fixed to the cells at the site where they were injected. In passive anaphylaxis the necessary latent period has always been explained by the upholders of the cellular theory as representing the time required for the passively introduced antibodies to become bound to the fixed tissues. The customary 24-hour period was taken over by experimenters with the P.-K. reaction. But it was later found that this interval between the sensitising serum-injection and the test-injection of allergen could be reduced to 1 minute (occasionally even to zero) or increased to 4 weeks. The antibody therefore fixes itself very rapidly to the cells and remains fixed for a considerable time. If the procedure is reversed, allergen being introduced first and the serum 24 hours later, no reaction occurs: but if the interval is reduced below 15 minutes a reaction may be obtained. The usual explanation is that allergen is not fixed by the cells but carried away from the site of injection. Unless there is still enough left by the time the antibody has become cell-fixed there is no reaction. But this is a little difficult to reconcile with the "distant reaction," where the allergen does not have to be carried away but starts at a distance. The discrepancy may only be a quantitative one. There is also the possibility that in 24 hours the allergen has become altered, whilst within 15 minutes there would still be enough unaltered

allergen to react with the antibody. There is evidence that some allergens, however, do remain unaltered in the body for considerable periods. Thus Levine, Philip and Coca found that pollen-extract circulates in the blood for at least several days after injection.

The distant reaction was taken a step further still when M. and A. Walzer showed that in cases of food-idiosyncrasy, if the patient's serum is injected as usual into the skin of a normal person, these sites alone react if the allergen is now given to the test-subject by mouth. The wheal develops within 3 minutes to 2 hours, and only on feeding the specific food. One wheal-formation generally desensitises the site, but if no antigen is administered it remains sensitive for more than a month. The reaction is stronger if for the test-dose of antigen the food is given uncooked. If the reactive substance is a protein it seems curious that it should be absorbed quickly enough to produce a reaction in 3 minutes. M. Walzer has, however, shown that in about 90% of normal individuals incompletely digested proteins are absorbed from the digestive tract. In any case, we have seen from W. Jadassohn's work that the reactive haptenic moiety is probably not protein and could come through by dialysis. The influence of cooking on the allergic action of foods is very obscure.

The P.-K. test has also been used as the basis of experiments for studying the *neutralisation* of antigen and antibody. Coca and others found that if antigen and idiosyncratic serum were mixed together *in vitro* the resultant mixture behaved like antigen, that is to say, the antibody had been destroyed. He thought that the activity of the antigen was not in the least reduced by being so mixed with its corresponding antibody. But according to W. Jadassohn and Storm van Leeuwen this is a question of proportion. They are convinced that when suitably diluted a demonstrable quantity of antigen can be neutralised when mixed with a strong idiosyncratic serum. The neutralisation requires a little time. Thus in the case of some antigens a fresh antigen-antibody mixture produces a positive reaction in normal skin, but if kept for 24 hours at room-temperature no longer does so, behaving like pure antigen. Repeated injections

of antigen, after a positive result has been obtained, cease to cause a reaction, as if the antibody is thereby used up. That this is not due merely to a refractory state of the cells is shown by the fact that introduction of fresh antibody at the same site will now once more sensitise it to subsequent injection of allergen, though generally the reaction is not quite so strong as before. Neutralisation experiments *in vitro* and numerous clinical observations point to the conclusion that very minute quantities of allergen in proportion to antibody are required to produce idiosyncratic symptoms. Thus it is quite enough for a person supersensitive to ascaris to be in the presence of another person who has been recently working with it. Levine, Philip and Coca made an observation which is inconsistent with the above results and very difficult to explain. A passively sensitised site was desensitised by successive injections of allergen of a certain strength. A new reaction could now be obtained by injecting allergen ten times as strong. When the site again became insensitive a further increase in strength of the allergen again evoked a reaction. It seems hardly possible in this case that the positive reactions can depend on the presence of antibody at all. Yet the site was originally rendered sensitive to the allergen by the transfer to it of sensitive patient's serum.

In the case of some idiosyncratic antibodies at any rate, they are not impaired by ½% phenol or by peptic and tryptic digestion: they cannot be dialysed. The sensitising power of idiosyncratic serum is destroyed by heating to 56° C. for 6 hours, though its power of neutralising antigen *in vitro* withstands it for 24 hours. Must we then assume two distinct specific antibodies for each antigen? Such an assumption is not necessary, for it is clear that the antibody must have two properties; (1) that of fixing itself to cells, and (2) of reacting with antigen. One of these properties may be more easily destroyed by heat than the other. According to W. Jadassohn there is some evidence that neutralisation is never absolutely complete, and that, as with a mixture of acids and bases, minute amounts of the two constituents remain free.

In Moro's study of infantile eczema he found that a little over 80% of the patients gave a positive von Pirquet test to egg-white:

all controls were negative. P.-K. tests performed with the serum of the eczema children ("eczema serum") and egg-white were also positive. It was extremely rare to get positive reactions with other allergens. True complement-fixation occurred in mixtures of eczema-serum and egg-white, but only within a narrow zone of dilution; the antigen had to be diluted at least to 1 in 30,000, and usually to over 1 in 10,000,000. This was found to distinguish the serum of an eczema child from an antiserum produced in a normal subject by previous treatment with egg-white. This difference was also brought out by the P.-K. test, for only eczema-serum could transmit sensitiveness to normal skin. Anti-egg-white rabbit-serum and serum of normal children experimentally "sensitised" by repeated injection of egg-white do not give a positive P.-K. reaction, even though the sera contain a high titre of ordinary egg-white antibody. He concluded that there were two distinct kinds of antibody, the immune antibody reacting with relatively concentrated antigen and the allergic antibody reacting only with highly diluted antigen and capable, on passive transmission, of sensitising normal skin. He called these special eczema-antibodies "trophergines." Moro considered that the P.-K. was the most sensitive and reliable test for the presence of the "allergic state." In infants whose serum merely contains the ordinary immune antibody to milk the P.-K. reaction and also the cutaneous reaction are negative; but the intracutaneous is nearly always positive. The latter also becomes positive in the normal subjects used as tests for the P.-K. reaction who have been repeatedly injected with egg-white. Thus the intracutaneous test may reveal reactive states which have nothing to do with the "allergic state" in the narrower sense.

We see, therefore, that Moro draws a distinction between the "allergic state," which he does not define, and ordinary experimental sensitisation, and thinks that the antibodies responsible for these two states are qualitatively different. We shall return to this question in the section on "Predisposition."

Now there are some *pitfalls* in the practical application of the P.-K. test. (1) Debesche and Frugoni observed that serum taken during an exanthem sensitised less than serum taken during an

interval. Doerr also emphasises that serum obtained immediately after a severe attack is unsuitable. Similarly, Biberstein found in his cases of atropine dermatitis that serum taken during the height of the eruption gave negative P.-K. tests, whilst that taken 3 months later from the same patient did passively sensitise. On the other hand, in ascaris idiosyncrasy W. Jadassohn found no conspicuous difference between specimens taken during and after an attack. (2) The sera from similar cases of idiosyncrasy are not equally uniform in their sensitising power. Biberstein, although he obtained positive passive transmission with the serum of all his 3 cases of atropine dermatitis, found that one of these would not sensitise all test-subjects. Hecht found that the serum of only one out of four individuals sensitive to bed-bugs could transmit sensitiveness. This is, however, quite in conformity with the theory that it is only the cell-fixed antibody that is responsible for the reactions, and this would not be transferable by means of the serum. (3) There is some variation in the behaviour of test-subjects: some may be quite refractory, especially syphilitics. (4) M. Walzer came across three sera which, when injected into the normal skin (of practically every test-subject), induced a non-specific supersensitiveness even to normal saline, distilled water or unaltered human serum. The degree of response, however, varied with the substance used. The induced supersensitiveness persisted for several weeks. The positive reaction at the injected site could not be elicited by stroking or rubbing but only by the intracutaneous injection of a solution. One reaction on a site did not exhaust its sensitiveness, but a second reaction there was generally smaller. These sera were obtained from asthmatic patients who, on direct testing, gave positive reactions to nearly every allergen tried. A P.-K. test cannot therefore be considered positive unless the presence of such non-specific supersensitiveness has been ruled out by a control-test with normal saline on one of the sites. But in controlling the P.-K. test against non-specific sensitisation the non-specific allergens should not be tested at the same time, since the specific allergen may give a positive distant reaction at the site tested with a non-specific substance.

THE BLISTER-METHOD OF PASSIVE TRANSMISSION. It is not only by means of the blood-serum that antibodies can be transferred. In 1924, Urbach studied a case of acquired specific idiosyncrasy to sodium cacodylate. The symptoms were evoked by subcutaneous or by percutaneous application. Passive transmission with the blood-serum by anaphylactic experiments in animals failed, as did also the P.-K. test. But he succeeded in transmitting the sensitiveness to normal human skin by the intracutaneous injection of fluid from a blister produced by cantharides-plaster on an area of the patient's skin very sensitive to the cacodylate. The intracutaneous or subcutaneous introduction of the drug in the passively sensitised test-subject produced general febrile symptoms and a local reaction consisting of vivid erythema and pain. Perutz (1927) injected the fluid from a blister caused by sticking-plaster in a patient sensitive to turpentine into the skin of a non-sensitive subject. The next day a little compress of turpentine was applied over this site (which at that time showed no sign of inflammation) and on a corresponding non-treated site on the opposite arm. A quarter of an hour later the treated site was already reddened, œdematous and beset with papules and blisters. In another experiment Perutz injected the fluid of a blister produced by iodoform in an iodoform-sensitive patient into the skin of both arms of a normal person. After 24 hours one of these sites, which was uninflamed, was painted with a solution of iodoform. This site, after a further 24 hours, developed a wheal with discrete nodules lasting 8 days. The unpainted site remained completely reactionless. The sensitising power of this blister-fluid was destroyed by " inactivating it " by heat. In this respect, therefore, the blister-fluid antibody resembles the serum-antibodies studied by W. Jadassohn.

A weakness of this method, if cantharides is used for producing the blister, is that cantharides is itself irritating and test-subjects can react differently to it. It would perhaps be preferable to make the blister with CO_2 snow.

This test has mainly been used for transferring sensitiveness from patients exhibiting a superficial eczematous rather than urticarial reaction, the blister-fluid being more likely than blood-

serum to contain the cell-fixed epidermal antibodies, though in Urbach's original case the patient's symptoms were chiefly itching, reddening and swelling. In reading the result of this test, even when the application of allergen to sensitised sites in the test-subject is made by injection and not by surface-application, one has to take account not only of the wheal, but also of the erythema. The latent period after the test-injection is often longer than in the P.-K. test.

Reaction-Types. When allergic manifestations are due to antigen-antibody (or more frequently hapten-antibody) interaction, the character of the symptoms depends on *the situation of the cells to which antibody has become fixed.* There are several factors that help to decide which cells are to become the seat of antibody. The first is the *individual* factor. Danysz, in 1920, pointed out that, if a number of rabbits are injected intravenously with small doses of horse-serum at frequent intervals for some weeks and are then kept under observation, it will be noticed 2 or 3 months after the completion of the injections that some will have developed nervous symptoms, others dermatoses, including alopecia and prurigo, and others arthritis. In the same way, out of a number of human beings sensitised to egg, one will respond to its ingestion by an attack of urticaria, another by sickness and diarrhœa, and another by asthma. W. Jadassohn and Zaruski describe a patient who habitually got urticaria and dyspnœa from celery and subsequently developed the same symptoms after drinking camomile-tea for the first time. The intracutaneous and P.-K. tests were positive. She was not known to be sensitive to anything else. Can the antigens contained in these two plants be the same? *A priori* that is most unlikely, as the plants are not related and the substance must be absent from all other plants with which she had come in contact. Yet the interesting observation was made that if her serum was mixed with celery it lost its sensitising power, not only against celery, but also camomile. Similarly, if it was mixed with camomile it lost the antibody for both. A second patient was observed in whom the external application of camomile produced eczema. No urticaria could be evoked by intracutaneous inoculation and the P.-K. test was negative.

These cases taken together show clearly how two individuals, both of whose skin was sensitised to a very common substance of which exceedingly few persons are intolerant, yet reacted to it in quite a different manner. This illustrates what has already been said that idiosyncratic symptoms are independent of the chemical and physiological actions of the causative substances. Though this is perfectly true, nevertheless some *antigens* are more prone to sensitise certain tissues than others. Thus Sulzberger has shown that while the skin of guinea-pigs can be easily sensitised to neoarsphenamine by a single intracutaneous injection, no demonstrable sensitisation takes place when the drug is administered into another organ, provided skin-contact can be avoided. [Incidentally these facts indicate the importance of careful avoidance of the skin in administering drugs that can sensitise it.] Moreover, no supersensitiveness of other organs can be demonstrated even in animals in which the skin has become highly sensitised. Now, that this is not due to the individual or species factor is shown by the fact that intracutaneous injections of horse-serum sensitise guinea-pigs' bronchioli and not the skin. Similarly, ascaris produces urticaria but not eczema, whilst primula produces eczema and has not been observed ever to cause urticaria. Similarly, though the same insect, for example, the flea, can produce an erythemato-hæmorrhagic macule in some persons and wheals in others, the latter reaction cannot be ascribed to a general urticarial disposition of certain individuals, as the same person may react with urticaria to one insect and with other types of lesions to other insects (Hecht). On Kemper himself fleas caused sometimes only little hæmorrhagic macules and sometimes wheals and flares, even if the bites were given at the same time. *Anopheles Maculipennis* produces in some persons a late papule and in others an immediate wheal. By the P.-K. method one can transfer whealing-power by injecting a whealing individual's serum into the skin of a person who ordinarily reacts with late papules. But it is curious that in the latter the wheal caused by the test-bite is followed by the usual papule. The converse experiment is negative, that is to say, one cannot diminish whealing-reaction by injecting the serum of a late-papule-forming person ; nor does the

whealing patient now produce a late papule. This does not prove that the papule is not the result of an antigen-antibody interaction. (The experiment was not made of injecting a papule-maker's serum into the skin of a non-reacting individual.) Hecht thinks it signifies a lesser degree of sensitisation. He groups the various types of reaction, on the antigen-antibody hypothesis, in the following degrees:—(1) *No reaction.* There is no antibody ready and no aptitude of the cells for rapidly producing it. (2) *Papular late reactions.* The new antigen stimulates the cells to make antibody. When it is ready it reacts with any antigen that still remains. (3) *Urticarial late reaction.* Similar to (2). (4) *Urticarial immediate reaction with negative P.-K. test.* The cells have enough antibody ready-formed to react at once with the antigen (or possibly the cells have already learnt to make antibody so quickly that they almost immediately produce enough to react with the antigen). (5) *Urticarial immediate reaction with positive P.-K. test.* There is not only enough cell-fixed antibody for the immediate reaction, but it is also free in the blood in demonstrable quantity. (6) *No reaction.* There is an unusually large amount of free antibody so that the antigens become saturated before they can interact with cell-fixed antibody.

As regards the sixth degree, if the test-injection is made directly into the cellular cutaneous tissue, I do not see how a reaction with cell-fixed antibody can be entirely prevented by free antibody. There is no certain evidence of the essential identity of the papular and urticarial reactions. If late papule-formation merely depends on there being no antibody ready and on its slow subsequent production, it is curious that the wheal produced in a papule-maker's skin after introduction of the serum of a whealing patient should still be followed by the usual papule. But this could be explained by the amount of antibody transferred with the "whealer's" serum not being enough to neutralise all the antigen.

Now we have seen that certain antigens do have a preference for sensitising certain tissues. On the antigen-antibody theory they can only have this preference by virtue of their corresponding antibodies having a special affinity for certain cells. It is possible

that, when the same antigen produces different reactions in different individuals, it is because it evokes antibodies of a slightly differing structure, which explains their affinity for different cells. Indeed, if to the same antigen every individual produces an identically constituted antibody, it is, I think, extremely difficult to understand why this same substance should have an affinity in one case to one type of cell and in another case to quite another type. This may also explain the observation of Biberstein and Froelich that passive transmission of sensitiveness to pyramidon, for instance, shows itself in an erythematous and not an urticarial reaction after the intracutaneous test-injection. The same thing was noticed in their case of sensitiveness to quinone-bodies, though the patient's own skin gave an eczematous late reaction. Of course a number of tissues may be sensitised: thus a positive intracutaneous reaction to pollen is almost constant in hay-fever. *May it not be that to any antigen a number of different antibodies can be produced according to the types of cell which elaborate them and to which they retain an affinity?*

The *route* by which the allergen reaches the selected organ is not always of paramount importance. Spain and Cooke have shown that the typical dermatitis venenata caused by *toxicodendron radicans* can be produced by oral or hypodermic administration of the extract. That *a purely superficial vesicular reaction can be produced by substances reaching the skin from the blood* has also been demonstrated in the case of supersensitiveness to iodide by Bloch, to resorcin by Urbach, to iodoform by Klausner and Frei, and to ephedrine by Abramowitz. (See also Sulzberger's experiments, p. 212.)

The cellular selectivity can be very precise. Thus Bizzozero and Ferrari described a case of superficial dermatitis due to iodoform, in which it was found necessary for the iodoform to come in contact with the superficial layers of the epidermis (stratum granulosum, lucidum and corneum) only for a few seconds to produce symptoms. If injected intracutaneously or applied to the base of a burst blister there was no reaction. It is particularly interesting that in this instance of exclusively epidermal sensitisation to a chemical, the sensitiveness could be passively transferred

by the P.-K. method by means of the blood-serum taken 10–30 minutes after the application of the antigen.

A further example is afforded by the so-called *fixed drug-eruptions*. Naegeli and others made a careful study of a case of antipyrin idiosyncrasy, in which sharply circumscribed fixed areas always flared up on the administration of the drug. The patches became bright red or slightly livid, recovered after a week with slight scaling and left behind a light brown, sharply demarcated pigmentation. Sometimes the patches developed blisters. A portion of the epidermis from an area which from the beginning of his illness had been severely involved in every attack was interchanged with epidermis from an unaffected area on the opposite side. But of the allergic area a strip of pigmented epidermis along the edge was left behind as a control. Three weeks after the transplantation, when all the grafts and wounds had healed and there was no sign of inflammation, antipyrin 0·1 gm. was administered by mouth. New areas now appeared on the face, followed by reddening of the earlier diseased patches, rhinitis and œdema of the eyelids, and finally itching and slight reddening in the middle of the portion of epidermis transplanted from an allergic to a normal area of skin. The reaction was typical and did not lead to necrosis. The healthy epidermis transplanted to a formerly allergic area remained quite unaffected, whilst the pigmented control-strip in the same allergic area reddened as usual. In addition to these transplantation-experiments some biochemical tests were made. Thin even layers of epidermis from sound and affected areas were put for 24 hours into (*a*) 70% alcohol, (*b*) normal saline, and (*c*) 10% antipyrin solution. On removing the allergic strip of epidermis from the antipyrin solution it was found to be macroscopically swollen; all the other five strips were unaltered. Histologically, the normal strips showed no changes. The allergic strips were all found to have thickened stratum germinativum and granulosum. But the allergic strip that had been in antipyrin solution showed in addition very conspicuous changes in the rete, which was in a state of far-reaching dissolution. In places where fragments of the papillary body had remained attached, it was seen that in the

early stages of inflammation the prickle-cells were involved, but the papillary body was quite intact. In the later stages there was a secondary participation of the papillary body with dilatation of



FIG. 14.—Phenolphthalein eruption. (W. K. D. Sibley, *Proc. Roy. Soc. Med.*, 1932, p. 125.)

the capillaries. These experiments indicate that in fixed antipyrin eruptions the antipyrin, transported by the blood, first damages the epithelial cells and that the products of this cell-damage secondarily irritate the blood-vessels of the corium. It is important to realise that even when the primary damage is

epidermal the most obvious clinical symptom is nevertheless an erythema.

But in a clinically very similar fixed exanthem caused by phenolphthalein (see Fig. 14) it is not the epidermis, according to Wise and Sulzberger's experiments, that is primarily sensitised. They transplanted the full thickness of the skin from an affected to a normal area and *vice versâ*. After complete healing, phenolphthalein was administered by mouth. The normal skin grafted on a previously affected area reacted positively whilst the other graft was unaffected. Moreover, direct cutaneous and intracutaneous tests with phenolphthalein produced no positive reactions on either affected or unaffected areas. In this case, therefore, the regional sensitisation depended on quite deep structures, but precisely which was not determined. In patients with phenolphthalein idiosyncrasy it has not been found possible to demonstrate the presence of the drug in the urine or tissues, either by *in vitro* methods or by colour-reaction *in vivo*. [Incidentally phenolphthalein may be ingested in many ways other than in the well-known laxatives, for example, in pink mouth-washes, tooth-pastes, sodium perborate preparations and icings on cakes. There are also rarer clinical manifestations, namely, subungual or periungual lesions or paræsthesiæ of the tongue and buccal mucosa without visible change.]

URTICARIA. The final mechanism responsible for the formation of a wheal is considered in Chapter I., where it is also emphasised that this mechanism can be set in motion by a large number of agencies, of which an *antigen-antibody interaction* is only one. In this last group the cells to which antibody has become fixed, and which are therefore primarily damaged, are probably situated in the superficial layer of the cutis and closely related to the minute vessels. Accordingly, in most cases of urticaria where the allergen is known, a test-reaction cannot be evoked by placing it on the unbroken skin. It must either be introduced by intracutaneous injection or through scarification. Sometimes, however, an urticarial response does seem to follow superficial application. Thus Whitfield describes how in his eczema patient the *fluid from a blister* running over apparently normal skin produced

first a red streak and after a few minutes a well-marked urticarial wheal, and finally vesicles. Similarly the reaction to the surface-application of a *paraphenylenediamine* hair-dye in a sensitised

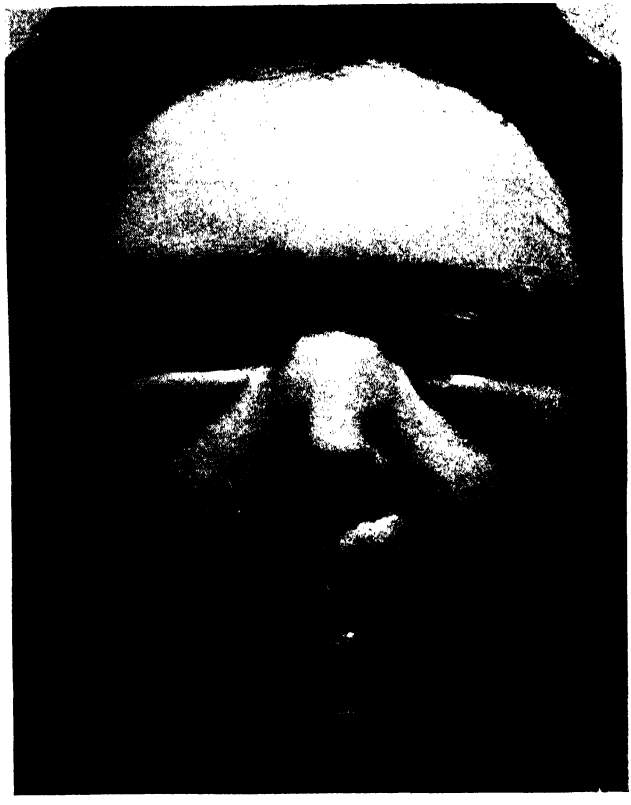


FIG. 15.—Inecto dermatitis. (Author's case.)

subject produces a deep œdema, even more conspicuously than epidermal changes (see Fig. 15). Of course, one might hypothesise minute cracks in the epidermis. But these are not essential, for the urticarial mechanism can be set in action by the products of damaged epidermis. Lewis has pointed out that a needle-prick

just deep enough to penetrate the horny layer and reach the living epidermal cells, but still far short of the true skin, always yields a vascular response. He goes so far as to conclude that the cells mainly responsible for the release of H-substance in the skin are the living epidermal cells. A secondary vascular response to epidermal injury has also been proved in *actinic* erythema and by Naegeli in his experiments on *antipyrin* exanthem. But, as I have said, testing with known allergens shows that they must usually be brought into direct contact with the cutis to provoke an urticarial reaction; so it is not surprising that in the majority of instances of clinical urticaria the allergen reaches the skin from within. In a very large proportion, if the allergen is known, the P.-K. test is positive. The number of allergens is extremely large. Among unsuspected ones it may be mentioned that according to Wise and Sulzberger urticaria is quite often caused by *epidermophyton interdigitale*, to which the P.-K. test is positive.

Particular interest has been aroused by cases, rather rare, in which urticaria is specifically caused by exposure to *cold*. In many of these it has been associated with paroxysmal hæmoglobinuria, usually in congenital syphilities. Paroxysmal hæmoglobinuria is known to be caused by a hæmolysin constantly present in the blood, which only becomes fixed to the red corpuscles at low temperatures and lyses them on re-warming. In a case associated with cold-urticaria Harris, Lewis and Vaughan were able to demonstrate that the latter was due to a closely related "dermolysin." They were repeatedly able to transfer sensitiveness to cold by injecting the serum into the skin of a test-subject. One reaction to cold desensitised the site of injection. The reaction is negative unless the cooling is performed soon after the injection. It therefore appears that the lysin does not get fixed to the cells prior to the cooling, when it does so almost instantly. They think therefore that cold-urticaria is due to a "dermolysin" present in the blood, which unites with the skin-cells at low temperature and lyses them on re-warming, setting free histamine. Positive P.K. tests have also been obtained in cases of cold-urticaria without hæmoglobinuria by these authors

as well as by Bernstein. The latter's observations differed in that the transmitted local sensitiveness lasted several days. Thus transmissible allergy is not necessarily dependent on antibodies as usually defined. The similarity of the mechanism affecting red corpuscles and skin is thought to be corroborative evidence that urticaria results from increased permeability of the skin-cells and discharge of part of their contents; for this is evidently what happens to the red cells. Possibly this mechanism plays a part in chilblains and in infantile eczema. Lehner and Pisacane state that the serum is most active if taken shortly after the appearance of an eruption. Rouquès marshals other arguments against the hypothesis that cold-urticaria is due to the production of ordinary antibodies against substances formed in the skin by the action of cold.

Some attempts have been made to distinguish wheals of allergic origin from other wheals by a study of their cellular content. Berger and Lang examined histologically allergic wheals, produced experimentally in persons sensitised to pollen, flour and fish and in P.-K. tests. They found an extraordinarily conspicuous intra- and extra-vascular eosinophilia. They also examined wheals produced by histamine and found both differences and resemblances. Eosinophilia was very marked in both. The chief difference was that in the histamine-wheal leucocytes were almost exclusively intravascular. W. Jadassohn confirmed Berger and Lang's observations, though he found more perivascular leucocytes in histamine-wheals than they, perhaps because he used a concentration of 1 in 1,000 instead of 1 in 100,000. Now such quantities of histamine as Jadassohn used are out of the question in the formation of allergic wheals; but H-substance need not be histamine itself, and one must admit that the differences observed by Berger and Lang are only quantitative. Jadassohn proceeded to investigate other wheals, too, namely, those caused respectively by stroking (dermographism), morphia, atropine and pilocarpine. None of the patients had eosinophilia in the blood. The histology was in all cases fundamentally the same, namely, intra- and peri-vascular collections of leucocytes, of which a large proportion were eosinophils. Jadassohn concludes that one must

not interpret local eosinophilia as a sign that the reaction is allergic. It seems rather to be an essential characteristic of the urticarial reaction-type.

PURPURA. Langdon Brown divides purpura into three groups. (1) Purpura caused by definite infections: this may or may not be allergic. (2) Purpura hæmorrhagica. This is accompanied by a low platelet-count and is greatly benefited by splenectomy: it is probably not allergic. (3) Arthritic purpuras (Schönlein's and Henoch's). These are often called "anaphylactoid." Schönlein's used to be considered truly rheumatic, as was erythema nodosum, just because it was accompanied by swelling of the joints.

In purpura the blood as a whole passes through the capillary wall, whilst in urticaria the exudation is confined to serous fluid and leucocytes. A patient may have purpura in one attack and urticaria in another. In giant urticaria Brown has found organisms in the stools similar to those occurring in Henoch's purpura. A typical case showed *B. welchii*. This organism can cause fatal intoxication with hæmolytic symptoms.

In Italy there is a rare condition, "fabism," an acute hæmolytic anæmia following a meal of beans (*Vicia faba*) at some period after the first and innocuous meal of the same food. This is a clearly allergic process.

Loewy has been able to prove that a typical case of Werlhof's disease (the severest form of thrombopenic hæmorrhagic purpura) and two milder cases of thrombopenic purpura were due to prolonged administration of the new hypnotic *sedormid* (allyl-isopropyl-acetyl-urea). In the first case, after recovery, thrombopenic purpura was produced at will by giving ½–1 tablet of the drug. Direct and P.K. tests with sedormid were negative. All three patients had taken the drug repeatedly for several months without apparent ill results. After prolonged use of a similar drug, *adalin*, itching patches and purpura Majocchi have been reported. *Abasin* (acetyl-adalin) has been known to produce not only purpura Majocchi and polycythæmia, but later also a mild thrombopenia. *Nirvanol*, which is similar to phenobarbitone, usually produces a "toxic reaction" with rash, fever and eosinophilia, if given in small doses daily for 1–3 weeks. In 1 case it

seems hardly a limit to the possible sources, which include such common, and generally unsuspected, objects as woods, insect-powders, hair- and mouth-washes, toilet-creams, powders and perfumes, many flowers besides the well-known primula, for example, pelargonium, marguerite, chrysanthemum and tulip, synthetic hat-bands, collar-studs, wireless ear-phones, wallpaper and wool-fat. In any particular case the responsible substance may be detected by means of the patch-test. Mayer has worked out the proper strengths for testing purposes of a very large number of common substances: if these are laid upon the unbroken skin-surface for 24 hours they produce no inflammation in normal persons. Of course, many complex substances must be used in their natural state. The patch-test is generally carried out by placing the substance in the centre of a square of white lint, which is kept in place by a larger square of adhesive plaster. In the case of a liquid a small piece of white lint moistened with it is covered by a somewhat larger piece of oil-silk, which is kept in place with plaster. The following is a selection from his list:—

Artificial Manures

Silver nitrate	10% watery solution.
Ammonium sulphate	,, ,,
Calcium nitrate	,, ,,
Urea	,, ,,
(Calcium) superphosphate	Original substance dry and moist.
Thomas' meal	Original substance; careful controls; necroses sometimes even in normal persons.

Cleaning Materials

Persil	10% watery solution.
Sodium carbonate	,, ,,
Sodium hypochlorite	,, ,,
Bleaching powder	10% suspension in water. Controls necessary.

Oils, Varnishes, Solvents, etc.

Benzine . . .	60% in olive oil.
Benzol . . .	
Toluol . . .	
Xylol . . .	
Carbon disulphide .	0·5% ,,
Trichlorethylene .	50% ,,
Mineral oils . .	60% ,,
Petroleum . . .	20% ,,
Mobiloil . . .	60% ,,
Turpentine . .	50% ,,
Tar, asphalt, pitch .	Undiluted. Painted on the skin without plaster.
Acetone . . .	Undiluted.
Alcohol . . .	
Methylated spirit .	

Acids and Alkalis

Hydrochloric acid	1% in water.
Sulphuric acid .	
Nitric acid .	
Boric acid . .	Solid, dry and moist.
Sulphurous acid .	2% in water.
Chromic acid .	0·5% ,,
Hydrofluoric acid	0·2% ,,
Formic acid .	1% ,,
Acetic acid .	3% ,,
Benzoic acid .	1% in alcohol.
Caustic soda .	0·5% in water.
Caustic potash .	0·5% ,,
Ammoniac .	1% ,,
Borax . .	Saturated solution.

Aromatic Oils

Lemon, peppermint, bergamot, etc., all 1% in alcohol.

Alkaloids

Codeine, Morphine, Atropine, Homatropine, Hyoscine, Cocaine, Quinine, Caffeine.	1% aqueous solution of salts.
Novocaine and the other local anæsthetics . . .	

Drugs of various Composition

Hypnotics	Solid, moistened.
Analgesics	
Ichthyol, Liq. Picis Carbon., Tuminol . . .	5% in vaseline.
Resorcin	1% in water.
Iodoform, Dermatol, Aristol, Bismuth Subnitrate .	Solid, moistened.
Tincture of iodine . .	Paint on skin without plaster.

Soaps

Hard soaps . . .	Small moistened shavings.
Soft soaps	Undiluted. Controls necessary.

Shoe-Creams and Dyes

Creams	60% in vaseline.
Dyes	50% in olive oil.

Paints and Dyes

Oil-paints in tubes . .	Undiluted.
House-paint . . .	50% in olive oil.
Lac dye	50% in lanoline.
Water-colours . . .	Solid, moistened.
Mineral colours . . .	Solid.
Printing dyes . . .	60% in olive oil.
Aniline dyes . . .	2% ,, ,, or vaseline.
Aniline	10% ,, ,,
Paraphenylenediamine .	2% in vaseline.
Photographic developer .	5% in water.

Disinfectants

Corrosive sublimate . .	0·1% in water.
Formalin . . .	10% ,,
Lysoform	1% ,,
Carbolic acid . . .	2% ,,
Cresol	0·5% ,,
Naphthalene . . .	Solid.

Inorganic Salts

Silver nitrate . . .	3% in water.
Copper sulphate . . .	10% ,,
Nickel sulphate . . .	10% ,,
Iron sulphate . . .	10% ,,
Potassium bichromate .	0·5% ,,
,, chromate . .	0·5% ,,
,, permanganate .	1% ,,
Sodium chloride . .	10% ,,

That eczema is in many instances allergic in the proper sense of the term, namely, due to acquired specific sensitisation, is beyond dispute. The process has been repeatedly enacted experimentally. Low produced typical eczema in human beings by gradual sensitisation to primula. The study of this sensitisation was rendered more practicable by Bloch and Steiner-Wourlisch's success in regularly producing eczema in guinea-pigs. They were able, by means of single or repeated painting with concentrated ethereal extract, to sensitise about 95% of the animals to the active principle of primula. This primula-allergy manifested itself in an inflammatory reaction which, clinically and histologically, had the characteristics of very acute vesicular eczema. The incubation-period from the original exposure up to the appearance of sensitisation was about 7–12 days. The latent period between the application of the test-extract in a sensitised animal and the manifestation of the allergic reaction varied from 2 hours to 1 day. The duration of the inflammation was from 2 to 6 days and occasionally much more. The allergy extended over the whole body-surface. It was possible even to originate the sensitisation

with pure crystalline primin. Similarly, in Mayer's experimental sensitisation, already described, of guinea-pigs to paraphenylenediamine the histological changes associated with the allergic reaction corresponded in every respect to the criteria of eczema.

But it is much more doubtful than in the case of urticaria whether eczema-allergy is the result of an antigen-antibody interaction. At any rate, the number of cases of eczema in which it has been definitely demonstrated is hitherto a small one. In Mayer's experiments, as well as those of Bloch and Steiner-Wourlisch, it was found impossible to transfer the sensitiveness passively. Passive transmissibility to normal individuals is demanded by Doerr as a criterion of the allergic nature of a disorder. But such a use of the term allergy, which practically makes it synonymous with anaphylaxis, would exclude many classical instances of allergy: for it is difficult, if not impossible, to demonstrate it even in tuberculosis, the study of which gave rise to the expression. It does not, however, follow from unsuccessful passive transmission that antibodies are not present and taking part in the symptoms. It may be that they remain strictly cell-fixed and so elude demonstration by that method. But it will not be justifiable to reckon them among the causative factors so long as they cannot be demonstrated with some regularity. Moreover, even in accepted allergic disorders in which the presence of antibodies can be shown, it is by no means certain that the symptoms are entirely due to antigen-antibody interaction. For these reasons I consider it a mistake to demand the demonstration of transmissible antibodies as a criterion of allergy.

As a matter of fact, however, there are by now quite a number of instances of eczema in which the presence of antibodies has been proved by passive transmission. In endogenous eczema it is sometimes possible to obtain a positive P.-K. test. Such was the case in a patient in whom asthma and eczema were produced by fish (Boss) and in eczema caused by ephedrine (Abramowitz and Noun). Passive sensitisation to urinary proteose has also been obtained in eczema of internal but not of external origin. But even in eczematous states from known *exogenous* allergens, passive transmission of sensitiveness is no longer a rarity, especially with

the blister-method of Königstein-Urbach. Biberstein, in 1923, was the first to obtain a positive P.-K. test in a case of exogenous mercury idiosynerasy. In Bizzozero and Ferrari's case of idiosynerasy to iodoform the P.-K. test was positive, in spite of the fact that it was clearly demonstrated that the patient's symptoms were due to a strictly epidermal sensitisation caused by external contact. [Sulzberger (1933) states that in his experience *no* patients with only eczematous reactions possess antibodies unless they also give the immediate wheal-type of reaction to intracutaneous tests. He thinks that probably all of the reported cases of positive transmission of sensitiveness in eczema-patients were due to the presence in addition of the urticarial type of reactivity. But at least in Bizzozero and Ferrari's case (see p. 214) the latter was expressly excluded.]

Perutz, in 1927, was the first to produce an *eczematous reaction* in the test-subject by transferring to his skin the blister-fluid from a patient with turpentine-eczema. Now, before accepting as genuine the passive transmission of sensitiveness in cases of eczema, Bloch insists that the reaction in the test-subject must, as in Perutz's case, also have the character of eczema. But Doerr does not think it justifiable to demand transmission not only of the supersensitiveness but also of the reaction-type. According to the prevalent views already discussed as to the factors which determine reaction-types, Bloch's demand is certainly unreasonable, for it is generally taught that the reaction-type does not depend on the particular antigen and its corresponding antibody, but mainly on the individual. But I have already shown how, nevertheless, certain antigens do bring about almost exclusively one type of reaction and given reasons for thinking that certain antibodies have particular affinity for certain cells and are therefore by preference eczematogenic, urticariogenic, asthmatogenic, etc. There is no reason why the same individual should not produce several slightly differing antibodies to the same antigen, and thereby exhibit more than one type of reaction. But I must emphasise the point that it is *only* if this hypothesis of separate antibodies for separate reactions is accepted that Bloch's demand has any justification. But whether it is justifiable or not,

there are, as a fact, already a number of cases on record which satisfy it. Moreover, it is to be noted that the ordinary P.-K. test is ill-adapted for transmitting epidermal sensitiveness. Both the transferred sensitising fluid, as well as the allergen, ought to be applied to the test-subject as in a patch-test.

It has already been indicated in the section on allergens that a chronic eczema may be maintained, after the original excitant has ceased to operate, by a process of general sensitisation of the skin to products derived from the damaged cells in the primary lesion. I will call this disorder "autosensitisation eczema." Sensitiveness to human epidermal material is also common in non-cutaneous allergic symptoms and forms the basis of the test introduced by Storm van Leeuwen, now generally known as the "Storm reaction." Recently, Miyazaki has tried this test in a large number of different diseases in patients of all ages. His material was prepared as follows. Scales from normal skin were dissolved in water to which was added 0·5% sodium chloride and 0·4% sodium bicarbonate. After 1 or 2 days the mixture was passed through a Berkefeld filter. Of the filtrate a 1% solution was made, to which ½% carbolic acid was added for preservation. Of this extract 0·05 c.c. was injected intracutaneously. Of all the patients about 20% gave a positive reaction—men more commonly than women and infants and old people only rarely. Of those suffering with eczema about 30% were positive. As regards course, positive results were commonest in chronic cases, as regards age in the puberty-period, and as regards morphology in the lichenified form. The Storm reaction was particularly often positive in individuals with an allergic family-history. It is to be noted that the tests were made intracutaneously, evoking an urticarial response, and were therefore not best adapted for demonstrating epidermal sensitisation in true eczemas.

Bloch's view that allergy is the only cause of eczema appears to me most improbable. It would be very remarkable if the epidermal cells could only be damaged in such a way as to behave eczematously by an antigen-antibody interaction or other allergic mechanism. Direct action must also be possible. Certain substances, such as mustard, cantharides and capsicum, produce

in every skin immediate inflammation which may be of an eczematous character. Moreover, as Michael points out, in the eczemas on a varicose or intertriginous basis the important factors are clearly the tissue- or nutrition-disturbances, whilst specific allergens play a subordinate part ; for such skin reacts to a host of different substances, including many that are used therapeutically. He thinks that the most varied pathogenic processes may lead to a similar clinical picture.

Percival made patch-tests with mercury perchloride, red mercuric iodide, chrysarobin, iodoform and picric acid on a number of non-eczematous individuals. He found that the same type of reaction, which he described as "eczema," was produced by all the different substances and that its intensity (but not its character) was to some extent proportional to the concentration. The maximal latent period was 3 days, but it was generally only some hours. He found that the substances fell into two groups. Group I. substances, which included mercury-salts and chrysarobin, if in adequate concentration, produced reactions in 100% of persons, whilst when very diluted they caused a visible effect in only a small percentage. This shows, as did Bloch's sensitisation-experiments, that idiosyncrasy is only a relative term, depending not only on the nature of the substance but also on its concentration. An increase of 20 times in the case of mercuric iodide, of 300 times (mercury perchloride) and of 1,000 times (mercury perchloride in vaseline and chrysarobin in vaseline) over the minimal concentration required to evoke a reaction still leaves from 5 to 18% of individuals who do not respond. These individuals are, therefore, idiosyncratic equally with those who react to excessively low concentrations. He does not make it clear whether the same individual was relatively tolerant or intolerant, as the case might be, to all the substances in Group I. or tolerant to one and intolerant to another. The substances in Group II., including picric acid, iodoform and paraphenylenediamine, while giving the same type of reaction as Group I., differed in that by increasing their concentration only a very slight increase in the number of positive reactions was obtained. Idiosyncrasy was therefore more obvious. Those individuals who failed to react

to high concentrations of either group continued to do so on subsequent testing, showing that they did not easily develop an increased sensitiveness. Percival says that though the reactions to Group II. substances could be explained as allergic, he has difficulty in accepting such an explanation of the effects of Group I. (He uses "allergy" as synonymous with antigen-antibody interaction, which is only one of its possible causes.) For he argues that, if an individual who shows an idiosyncrasy by reacting to a low concentration does so as the result of the intervention of an "allergic" process, then the reactions to higher concentrations must be allergic also, and implies that probably neither of them are. This is surely false reasoning. In any particular instance it may or may not be allergic. The essence of allergy is that an individual who formerly reacted to one concentration, or not at all, at a subsequent period reacts to quite a different concentration, the problem being to explain the change in sensitiveness. It is quite unknown whether Percival's subjects had been exposed to these substances before or not. It would be important to find out whether new-born babies would show the same differences of sensitiveness. He himself has noted that the concentration and reaction-incidence curves of Group I. are similar to curves of cutaneous supersensitiveness to varying concentrations of tuberculin in a clinically non-tuberculous population aged over 21 years, whilst Group II. gives a curve resembling that obtained with tuberculin in clinically non-tuberculous children aged from 0 to 5 years. Surely this is a strong argument in favour of, rather than against, the explanation of the drug-actions on an allergic basis. The actual inflammatory symptoms are probably in every case secondary to primary damage of the skin-cells and the primary damage can, in some instances, be due to an antigen-antibody interaction and in others to direct action of the noxa. It is to be remembered that Lewis showed that at any rate the urticarial triple response evoked by an antigen-antibody interaction is indistinguishable from that elicited by other agencies such as trauma or heat.

Nutritive Allergic Eczema. Urbach and Fasal hold that a group of chronic eczemas depend on an alimentary idiosyncrasy. They

adduce as evidence the following observations. In a case of eczema of 11 months' duration the symptoms were abolished by omission of egg-white from the diet or, alternatively, by the administration before meals of type-specific peptone (propeptan) while egg-white was still taken. But new feeding of egg without previous peptone gave rise to new attacks of eczema. Passive transmission with egg-white as antigen succeeded in evoking in the test-subject a reaction both clinically and histologically eczematous. In a series of other cases passive transmission did not produce an eczematous but a late papular reaction, but this was specific. In the patients themselves intracutaneous tests are generally negative.

Infantile Eczema. In 1932 Moro published the results of some systematic investigations on infantile eczema. He had started with a bias in favour of Kreibich's neurogenic theory, but it was in the field of allergy, though originally sceptical as to its importance, that he obtained the most significant positive findings. His remarkable observations on the prevalent sensitiveness to egg-white have been described on p. 207. It is suggested that the sensitisation probably occurs through the placenta. It could also be derived from the mother's milk. [For it has been shown that the milk of women can act as allergen in a P.-K. test, if they have eaten raw eggs, but not if they have eaten only cooked ones. This is probably only a question of quantity, since in Walzer's oral method of carrying out the P.-K. test the giving of cooked egg to the test-subject gives positive though weaker reactions than raw egg.] The presence of an allergic state in infantile eczema has therefore been demonstrated with certainty; but that alone does not explain the genesis of the eczema, for none of the tests, either direct cutaneous or P.-K., resulted in the appearance of an eczematous but only an urticarial reaction, and superficial patch-tests in the patients themselves were negative. Moro comes to the conclusion that it is the subepidermal tissues that are specifically allergic and that the eczema itself is a secondary effect of their disorder and can be determined by non-specific agents, such as irritation of nerve-endings by rubbing. In many cases the first onset of eczema corresponded with the first intro-

duction of hen's egg into the diet. In one case of very obstinate eczema in a child fed on human milk and butter-milk, healing was initiated by the omission of egg from the foster-mother's diet.

Urbach has also found that many have a supersensitiveness to egg-white which can be passively transmitted, and W. Jadassohn and Schaaf showed that the serum of egg-white-positive eczema-children can neutralise the antigen *in vitro*. Miyazaki (1934) tested this egg-white sensitiveness in a large number of different dermatological disorders in patients between the ages of 2 months and 71 years. He obtained a positive cutaneous response in only 9·6% of the total. But considering only the children under 5 years of age suffering from eczema the percentage was about 42%, and was greater among males and most constant during the first month after the onset of the disease. He thinks that the egg-white sensitiveness is only one symptom of infantile eczema and has no direct relationship to its cause. Urbach holds the same view and points out that omission of egg from the mother's diet in breast-fed children is only rarely beneficial. Perhaps it forms the basis of or predisposes towards other sensitisations. He and Oliver have both noticed that new flares often accompany infections such as otitis or bronchitis, and that such children show an intense cutaneous sensitiveness to streptococci. The occurrence of egg-white and cow-milk sensitiveness Finkelstein, too, confirms, but also considers that they do not explain the ætiology. His view is that children who have eczema on other grounds also have the potentiality to become sensitised. He has not observed super-sensitiveness to bacteria or skin-scales. He looks on infantile eczema as a non-specific reaction of an over-sensitive skin to the most varied non-specific external irritants and cannot at present attribute it to an anaphylactic process.

Peck and Salomon (1933) investigated 15 cases and found that 4 gave positive reactions, mainly by patch-tests, to feathers, 1 to cattle-hair and sheep's wool, and 1 to cotton-seed, pyrethrum, kapok and orris-root. In all these cases there was a sudden dramatic improvement when the indicated substance was removed from the environment. On the contrary, in several cases both in infants and in later childhood, where there was a positive scratch-

test to some food such as egg-white, no improvement followed its elimination from the diet. They conclude that eczema of infants and children does not differ ætiologically from that of adults : the main factor is sensitisation of the skin to substances in the environment. Though this may occasionally be inherited, in the majority of cases it is acquired.

The majority of infantile eczemas heal spontaneously in the second year, but there is a tendency for later relapses. A minority pass straight into Besnier's flexural prurigo.

Neurodermatitis. This name is used with some diffidence to include the conditions also referred to as prurigo diathésique, lichen chronicus simplex (Vidal) disseminatus, pruritus with lichenification, allergic eczema, flexural eczema, atopic eczema, Besnier's prurigo or late exudative eczematoid (Rost). Its relationship to the nervous system has been discussed in Chapter IV., where it was also noted that histologically it is essentially similar to eczema. In American literature it is, in fact, just this condition that is frequently meant by the term "eczema." Biberstein and Fröhlich in 1932 found specific sensitisation to cow's milk, horse-hair, cat's hair, feathers or egg-white in cases of asthma together with Besnier's prurigo. In 1 case there was no immediate reaction on intracutaneous testing with cat's hair, but a positive late erythematous response was obtained by the scratch-though not the patch-test ; the P.-K. test was positive. An attack of lichen Vidal was provoked by contact of the skin with a living cat. It appears to me likely that this occurred through inhalation. In 2 cases of lichen Vidal without asthma there was supersensitiveness to wheat, rye and pea flour. Urbach considers neurodermatitis intimately related to eczema and definitely allergic. He, too, has found in certain cases of neurodermatitis diffusa general and cutaneous reactions to the oral administration of certain foods : in particular there was a high degree of cutaneous idiosyncrasy to egg-white. But in a greater proportion of the cases he has found the allergen to be an epidermal substance, such as horse-hair, horse-scales and feathers, or dust. Sulzberger, Spain, Sammis and Shahon studied 9 typical cases of neurodermatitis disseminata. There was a positive family-history of

allergic disorders in all except one. Two-thirds of the cases had other allergic manifestations, including asthma and hay-fever. Two-thirds had had infantile eczema. All gave a strongly positive reaction to direct testing with foods and inhalants (scratch-tests). Some of these were extremely severe and included general manifestations. Sometimes the excitants caused focal reactions of the skin-lesions. The supersensitiveness was markedly polyvalent. Antibodies could be demonstrated in the sera of all but one. In some were found antibodies to many different substances, and some sera had an extremely high antibody-titre. In spite of this high degree of polyvalent supersensitiveness to direct scratch-tests (shown by immediate wheal and flare) and in spite of the presence of antibodies, these cases did not react to the type of test which is positive in typical cases of contact-eczema ; for to patch-tests, performed with a routine series of common contact-irritants as well as with the fat and protein fractions of all the substances which had given positive scratch-tests, no case gave a definite eczematous response. In all of them foods seemed to be responsible at least in some degree for the exacerbation of the skin-manifestations. All improved when the foods giving positive tests were eliminated, and lapses from the prescribed diet were frequently followed by recurrences often within 1–2 hours. Incidentally, the majority of the cases were strongly positive to a direct test with silk and had silk-antibodies. Many had some neurovascular instability and all complained of severe itching.

The view that silk produces skin-manifestations of this type by coming in contact with the skin is, according to the researches of Figley and Parkhurst, mistaken. They find that it acts chiefly by inhalation. The rare cases of contact-sensitisation seem to be due to substances used for increasing the weight of silk. They described 5 cases in which inhalation of silk led to cutaneous symptoms. Intracutaneous and scratch-tests with diluted silk-extracts were positive, whilst the laying of silk on the surface of the skin caused no reaction. From a subject of classical neuro-dermatitis disseminata, giving strongly positive scratch-tests to silk, Sulzberger and Vaughan injected the serum into the skin

of a normal person and showed that the injected sites could be activated by the test-person inhaling silk.

Peck and Salomon's observations do not agree with those of Sulzberger and his co-workers. But the results are not strictly comparable, as Peck and Salomon include chronic eczemas and typical Besnier's prurigo in one group. In only a quarter of their patients between the ages of 1 and 12 years were positive reactions obtained to scratch-tests with foods. Elimination of the foods did not improve the clinical condition. There were no positive reactions to scratch-tests made with contact-substances. But nearly half of them gave positive patch-tests with contact-substances, especially feathers. In the majority of cases, when the contact-substances that had given positive patch-tests were removed from the environment, there was definite improvement. Passive transfer was obtained in several of the cases in which scratch-tests were positive, but in only one instance was the P.-K. reaction obtained with a substance giving only a positive patch-test. The scratch-tests, even when the results were positive, proved valueless in tracing the actual causative agents. They point out that their results may hold good only for the local material and that in other countries or cities an entirely different group of test-substances may be necessary. They think that eczema of all types is caused, as a rule, by exogenous substances.

Miyazaki's results with the Storm reaction led him to think that lichen Vidal and lichenified eczema are different diseases, for the former generally reacted negatively and the latter positively. Similarly, Haxthausen draws a distinction between Besnier's prurigo and lichen Vidal, on the ground that in the former he always found pronounced cutaneous supersensitiveness to food, and in the latter never. So far it has not been possible by means of the P.-K. test or its modifications to induce a neurodermatitic type of lesion in the test-subject.

Predisposition. We have seen that specific supersensitiveness to many substances can be acquired by the elaboration of specific antibodies, and that this process occurs more readily in some individuals or families than in others. If it is a fact that the clinical manifestation is always ultimately brought about by the

liberation of H-substance from damaged cells, are we to conclude that some individuals' skin is more readily acted upon by histamine than others? This is not the case (Lewis). A dermographic individual, for instance, does not wheal any more easily to histamine than do normal controls. His supersensitiveness is, therefore, an exaggerated susceptibility to trauma. In the case of allergic disorders the individual predisposition seems to consist in "a pathological increase of the physiological sensitisability" (Doerr). This pathological increase may itself be either inherited or acquired.

HEREDITY. The estimation of the hereditary influence is, as always, rather difficult, and depends largely on family-history and statistics. Coca has essayed to set up a separate group of allergic disorders in which heredity is the paramount causal factor. This inherited state he calls "atopy" (ἀτοπία = out-of the-wayness, hence strangeness). As examples of disorders due to atopy he includes asthma, hay-fever, eczema (infantile eczema and neurodermatitis), urticaria and migraine. He draws a number of distinctions between atopic and anaphylactic sensitivity, between anaphylactic antigens and "atopens" (the allergens that evoke atopic disorders), and between anaphylactic antibodies and human atopic antibodies, which he calls "reagins." Active sensitisation to an atopen, as contrasted with anaphylaxis and contact-dermatitis, cannot be induced by artificial contact in persons not hereditarily atopic. Anaphylactic antibodies, he says, have the essential properties of precipitins, whilst such precipitins have not been found responsible for human allergy. He further states that reagins are peculiar to human beings and are incapable of passively sensitising guinea-pigs. He thinks that both kinds of antibodies are produced by human beings against the same antigen (Otto's "Doppelgänger"). As already explained in the section on antibodies, György, Moro and Witebsky have demonstrated certain distinctions between ordinary human anti-egg antibodies and those antibodies which occur in subjects of infantile eczema with supersensitiveness to egg-white. Moro called the latter "trophergines," and they correspond with Coca's reagins. Similarly Schloss has shown that egg- or milk-precipitating sera of children that have received these proteins in their food are capable

of passively sensitising the guinea-pig's uterus, whilst the atopic reagins lack this property (Spain and Cooke). On the other hand, Moro found that it was only the reagin that could transmit sensitiveness to normal human skin. Freund also tries to distinguish atopic reagins from other antibodies on the score of their tenacious affinity for tissues. He reports that bacterial agglutinins and anaphylactic antibodies diffuse readily from the site of their cutaneous injection, disappearing within about 18 hours. Reagins, on the contrary, attach themselves within 2 minutes to the tissues at the site of their intracutaneous injection and remain demonstrable there for several weeks. But he has only shown this difference in tenaciousness with regard to the skin. I have already adduced reasons for supposing that there are considerable structural differences between individual allergic antibodies and between individual anaphylactic antibodies and that these structural differences are marked by affinity for different tissues. It appears to me that the distinctions drawn by Coca, Freund and others are not fundamental but merely show that those antibodies responsible for human cutaneous allergic manifestations have a special affinity for the skin. Moreover, as regards Coca's distinction on the grounds of precipitation, Alexander, in 1924, found that guinea-pigs could be rendered anaphylactic to rye-pollen in spite of the fact that he could not induce the formation of precipitate or complement-fixation in detectable amounts. Conversely, Cocker and Ramsden have produced precipitins to rag-weed pollen in rabbits and guinea-pigs. Doerr, too, holds that reagins (the antibodies responsible for positive P.-K. tests) are identical in all essentials with anaphylactic antibodies. Similarly, especially in view of our present knowledge of the properties of haptens, it is impossible to make any sharp distinction between antigens and atopens. Topley points out that the hereditary factor in animal-anaphylaxis has hardly been studied at all, and on the premises of our present knowledge of the influence of genetic factors operating in anaphylaxis and in atopy he considers that there are insufficient grounds for postulating an essential difference between them.

The influence of heredity is shown in the following ways. (1) The stronger the influence the greater is the number of

affected offspring. (2) The stronger the influence the earlier is the age at which symptoms begin. (3) The clinical form of the sensitivity is, to some extent at least, determined by heredity. Balyeat studied the influence of heredity in 181 cases of "atopic eczema" (not obviously caused by external contact); 12·3% gave a bilateral and 64·3% a unilateral positive family-history. It was therefore negative in only 23·4%. This is a small proportion when compared with the 39·9% and 41·6% of negatives found by Balyeat and by Spain and Cooke respectively in their large series of asthma and hay-fever patients. The curves of the age of onset of symptoms were similar to those obtained by Spain and Cooke in asthma and hay-fever. These curves show that "under conditions that promote adequate exposure to the excitant the date of onset of symptoms is determined by heredity for each atopic individual."

Coca thinks that even the particular atopen to which an individual is going to become sensitised is predetermined by heredity and adduces the following evidence. After administration of therapeutic horse-serum to non-atopic and atopic persons (the latter were insensitive to horse-serum but sensitive to other allergens), supersensitiveness to the serum developed just as frequently in the non-atopic as in the atopic individuals (Cooke and van der Veer). This observation was confirmed and extended by Brunner, who injected typical atopens over a period of weeks into atopic persons who were sensitive to other allergens, but not to the ones injected. Only in a single case did a transient supersensitiveness develop.

Just as in his observations on serum-disease already discussed, so in atopy Coca doubts whether the antibodies are really responsible for the clinical symptoms. Thus Baldwin, in a study of 36 offspring of atopic parents, found that the production of atopic reagin did not begin till after the onset of symptoms. This is not a cogent argument: because antibodies could not yet be demonstrated in the serum, it does not follow that they were not present in the cells concerned in the allergic symptoms (the probable site of their elaboration). Nevertheless, there certainly are great difficulties in correlating clinical symptoms with the

presence of antibodies. Thus Sulzberger asks :—" Why do patients with hay-fever and asthma, who possess reagins which can create urticarial skin hypersensitivity (as shown by P.-K. test), have no perpetual and generalised urticaria ? " This may be merely because under natural conditions the allergen does not reach the cutis in adequate amounts. For if pollen-extract is pricked into the skin of hay-fever subjects it *does* cause whealing.

On the ground of heredity, Coca further tries to separate atopic disorders from contact-dermatitis, which, he says, is just as frequent in non-atopic as in atopic persons. He adduces Bloch's 100% successful experimental sensitisation of adults to primula, but disregards the fact that they were not all equally easily sensitised and will not accept the steadily increasing evidence, which I have already given, that in this type of sensitisation specific antibodies are sometimes demonstrable.

Langdon Brown suggests the possibility that the familial and hereditary predisposition to allergy is due to a lack of the specific ferment histaminase, discovered by Best and McHenry in 1930, which in the normal individual destroys histamine as soon as it is set free. Garrod has shown that many inborn errors of metabolism are due to the lack of some such specific ferment, and that this lack can be transmitted along Mendelian lines. In that case one would expect to find abnormal amounts of the products of protein-disintegration in the blood or urine in allergic subjects.

Metabolism. Barber and Oriel, feeling that there must be some inborn metabolic error, conducted extensive biochemical investigations to try and support that hypothesis. Among the clinical conditions studied were asthma, urticaria, angioneurotic œdema, migraine, prurigo and infantile eczema. The following is a summary of their results. (1) Certain phenomena occur with remarkable constancy in various manifestations of the allergic state ; some of these have already been noticed in experimental anaphylaxis and in serum-sickness. (2) In the allergic state, whether it be intermittent, as in certain cases of urticaria, angioneurotic œdema and asthma, or more or less chronic with periodical exacerbations or remissions, as in Besnier's prurigo

and infantile eczema, there can be recognised a definite cycle of events corresponding to the pre-paroxysmal stage, the actual paroxysm and the post-paroxysmal stage :—(*a*) rise in the amino-acid content of the blood ; (*b*) rise in the ammonia-excretion out of all proportion to the excretion of acid in the urine ; (*c*) diminution of chloride in the corpuscles, its retention during the paroxysm and its subsequent excretion, as in pneumonia and other acute infections ; (*d*) deposition of urates in the pre-paroxysmal or paroxysmal stages ; (*e*) ether-reaction in the urine during the period of active manifestations ; this probably depends on the presence of the proteose described in the section on allergens ; (*f*) diuresis, with decreasing acidity and sometimes marked alkalinity of the urine in the post-paroxysmal stage.

It is not clear whether these changes are, as the authors suggest, inborn predisposing metabolic disorders, so much as part of the symptomatology of allergic reactions. Moreover, in many of the conditions studied it is far from certain that the clinical symptoms did, in fact, depend on allergy.

That allergic disorders depend on other factors, often temporary ones, besides specific sensitisation is also indicated by the following facts (Beckman) :—(1) Skin-tests give positive reactions in only about 50% of the cases. (2) Clinical cure can exist in the presence of the offending substances, in spite of the fact that the skin-reactions remain positive. (3) Numerous persons give positive skin-tests, though they have never, throughout their lives, manifested any allergic symptoms. (4) Allergic patients are peculiarly susceptible to emotional influences and atmospheric conditions, being frequently benefited by a sea-voyage or sojourn at a high altitude. Beckman thinks that allergics have the tendency to store up too much reserve alkali, that is, to neutralise too rapidly or too effectively the acid substances constantly being liberated into the blood-stream. He argues that allergic states rarely occur in those conditions tending towards acidosis, such as diabetes mellitus, starvation, pregnancy and acute infectious diseases. (I doubt if this is quite true as regards diabetes and pregnancy.) Sea-voyages tend to produce a degree of acidosis, especially if there is vomiting. At high altitudes

there is loss of alkali-reserve. Hurst has shown that patients sensitised to cats in the lowlands are not affected by cats in the highlands. Calcium, which is often beneficial, can only reach a higher level in the blood by increasing the relative acidity.

Diet. As a result of an allergen-poor salt-poor diet, Gerson has observed that oversensitiveness to food and other endogenous substances may appear for the first time, *e.g.*, to meat, salt, egg-white, milk, nicotine, salicylic derivatives and opiates. The Gerson diet therefore has, to start with, a strong sensitising effect.

Sulzberger and Mayer attempted to appraise the influence of diet on the sensitisation of guinea-pigs to arsphenamine, paraphenylenediamine, phenylhydrasine, etc. They found striking differences between animals fed on green summer-fodder and those fed on dry winter-fodder. The green fodder (alkaline ash) inhibits sensitisation and the dry fodder favours it. This was demonstrated conclusively both with arsphenamine and paraphenylenediamine, the reactions to both of which were of an eczematous type. Further experiments showed that the difference depended not so much on vitamin-content as on the acid-base balance. Stokes and Pillsbury's views on the relationship of the acid-base balance to the emotions and their effect on allergy have been discussed on p. 105. It is difficult to draw any conclusion on the acid-base problem from the work of these several observers; for, according to Barber and Sulzberger, sensitisation is favoured by a shift to the acid side, whilst, on the contrary, Beckman and Stokes blame a deficiency of acid. It is by no means to be assumed that every variety of sensitisation requires the same set of predisposing factors. At any rate, Sulzberger's experiments clearly demonstrate the effect of diet on sensitisability, and this in turn may explain some instances of seasonal variation.

A *seasonal* variation with peaks in spring and autumn has been found by Mayer and Cajkovac to occur in general non-specific sensitiveness of the skin to a series of test-substances, not only in eczematics, but also in subjects of lichen Vidal and prurigo of Hebra. Such a regular fluctuation is less obvious in other skin-diseases. In lichen Vidal and prurigo of Hebra there is, in addition, a pronounced summer peak.

Sulzberger made the interesting discovery that, whilst in Breslau he could sensitise 98% of guinea-pigs to neoarsphenamine, in Zürich he obtained only 50% of positive results and in New York none at all, in spite of every care to reproduce the same technique and using the same brand of neoarsphenamine. This *geographical* variation may account for some of the puzzling difficulties which one worker has in confirming the findings of another. At first he thought the cause lay in difference of race or stock, but later he showed that New York guinea-pigs when transported to Breslau and Zürich could there be sensitised with the same regularity as the indigenous animals.

Nervous System. Dixon in 1907 showed that after the vagus to the heart had been stimulated a substance could be extracted from the heart-muscle which was antagonised by atropine. Dale confirmed Dixon's experiments and further showed that adrenalin directly antagonises histamine. Langley showed that the cells in the adrenal medulla which produce adrenalin are identical with those which, in other sympathetic ganglia, form the post-ganglionic fibres. (Masson supposes a genetic relationship between the adrenal medullar cells and the epidermal Langerhans cells.) That is perhaps why adrenalin produces on any part the same effect as stimulation of the sympathetic nerve to that part. Dale's observation explains why adrenalin is so effective in an allergic crisis, for it both neutralises histamine and stimulates (or has the same effect as) the sympathetic, *i.e.*, inhibitory nerves to plain muscles. It is also clear how the poisonous effect of histamine would be predisposed to by vagotonia, which is present in states of mental worry, and how a sudden shock which liberates adrenalin can cut short an allergic attack. Most allergic manifestations are worse at night, which Brown attributes to predominance of vagal activity. It is, however, difficult on this basis to explain some instances of urticaria, apparently evoked by fright. The relationship of the emotions to allergy has been discussed on p. 105.

Reiss tested the effect on allergic reaction of administering various endocrine-pharmacodynamic substances that act on the vegetative nervous system. He found that the greatest

effect was produced by testicular and thyroid extracts, which increased the reaction. Testis increased its extent and thyroid the degree of local swelling. It was also somewhat strengthened by atropine. On the other hand, hypophysis and adrenalin weakened it. The allergens whose effects showed the greatest difference, according to whether they were injected before or after the period of treatment with endocrine substances, were peptone and horse-serum. The responses to histamine were influenced in the same way.

Infection and Intoxication. There is little doubt that various intercurrent infections and intoxications can profoundly influence the course of allergic processes. Stokes and Kulchar have made a study of this subject with special reference to arsphenamine dermatitis and mycotic infections. They conclude that not only can minute amounts of arsphenamine in arsphenamine-sensitive persons light up and tend to generalise a local mycotic dermatitis, but conversely dermatophytic infections can extend the range and increase the severity of the allergic dermatitic reaction to the drug. They further suggest that a dermatophytic focus may possibly serve through the induction of local vasodilatation as the starting-point of a salvarsan dermatitis.

Bloch pointed out in 1924 that sensitisation might become *polyvalent*, whether it took place from within or without, and that fungi and fungous products might induce sensitiveness to drugs and other substances in two ways:—(1) through the polyvalent broadening of the sensitivity to include drugs in addition to trichophytin; (2) through actual injury to the skin caused by the mycotic inflammatory process permitting the penetration and intimate contact of applied medicament. That in an allergic individual sensitisation is apt to be polyvalent, is also suggested by the observations of Moore, Woo and Robinson (1931), who found that atopic subjects reacted distinctively and more strongly to the intracutaneous injection of arsphenamine than normal controls. Stokes and Cathcart (1923) brought evidence to show that bacterial infection, focal or intercurrent, was a significant factor in precipitating or modifying the course

of arsphenamine dermatitis, and Kerl in 1932 described a case in which there were temporary exacerbations of the eruption with each extraction of infected teeth, with final recovery when all had been removed.

It is well known (see p. 428) that certain circulating substances, either endogenous like hæmatoporphyrin and tissue-products or exogenous like arsenic and flavine, can enormously increase the sensitiveness of the skin to ultra-violet rays. Here the mechanism of antibody-production seems hardly applicable. It is almost certain that a similar process accounts for many instances of raised sensitiveness to other allergens, and that some idiosyncrasies are to be explained on the basis of such intoxication rather than by anaphylaxis.

LOCALISATION. Auer in 1920 pointed out that the mere induction of a localised vasodilatation, as with xylol, in a sensitised animal, led to an exaggerated local inflammatory response to the injection of the specific allergen. Urbach observed that a patient who had had several attacks of erysipelas confined to one limb became locally sensitised to quinine given by mouth. This had been well tolerated, but now evoked an eczematous reaction in that limb alone. Freeman thinks that localisation of clinical manifestations in allergic subjects is determined by previous tissue-damage.

At any rate, it is important to remember that a person's skin may not be equally sensitive to the same substance in every area at a given time. Sulzberger and Kerr have noticed in several cases of eczema of the face caused by face-powder that the reactivity to patch-tests of the V-shaped sterno-clavicular area of the neck was much greater than that of the back or forearms and was equal to that of the face. Therefore the V-area of the neck is admirably qualified as a testing-ground in cases of dermatitis of the face. In employing patch-tests in occupational dermatitis the sites of previous eruptions must be tested before a substance can be exculpated.

A patient of my own who suffered from recurrent severe attacks of eczema of the scalp and face was thought for a long time to be suffering from seborrhœic eczema. The attacks were, however,

eventually traced to the wearing of a hat lined with brown silk. This lining gave a positive patch-test on her forehead. Tests with silk were negative. Patch-tests were then made with paraphenylenediamine 2% in vaseline on her arm. This was quite negative, but a similar test on her forehead was strongly positive. Moreover, it evoked a flare-up of the site previously tested on the arm. The forehead did not react to any other suspected substances.

Immunity

There is really no sharp distinction between anaphylaxis and the kind of immunity that is conferred by specific antibodies. Anaphylactic shock depends largely on the mode of introduction of the antigen, being nearly always due to its injection. If, however, in the anaphylactic state recontact with the antigen takes place through the skin or mucous membrane protected by epithelium, there ensues a local anaphylactic inflammation which, according to Roessle, by virtue of the œdema, hinders absorption and thereby serves a useful purpose. Doerr also considers that there are only quantitative differences between anaphylaxis and immunity.

But phases occur in specific supersensitiveness, in which the exhibition of allergen no longer causes *any* morbid effect. Tissue-immunity probably does not depend on the presence of circulating antibodies. We have seen that P.-K. antibodies are demonstrable in individuals presenting allergic symptoms. There are at least two possible explanations for this. (1) The free antibodies are not enough to saturate the antigen. It has already been shown that very large amounts of antibody are necessary to neutralise small quantities of antigen. (2) The antigen reaches the reacting cells and combines with cell-fixed antibody without previously entering the circulation. Immunity would also arise if the cells lost their antibody or ceased to produce any. Further, Kellaway and Cowell have shown that in anaphylaxis plain muscle cells may, under certain circumstances, be rendered less vulnerable to the result of antigen-antibody interaction. This is therefore a true cellular immunity.

Treatment

It will, of course, be impossible to deal here in detail with the treatment of all the individual dermatoses attributed to allergy.

When possible, *exposure to the responsible allergen must be avoided.* In *eczema* and *neurodermatitis* Peck and Salomon, and also Urbach, found that elimination-diets proved of great value in a small number of cases in all age-groups. Allergens arising from excessive intestinal putrefaction can be countered by suitable diet, administration of digestive aids, such as pancreatic tablets, antiseptics or aperients. Allergens from infective foci can be eliminated by surgery. In a case described by Marchionini and Ottenstein of urticaria caused by the patient's abnormally acid sweat, the skin being proved to be supersensitive to acid, it was possible to improve the condition by an alkalising diet and medication. In autosensitisation from tissue-damage the absorption of allergen is minimised by local sedatives and the prevention of rubbing and scratching.

But only too often the avoidance of exposure to the allergen is an impossibility and one has to resort to methods of "desensitisation."

Specific Desensitisation. SCEPTOPHYLAXIS. Albertoni (1880) was the first to point out a way of avoiding anaphylaxis. He showed that the shock which otherwise follows the second injection of an antigen can be prevented by injecting a minute quantity of the same substance about one hour previously. This method was called "sceptophylaxis" by Ancel and Bouin and has been modified in various ways. Thus Pagniez and Pasteur-Valéry-Radot claimed in 1916 that one can sometimes prevent attacks of *alimentary urticaria* and *Quincke's œdema* by giving the patient one hour before the meal small quantities of the foods to which he is intolerant. Frei has also reported successes in food-idiosyncrasies by giving tiny amounts before meals. This method has been more recently elaborated by Luithlen and Urbach, who use specific peptones for various foods under the name of "propeptans." Urbach has found it successful in certain *chronic eczemas*, due to an alimentary idiosyncrasy in which the

skin-tests are negative and cutaneous desensitisation fails. But it never succeeds in neurodermatitis, even if a food seems responsible. But the supposition of Luithlen and Urbach, that their propeptans retain the specificity of the protein from which they have been prepared, could not be confirmed by W. Jadassohn and Schaaf using Dale's method. For uterus-horns of guinea-pigs sensitised to extract of pork or egg-white still responded as usual to their respective proteins, even if they had been exposed for 30 minutes beforehand to solutions of the corresponding propeptans. Sceptophylaxis has also been applied successfully in *drug-idiosyncrasies*, for example, in antipyrin-intolerance by Widal. The single doses give protection for only a few hours, but occasionally after long-continued treatment the intolerance disappears.

Sulzberger carried out some experiments on the prevention of *sensitisation to neosalvarsan*, which are of particular interest in that neosalvarsan is a defined chemical substance. Guinea-pigs injected intracutaneously with neosalvarsan showed a " flare-up " at the site of injection, beginning from the sixth to the fifteenth day and increasing in strength for several days ; but if, 24 hours after the intracutaneous injection, they were given intracordially a third of an M.L.D. of 914, they behaved quite differently. A small papule appeared at the intracutaneous site within the first 24 hours and disappeared after about two days ; but no " flare up " occurred ; it seemed to have been prevented by the intracordial injection. Thirty-one days after the preparatory intracutaneous injection a second intracutaneous injection of the same amount produced an intense supersensitive reaction in those that had not been treated intracordially and none in those that had. In the not intracordially treated group the test-injection produced a synchronous focal reaction at the site of the preliminary injection, which had previously returned to normal. No such focal reactions occurred in those treated intracordially. Moreover, in the latter the second intracutaneous injection did not itself act as a sensitising one. If the intracordial injection was delayed till 14 days after the sensitising one, it was no longer capable of preventing or reducing a supersensitiveness already evidenced by a " flare-up."

The delayed intracordial injections never produced shock, but sometimes caused a morbilliform eruption, and in one case a very severe generalised dermatitis. Salvarsan dermatitis in man has sometimes been observed after a paravenous injection, followed after a considerable interval by an intravenous one. It might, therefore, be wise to follow up an accidental paravenous injection by a full intravenous one, either immediately or within 24 hours. There is no evidence at present as to whether the prevention of salvarsan supersensitiveness by intracordial injection of salvarsan is a *specific* effect. Though Frei could sensitise 8 out of 66 normal individuals, he could not sensitise any luetic patient who was being treated intravenously with salvarsan. But it has been observed that luetics are resistant to sensitisation with other substances also, and they are unsatisfactory as test-subjects for the P.-K. reaction. This might be due to the infection, or possibly to an unspecific protection against sensitisation resulting from salvarsan injections.

ANTI-ANAPHYLAXIS. A state of anti-anaphylaxis has been found to follow the injection of several gradually increasing doses of an antigen, beginning with very minute quantities. It can be induced in a short time, even 1–2 hours, but it only lasts for some weeks. Too high doses may have the opposite effect of bringing about an attack, followed by heightened sensitiveness which may persist for a long time. Even if such treatment is at first successful, continuation with higher doses may be accompanied by renewed sensitisation. After the first dose, which must be extremely small, van Leeuwen recommends as a general plan that it should be increased every second day till the active dose, as indicated by the following signs, is reached :—(*a*) *diminution of the allergic symptoms*, or (*b*) *general reactions*. I would add *a manifest focal reaction*. In the case of (*a*) no further increase in the dose is necessary or advisable ; the same dose can be continued twice a week. After all symptoms have ceased an injection should be given every 14 or 28 days for at least 6 months. It is unwise to attempt to obtain complete desensitisation by raising the dose, as there is danger of re-sensitising. In the case of (*b*) the injections should be stopped for 2 or 3 weeks, and the first dose of the new

series should be 1/1,000 of the one last given. Occasionally a severe reaction is followed by desensitisation, but it should not be aimed at deliberately, as it is too dangerous.

Boss reported a striking instance of asthma and *eczema* which began at the age of 6 weeks and persisted for 19 years. The skin of the entire body was involved. Intracutaneous tests with fish-extracts produced typical asthmatic attacks with extreme itching over the whole body. Treatment with increasing doses of fish-extract intracutaneously produced considerable improvement. When further progress ceased, different sorts of raw, cooked and smoked fish were given orally in quantities increasing from 5 to 100 gm. in a period of about 5 weeks. He was discharged cured about 10 weeks after the discovery of the cause. No local treatment was used. The P.-K. reaction was positive. It is interesting that it remained just as strongly positive after clinical desensitisation, which shows that by this method the free circulating antibodies are so far from being saturated that they do not appear to be even diminished.

Similarly, Spain and Cooke achieved clinical immunity in a case of *dermatitis venenata* due to *toxicodendron radicans* by giving the extract hypodermically or orally. They made the remarkable observation that the development of clinical immunity to natural exposure was not accompanied by any demonstrable weakening of the patch-test. As in Boss's case, the desensitisation does not appear to depend on saturation of antibodies, for if the treatment is increased in strength too rapidly, or if the intervals are too short, general itching or the lesions typical of ivy-poisoning may ensue.

In *exogenous contact-eczema* a few striking successes have been reported. Thus Coca mentions a painter, who, on account of his sensitiveness to turpentine, had been obliged to give up his work for two years. After a few injections of turpentine at 7-day intervals he was able to resume his occupation without further trouble. Against this particular noxa Perutz has also desensitised patients by giving small increasing doses internally, and Gougerot and Blamoutier have succeeded with repeated cutaneous inoculations. But in exogenous eczema these instances remain the

exception, and it is significant that in the experimental sensitiveness to primula produced by Bloch in guinea-pigs it was not found possible by means of repeated cutaneous applications to bring about even relative desensitisation.

In *infantile eczema* Moro found that attempts to desensitise against egg-white led to the opposite of what was desired; but we have seen that the sensitiveness to egg-white is probably a symptom rather than the cause of infantile eczema.

Urbach has sometimes found the method successful in those cases of *eczema*, generally endogenous, in which the intracutaneous test is positive, and in which there are generally other allergic manifestations; but not in cases where the noxa has a direct exogenous action. He has also succeeded with it in *neurodermatitis*, giving intracutaneous injections of the appropriate allergen, which has generally proved to be epithelial, such as horse-hair, horse-scales or feathers. Biberstein and Frölich succeeded in curing a case of disseminated *lichen Vidal*, in which there was sensitiveness to wheat, rye and pea flour, by specific and successive desensitisation to each allergen. Similarly, in Figley and Parkhurst's cases of *neurodermatitis*, attributed to the inhalation of silk, gradually increasing injections of diluted extract of silk were found useful.

Proteose. Barber claims very good results from the intracutaneous injection of autogenous proteose in *neurodermatitis*, *dermatitis herpetiformis*, *urticaria*, *angioneurotic œdema*, and, to a less extent, in *Besnier's prurigo*. Psoriasis combined with rheumatoid arthritis responds well, but not uncomplicated psoriasis. He finds that patients are extremely sensitive to their own proteose, and that an excessive dose causes an acute exacerbation. Sometimes it has been successful after other (non-specific) methods such as autohæmotherapy, intravenous injections of sodium thiosulphate, etc., have failed. The initial dose may have to be as small as 0·05 c.c. of a 1 in 1,000,000 dilution. Burgess considers the clinical results of treatment are encouraging, especially in chronic *urticaria* and *eczema*. For the initial dose he advises 0·01 of 1 in 100,000 or 1 in 1,000,000. He had some success in psoriasis too. In those that were clinically cured the skin-reaction

to proteose before treatment was positive, whilst after treatment it was negative. As to the specificity of this method, he does not mention whether the proteose of other persons, not suffering from the same disease, was tried.

On the whole, therefore, specific desensitisation is very uncertain. Moreover, its rationale is extremely doubtful. I have already pointed out that apparent clinical cure is often unaccompanied by any evidence of saturation of antibodies. If this is the object, how can it be achieved by small doses if large ones always make matters worse? Van Leeuwen says he cannot cure his patients by desensitisation if the environment is full of the allergen. If these large quantities cannot use up antibody, surely small intracutaneous injections cannot be expected to.

Non-specific Desensitisation. Even when the allergen is known, non-specific methods are often more efficacious than specific, and in many instances of supposed specific desensitisation it is difficult to be sure that the process is in reality a specific one. Oversensitiveness to a certain substance can, at any rate, often be reduced by the injection of small quantities of some other allergen, provided that the patient is supersensitive to this other allergen also. It is even doubtful whether this proviso must always be satisfied.

Tuberculin Treatment. Van Leeuwen was struck by the very high proportion of his allergic patients (chiefly asthmatics) that presented oversensitiveness to tuberculin. By this he means an increased reactivity to its subcutaneous injection, which is by no means always accompanied by a positive von Pirquet test. He was thereby led to use it as a desensitising agent with considerable success. It was first introduced for this purpose in 1920 by Pietroforte and by Ranke. Injections of Koch's T.O.A. are given subcutaneously and may have to be continued for about a year. If the patient gives strongly positive skin-tests, or if there is any suspicion of active tuberculosis, the first dose should be 1 c.c. of a 1 in 10,000,000 dilution. If the skin-tests are only moderately positive and there is no suspicion of active tuberculosis, it can be 1 in 1,000,000, and in those with negative tests 1 in 100,000. The doses are increased by 0·1 c.c.

on a similar plan to that outlined in the section on anti-anaphylaxis. Practised in this way tuberculin treatment has been found to be harmless. Clinical improvement may manifest itself only after some months.

REACTION TREATMENT. This is based on the experience that during an acute infectious disease a patient who has been suffering from severe allergic attacks may completely lose them. This period of well-being may last up to 3 or 4 weeks after the intercurrent disease has been cured ; then the old allergic attacks often reappear. On the other hand, sometimes such intercurrent diseases make the allergy worse. It is therefore not astonishing that injection of some material which provokes a reaction, namely, a local aseptic inflammation and general disturbances, such as fever and headache, may either improve the allergic condition or make it worse. The mode of action may possibly be explained by the discovery of Gottlieb and Freund that after intramuscular injections of milk or other proteins in rabbits the sensitiveness of the animals to adrenalin may remain increased for a period of some weeks. It is possible that tuberculin treatment, and also many supposed specific treatments, really belong in this category.

Milk Injections. Van Leeuwen's routine is as follows :—first day, 0·1 c.c. of sterilised milk is injected subcutaneously, followed six hours later by 1 c.c. ; second day, 2 c.c. subcutaneously ; third day, 5 c.c. intramuscularly ; fourth day, 10 c.c. intramuscularly ; fifth day, 2 c.c. subcutaneously ; sixth day, 2 c.c. subcutaneously ; seventh day, 0·2 c.c. subcutaneously ; eighth and following days, 0·1 c.c. subcutaneously. Generally the first and smaller doses are tolerated without any inconvenience, but after the larger injections of 5 or 10 c.c. the patient usually has a general reaction, consisting of headache, malaise and fever. With these reactions in the majority of cases there is some improvement of the allergic condition. If, on the contrary, it is made worse, the milk injections must be stopped or continued in small doses only. It must be remembered that the patient may be supersensitive to milk ; hence the necessity of the preliminary doses of 0·1 c.c. and 1 c.c. Moreover, after a first series of milk injections, the patient, although not supersensitive before, may

have become sensitised ; therefore the second series of injections, if given after an interval longer than 8 days since the last injection of the first series, must again be preceded by a preliminary injection of 0·1 c.c. Disregard of this rule has caused death in more than one case. In an instance reported by van Leeuwen, the victim was not even known to be an allergic subject and was under treatment as an ordinary case of gonorrhœa.

In this method the decision as to whether the therapy is going to be successful or not is reached within a few days. But even after it has been applied for a considerable time the symptoms tend to reappear if it is discontinued. Van Leeuwen often uses it during the first period of tuberculin treatment before the active dose of the latter has been reached.

Peptone. After Pagniez and Pasteur-Valéry-Radot's demonstration that attacks of alimentary urticaria can sometimes be prevented by giving small quantities of the offending foods shortly before the meal, it was soon found that a similar effect could be obtained by giving non-specific peptone. It is best to give it exactly three-quarters of an hour before every meal in doses of ½ gm. No food whatever should be taken between meals. It should be apparent after some days whether the treatment is succeeding, if so, it should be continued for one or two months. This is the method chiefly recommended by van Leeuwen for *urticaria*. Its efficacy is increased by giving hydrochloric acid as well. On this I would comment that I have seen cases of urticaria following directly after meals which were cured by giving hydrochloric acid alone. Peptone was first used by injection as a general desensitiser by Auld in 1917. A 7½% solution is used for intramuscular administration. The dosage ranges from 0·3 c.c. up to 2·5 c.c. As a rule the doses are increased slowly and given every fourth or fifth day ; they can also be given on a plan similar to that for milk. Some patients respond better to one and some to the other remedy, but van Leeuwen has found peptone to be less often successful than milk.

Sulphur Injections. Sulphur has the very great advantage over milk that it cannot *per se* cause anaphylaxis. Moreover, the reactions produced by it are more regular. The standard dose

is 1 c.c. of a 1% suspension of sulphur in olive-oil intramuscularly. In most patients this produces in about 12 hours a painful local reaction, fever and headache. If during this period the allergic symptoms diminish, van Leeuwen continues with the treatment once a week; but he now tries to find a dose which gives little or no fever and still improves the patient's condition. This is generally between 0·2 and 0·5 c.c. of the 1% solution. If, after improvement for some months under this treatment, a relapse ensues, the dose has to be considerably reduced, as a rule to about 0·1 c.c. of a 1 in 1,000 suspension. He has had considerable success by this method in a series of *eczemas*, allergic in character, but in which the specific allergen was not found. It included many instances of the *late exudative eczematoid of Rost*, and some cases of facial eczema which habitually disappeared in mountain-air and returned some days after coming down. Some cases of *urticaria* which had not benefited from peptone were cured by sulphur injections.

Autohæmotherapy. Injection of a patient's own blood was originally introduced by Sicard and Gutman in 1912 for the treatment of epilepsy, and was stated by Spiethoff and Luithlen as early as 1913 to cause a diminution of the action of external irritants on the skin. It was first used with the idea of desensitisation in cases of *occupational eczema* by Tzanck in 1921. Burgess tried autohæmotherapy in psoriasis, eczema, varicose dermatitis with autosensitisation-eruption, chronic urticaria, toxic erythema, furunculosis, idiopathic general pruritus and Besnier's prurigo. Half the cases were cured or greatly relieved, the best results being obtained in *acute psoriasis* and *autosensitisation-eczema* supervening on chronic varicose dermatitis. He had little success in chronic urticaria. From his studies of its mode of action he concluded that its effects do not depend on leucocytosis, and that it has no influence on the sedimentation-rate of red corpuscles or any constant influence on the production of proteose. Those cases that were relieved by the treatment had given a positive reaction to their proteose before it and after it were found to be negative; those that were not relieved had either given a negative reaction before or continued to be positive after.

The diminution of sensitiveness to proteose was not compared with changes in reactivity to other substances and was probably not specific. Thus in a hay-fever patient whose skin gave immediate reactions to extracts of several pollens, I found that this reactivity had disappeared after a course of autohæmotherapy. I agree with Burgess as to its efficacy in autosensitisation-eczema, but have also found it very effective in certain cases of persistent *urticaria* and of *general pruritus* of obscure origin. Van Leeuwen has found it the best treatment for those cases of urticaria that correspond with the menstrual period. He gives 10 c.c. weekly for 6–8 weeks.

Febrile reactions can also be achieved by injecting T.A.B. vaccine. But fever and other unpleasant general symptoms are by no means essential for the production of desensitisation, and in my experience the best results have been obtained without them. The effects of fever should, in fact, be studied quite separately. In the case of autohæmotherapy, Brooks, Pack and Goode came to the conclusion in 1923 that the usual "reaction" was not a useful focal one, and that it was due to a certain group of proteins differing from the group responsible for the clinical improvement. They prepared a definite mixture of protein fractions from ox-blood-fibrin by peptic digestion and subsequent fractionation by precipitation. When given intravenously it had a favourable influence in infections without the production of fever, chills or sweating. It is available under the name "hemoprotein" in sterile 10% solution, of which 0·2 up to 3 c.c. or even more can be given, in acute cases once or twice daily and in chronic once a week. It has not yet been extensively tested in cutaneous allergy.

If there is the slightest evidence that other organs are sensitised in addition to the skin, it is unwise to administer any of the above remedies intravenously. So far no rule can be laid down as to the choice of the most suitable substance in any individual disorder, for, even if presenting apparently identical clinical symptoms, some individuals will respond better to one and some to another.

DIET. The effect of diet in relation to the acid-base balance has been discussed in the section on metabolism. Van Leeuwen

thinks all allergics ought to avoid foods rich in purin. With regard to the prevention of *neosalvarsan dermatitis*, which is widely thought to be favoured by hepatic damage, it has hitherto been taught that there should be a preponderance of carbohydrate in the diet. This was based on investigations into the influence of various diets on the liver-injury produced by chloroform, which is chemically quite dissimilar. Craven, from his experiments in 1931, came to quite a different conclusion, namely, that a high fat (and, to a less degree, high protein) diet provides the maximal protection against the liver-injury caused by arsphenamine. High carbohydrate diet and starvation increased the susceptibility. It has, however, been objected that these experiments were performed on dogs, which are never very tolerant of much carbohydrate.

Drugs. Those drugs which by their pharmacological action diminish supersensitiveness act for the most part on the vegetative nervous system. *Adrenalin*, which stimulates the sympathetic, is of indisputable value in shock, and is stated to be efficacious in acute *urticaria* and *Quincke's œdema*, though I have been unable to confirm this. In any case its action is not lasting. A more prolonged effect is obtained with *ephedrine*. *Pilocarpine*, which, on the contrary, stimulates the vagus and parasympathetic, was noticed by Pollitzer to have a sedative effect in *urticaria*. Lévy-Solal and Tzanck have demonstrated its anti-shock action, by virtue of which it is possible to arrest not only urticaria but puerperal eclampsia. It is given in a dosage of ½ c.c. of the 1% solution subcutaneously, repeated three to four times in 24 hours. This drug was also found a useful adjuvant in the treatment of *neurodermatitis* by Sulzberger, Spain, Sammis and Shahon. In certain cases of *urticaria*, *pituitrin* has proved the most effective, but its action is not lasting and sometimes produces headaches. *Bromide* has been recently recognised as of real value in the treatment of the cutaneous manifestations of the supersensitive state. One can give intravenous injections of 5–10 c.c. of 10% *sodium* or *strontium bromide* in saline every other day, but it is also very useful when given by mouth. When *urticaria* appears to be of psychogenic origin *luminal* is often the best drug.

To avoid sensitisation to neosalvarsan, Savulesco advocates the solution of each dose of " 914 " in 5 c.c. of a 20% solution of *sodium dehydrocholate*. This bile-salt is believed to tone the liver and protect it against the effect of the arsenobenzol. With the idea that *neosalvarsan dermatoses* are, to some extent at any rate, dependent on hepatic insufficiency, Spiethoff has treated them successfully with *liver-extract*, either by mouth or intramuscularly. Milbradt has confirmed Spiethoff's clinical findings and has found also that in animals sensitised by intradermal injections of salvarsan the sensitiveness can be very considerably reduced by the use of liver-extract.

The *hyposulphite of sodium*, *magnesium* or *calcium* has been used, apparently with benefit, not only in dermatitis due to neosalvarsan, mercury or bismuth, but also in other allergic states. The magnesium-salt is given intramuscularly in doses of 5 c.c. to 10 c.c. of the 10% solution about every 4 days. The sodium-salt is generally given intravenously in doses of 0·45–0·75 gm. and can be repeated daily for several weeks without danger; larger doses may make matters worse. The calcium-salt can be given either intravenously or intramuscularly in 10% aqueous solution, the average dose being 6 c.c.

IRRADIATION. When all the above methods are powerless, an extraordinary degree of relief can nearly always be obtained by X-rays in *exogenous dermatitis*, *chronic eczema* and *neurodermatitis*.

Definitions

Allergy. A specific change in the degree of sensitiveness towards a definite substance or physical stimulus on the part of an individual or of one or more of his tissues.

Allergen. A substance or physical stimulus towards which the degree of specific reactivity of an individual, or some of his tissue, is altered.

Antigen. A substance which, when introduced parenterally, stimulates the production of antibody and, when mixed with that antibody, reacts with it in some observable way.

Antibody. A substance that appears in the body-fluids in

response to the stimulus provided by the parenteral introduction of an antigen and which, when mixed with that antigen, reacts with it in some observable way.

Hapten. A substance which, though unable by itself to stimulate the formation of antibody, can unite specifically with preformed antibody. (The result of this union in the case of a simple hapten is a compound which remains in solution, and in the case of a complex hapten a precipitate.)

Complete Antigen. Consists of (*a*) hapten, which confers immunological specificity, and (*b*) protein component or some physical state of dispersion which confers the power of stimulating antibody-formation.

Anaphylactic. Attributable to the interaction of antigen with cell-fixed antibody.

Idiosyncrasy. A peculiarity distinguishing certain individuals from the majority of their fellows. In a restricted sense, a peculiar degree of specific sensitiveness to certain substances or physical stimuli.

Atopy. An inherited state which constitutes the paramount causal factor in a certain group of allergic disorders.

Atopen. An allergen, sensitisation to which is dependent on, and causes symptoms characteristic of, atopy.

Reagins. The antibodies that are called into being by, and unite with, atopens.

Eczema. Inflammation of the skin in which the epidermis is predominantly involved ; characterised in the early stage clinically by clusters of tiny vesicles and histologically by epidermal spongeosis.

Flare-up. A delayed inflammatory reaction (at least several days) after a single cutaneous inoculation or physical stimulation.

Bibliography

ABRAMOWITZ, E. W., and NOUN, M. H. "Ephedrin Dermatoses," *Brit. Journ. Derm. and Syph.*, 1933, **45**, 225.

BARBER, H. W., and ORIEL, G. H. "Biochemical Investigations in Allergic Conditions," *Brit. Med. Journ.*, 1928, **2**, 880.

BECKMAN, H. "Allergy and the Acid-Base Balance," *Journ. Amer. Med. Assoc.*, 1930, **95**, 1582.

BERGER, W., and LANG, F. J. "Ein Histopathologischer Beitrag zur Histaminhypothese der allergischen Reaktion," *Ztschr. Hyg.*, 1931, **113**, 206.

BERNSTEIN, F. "Zum allergischen Charakter der Kälteurtikaria," *Derm. Zeit.*, 1932, **64**, 242 (cit. Rouquès).

BIBERSTEIN, H., and FRÖLICH, H. "Weitere Beiträge zur Kenntnis der allergischen Dermatosen," *Arch. f. Derm. u. Syph.*, 1932, **166**, 101.

BIZZOZERO, E., and FERRARI, A. V. "On Idiosyncrasy to Iodoform," *Giorn. Ital. di Derm. e Sif.*, 1931, **72**, 3.

BLOCH, B. "Allergie, Anaphylaxie und Idiosyncrasie in der Dermatologie," *Klin. Woch.*, 1928, **7**, 1065 and 1113.

BLOCH, B., and STEINER-WOURLISCH, A. "Sensitisation of Guinea-pigs to Primula," *Arch. f. Derm. u. Syph.*, 1930, **162**, 349.

BOSS, A. "A Case of Fish Allergy cured by Desensitisation," *Arch. f. Derm. u. Syph.*, 1930, **162**, 454.

BOYCOTT, A. E. "Sensitisation to Insect Bites," *Univ. Coll. Hosp. Mag.*, 1928, **13**, 200.

BROOKS, C., PACK, G. T., and GOODE, H. "Further Studies on the Physiological Action of non-specific Antigens prepared from Shattered Hemoproteins," *Proc. Soc. Exper. Biol. and Med.*, 1923, **21**, 321.

BROWN, W. L. "On Allergy and some Allergic Diseases," *The Practitioner*, 1932, **774**, 641.

BURGESS, N. (*a*) "Further Observations on Autohæmotherapy," *Brit. Journ. Derm. and Syph.*, 1933, **45**, 333. (*b*) "Experiences with Proteose in the Treatment of Diseases of the Skin," *Brit. Med. Journ.*, 1933, **1**, 914.

COCA, A. F. (*a*) "Relation of Atopic Hypersensitiveness to Anaphylaxis," *Arch. of Path. and Lab. Med.*, 1926, **1**, 96. (*b*) "A Critical Review of Investigations of Allergic Diseases," *Erg. der Hyg.*, 1933, **14**, 538.

DOERR, R. "Allergie und Anaphylaxie," *Handbuch der Path. Mikro-organism, Kolle und Wassermann*, 3rd Ed., 1929, **1**, 759.

FIGLEY, K. D., and PARKHURST, H. J. "Silk Sensitivity with a special reference to its *rôle* in Atopic Eczema," *Journ. of Allergy*, 1933, **5**, 60. (Abstr., *Zbl. Hautkrank.*, 1934, **47**, 492.)

FREEMAN, J. (*a*) "Tissue Damage in the Asthma Syndrome," *The Practitioner*, 1929, **123**, 43. (*b*) "Asthma Research," *Brit. Med. Journ.*, 1931, **2**, 1011.

FREI, W. "Über willkürliche Sensibilisierung gegen chemisch-definierte Substanzen," *Klin. Woch.*, 1928, **22**, 1026.

GERSON, M. "Unspezifische Desensibilisierung durch Diät bei allergischen Hautkrankheiten," *Derm. Woch.*, 1935, **1**, 441 and 478 (Abstr., *Zbl. Hautkrank.*, 1935, **51**, 498).

GOUGEROT, F. "Eczema aigu professionnel," *Bull. Soc. Franc. Derm.*, 1930, 115.

GOUGEROT, F., BARTHÉLEMY, and UHRY, P. "Dermite artificielle eczémateuse médicamenteuse," *Bull. Soc. Franc. Derm.*, 1929, 441.

HARRIS, K. E., LEWIS, T., and VAUGHAN, J. M. "Hæmoglobinuria and Urticaria from Cold occurring Singly or in Combination," *Heart*, 1929, **14**, 305.

HAXTHAUSEN, H. "Experimentelle cutane Ueberempfindlichkeit gegen Sublimat," *Arch. f. Derm. u. Syph.*, 1934, **170**, 378. (Abstr., *Zbl. f. Hautkrank.*, 1935, **50**, 670.)

HECHT, O. "Skin Reactions to the Bites of Blood-sucking Insects and Mites as Allergic Manifestations," *Zbl. f. Hautkrank.*, 1933, **44**, 241.

JADASSOHN, W. (*a*) "Allergiestudien bei der Ascaridenidiosynkrasie," *Arch. f. Derm. u. Syph.*, 1928, **156**, 690. (*b*) "Eosinophilie und urticarielle Quaddel," *ibid.*, 1932, **166**, 458.

JADASSOHN, W., and SCHAAF, F. (*a*) "Experimental Investigations on the Mechanism of the Urticarial Egg-White Idiosyncrasies of the Eczema-Child," *Zeitschr. f. Immun.*, 1933, **79**, 407. (*b*) "On the Propeptan Treatment of Luithlen-Urbach," *Arch. f. Derm. u. Syph.*, 1933, **169**, 354.

KELLAWAY, C. H., and COWELL, J. S. (*a*) "Non-specific Desensitisation," *Brit. Journ. Exper. Path.*, 1922, **3**, 268. (*b*) "Spontaneous Desensitisation," *ibid.*, 1923, **4**, 255.

LEVINE, P., and COCA, A. F. "Studies in Hypersensitiveness," *Journ. of Immun.*, 1926, **2**, 411.

LÉVY-SOLAL, E., and TZANCK, A. "Anaphylaxie et action empêchante du chlorhydrate de pilocarpine," *Compt. rend. Soc. de Biol.*, 1923, **89**, 503.

LOEWY, F. E. "Thrombopenic Hæmorrhagic Purpura," *Lancet*, 1934, 845.

LOW, R. C. "Anaphylaxis and Sensitisation," Green, Edinburgh, 1924.

MAYER, R. L. (*a*) "Zur Atropinüberempfindlichkeit," *Arch. f. Derm. u. Syph.*, 1928, **154**, 574. (*b*) "Die Ueberempfindlichkeit gegen Koerper von Chinon Struktur," *ibid.*, 1928, **156**, 2. (*c*) "Das Gewerbeekzem," Berlin; Springer, 1930. (*d*) "Ursol Idiosyncrasy in the Guinea-pig," *Arch. f. Derm. u. Syph.*, 1931, **163**, 223 and 244.

MAYER, R. L., and CAJKOVAC, S. "Zur Frage der jahreszeitlichen Schwankungen der Krankheiten," *Arch. f. Derm. u. Syph.*, 1932, **166**, 325.

MAYER, R. L., and SULZBERGER, M. B. "Influence of Diet on Sensitisation," *Internat. Derm. Congress*, Copenhagen, 1930, 629.

MILBRADT, W. "Zur Ætiologie und Therapie der nitroiden Krise und der Salvarsandermatitis," *Münch. med. Woch.*, 1931, **78**, 1860.

MIYAZAKI, M. (*a*) "On the Egg-White Reaction," *Zbl. f. Hautkrank.*, 1934, **47**, 570. (*b*) "On the Storm Reaction," *ibid.*, 1934, **47**, 561.

MOORE, J. E., WOO, S. T., and ROBINSON, H. M. "Arsphenamine Dermatitis," *Arch. of Derm. and Syph.*, 1931, **23**, 74.

MORO, E. "Ekzema Infantum und Dermatitis Seborrhoides," Berlin; Springer, 1932.

MURRAY-LYON, R. M., PERCIVAL, G. H., and STEWART, C. P. "A Note on Urinary Proteose," *Brit. Med. Journ.*, 1932, **1**, 136.

NAEGELI, O., DE QUERVAIN, F., and STALDER, W. "Demonstration of the Cellular Location of the Allergy in Fixed Antipyrine Exanthem," *Klin. Woch.*, 1930, **20**, 924.

ORIEL, G. H. "Some Observations on the Pathogenesis of Eczema of Internal Origin and other Allergic Diseases," *Proc. Roy. Soc. Med.*, 1931, **24**, 1171.

PASCHER, F., and SULZBERGER, M. B. "Ragweed Dermatitis," *Arch. of Derm. and Syph.*, 1933, **28**, 223.

PECK, F., and SALOMON, G. "Eczema of Infancy and Childhood," *Amer. Journ. Dis. of Children*, 1933, **46**, 1308.

PERCIVAL, G. H. "Some Quantitative Observations on the Eczema Reaction," *Brit. Journ. Derm. and Syph.*, 1933, **45**, 49.

PRAUSNITZ, C., and KUESTNER, H. "Studien über die Ueberempfindlichkeit," *Zbl. f. Bact.*, 1921, **86**, 160.

REISS, H. "Über Veränderungen der Hautallergie unter Einwirkung von Drüsenextrakten und vegetativen Giften," *Arch. f. Derm. u. Syph.*, 1930, **161**, 462.

ROUQUÈS, L. "L'urticaire par le chaud et par le froid," *Nutrition*, 1935, **5**, 29.

SIMPSON, R. H. "Hæmoclasic Crisis and the Leucocyte Count," *Brit. Journ. Radiol.*, 1933, **6**, 705. (Abstr., *Brit. Med. Journ.*, 1934, 586.)

SPAIN, W. C., and COOKE, R. A. "Dermatitis Venenata: Observations upon the use of a Modified Extract from Toxicodendron Radicans," *Journ. of Immun.*, 1927, **13**, 93.

SPIETHOFF, B. "Der Wert der parenteralen Lebertherapie," *Münch. med. Woch.*, 1931, **78**, 1009.

STOKES, J. H., and KULCHAR, G. V. "The Infection Allergic Complex in Arsphenamine Dermatitic Reactions," *Brit. Journ. Derm. and Syph.*, 1934, **46**, 134.

SULZBERGER, M. B. "Arsphenamine Hypersensitiveness in Guinea-pigs," *Arch. of Derm. and Syph.*, 1930, **22**, 839.

SULZBERGER, M. B., and KERR, P. "Sensitisations of Eczematous Type," *Journ. of Allergy*, 1933, **4**, 326.

SULZBERGER, M. B., and MAYER, R. L. "Sensitisations," *Arch. f. Derm. u. Syph.*, 1931, **24**, 537.

SULZBERGER, M. B., and SIMON, F. A. "Arsphenamine Hypersensitiveness in Guinea-pigs," *Journ. of Allergy*, 1934, **6**, 39.

SULZBERGER, M. B., SPAIN, W. C., SAMMIS, F., and SHAHON, H. I. "Studies in Hypersensitiveness in Certain Dermatoses," *Journ. of Allergy*, 1932, **3**, 423.

SULZBERGER, M. B., and VAUGHAN, W. T. "Experiments in Silk Hypersensitivity and the Inhalation of Allergen in Atopic Dermatitis (Neurodermatitis Disseminatus)," *Journ. of Allergy*, 1934, **5**, 554.

TOPLEY, W. W. C. "An Outline of Immunity," London; Arnold, 1933.

URBACH, E. "Zur Pathogenese der cutanen Idiosynkrasien," *Arch. f. Derm. u. Syph.*, 1924, **148**, 146.

URBACH, E., and FASAL, P. "Alimentary Idiosyncratic Eczema," *Arch. f. Derm. u. Syph.*, 1931, **164**, 133.

VALÉRY-RADOT, P., and BLAMOUTIER, P. "Sensitization to Chloroplatinite of Potassium. Serious Shock following a Cuti-reaction with the Salt," *Bull. Soc. Méd. des Hôp. de Paris*, 1929, **5**, 222.

VAN LEEUWEN, STORM. (*a*) "Allergic Diseases," Philadelphia; Lippincott, 1925. (*b*) "Über die Bedeutung von Hautreaktionen für Diagnose und Therapie allergischer Krankheiten," *Klin. Woch.*, 1926, **5**, 1525. (*c*) "Über die Hautreaktion mit Extrakten menschlicher Kopfhautschuppen bei allergischen Krankheiten," *ibid.*, 1926, **5**, 1023.

VAN LEEUWEN, STORM, and KREMER, W. "Uebertragungs-und Hemmungssubstanzen im Blute von Allergikern," *Zschr. f. Imm. Forsch.*, 1927, **50**, 462.

WALZER, M., and WALZER, A. "Studies in Urticaria," *Amer. Journ. of Med. Sci.*, 1927, **173**, 279.

WHITFIELD, A. "Auto-sensitisation Eczema," *8th Internat. Congress of Derm.*, Copenhagen, 1930, 142.

WISE, F., and SULZBERGER, M. B. (*a*) "Urticaria and Hay-Fever due to Trichophytin (Epidermophyton Interdigitale)," *Journ. Amer. Med. Assoc.*, 1930, **95**, 1504. (*b*) "Drug Eruptions," *Arch. of Derm. and Syph.*, 1933, **27**, 549.

CHAPTER VIII

TUBERCULOSIS

ALTHOUGH the tubercle-bacillus is a well-defined micro-organism which has been known for over half a century, we are still very uncertain as to its causal relationship to many dermatoses. Those known to be due to it are relatively uncommon, but all kinds of commoner ones are continually being attributed to it on inadequate evidence. For the sake of convenience, and I hope lucidity, I will start by giving a classification of dermatoses of definite or probable tuberculous origin, which seems to me to conform most closely to modern knowledge. It is based on that of Volk, but is considerably modified. The terms in brackets might with advantage be dropped.

Localised Progressive Forms

LUPUS VULGARIS.
TUBERCULOSIS FUNGOSA.
TUBERCULOSIS VERRUCOSA CUTIS.
TUBERCULOSIS COLLIQUATIVA (*Scrofulodermia*).
ULCERS (*Tuberculosis Cutis Propria*).

Exanthematic Forms

TUBERCULOSIS MILIARIS.
TUBERCULOSIS LICHENOIDES (*Lichen Scrofulosorum*).
TUBERCULOSIS PAPULONECROTICA.
Superficial Form (*Follicular Lupus, Folliclis, Lupus Miliaris Disseminatus, Miliary Lupoid Tuberculide*).
Deep Form (*Acnitis, Acne Cachecticorum, Acne Agminata*)
Facial Type.
TUBERCULOSIS INDURATIVA SUBCUTANEA (*Erythema Induratum Bazin, Subcutaneous Sarcoid*).

LUPOID.

Lupoid of Boeck (*Sarcoid, Miliary Lupoid*).
Lupoid Pernio (*Lupus Pernio of Besnier*).

We are faced with two questions :—(1) Which clinical cutaneous disorders are attributable to tuberculosis ? (2) What are the cause and prognostic significance of the different guises assumed by the same infection ? The two questions are interdependent and cannot be dealt with separately.

The whole problem was crystallised by Darier in 1896, when, side by side with the skin-disorders of tuberculous origin, as proved by regular demonstration of bacilli in the lesions and positive guinea-pig inoculation from them (a group which corresponds with the localised progressive forms of the above table, together with miliary tuberculosis), he set up a separate group of eruptions under the name " Tuberculides." These were generally, if not always, associated with indubitable manifestations of tuberculosis elsewhere and often with one another. Their histological structure often resembled that of tubercle, but the bacillus could not be demonstrated in the lesions or by inoculation. The group at first included lichen scrofulosorum, papulonecrotic tuberculide and erythema induratum of Bazin. These eruptions have the following common clinical features :—they appear suddenly in crops of disseminated lesions without fever or general symptoms ; they often have a symmetrical distribution and their duration is variable ; they have a marked tendency to spontaneous healing and are not prone to local extension. Before discussing in detail our present knowledge of the nature of " tuberculides " I will give a brief sketch of earlier theories.

In the same year as Darier invented the name " tuberculides " Hallopeau ascribed the same conditions to *tuberculous toxin*. But it is difficult to conceive of lesions with the features described being caused by a soluble toxin from a distant source. [Nevertheless, one must remember that acneiform lesions can be produced by bromide or iodide.] One would expect them to be most evident in conditions of greatest activity of bacilli, such as florid phthisis ; the opposite is, in fact, the case. Moreover, there is

no known toxin produced by tubercle-bacilli, in cultures or in the body, which can produce such symptoms in normal animals or men. It would at least be necessary to stipulate allergy of the skin.

The first explanation that Darier and Haury gave of the failure to demonstrate the bacilli was that the lesions were caused by *dead* or *attenuated bacilli*. [I should make it clear at this stage that by now it has been possible in all the conditions named in the table to demonstrate the presence of tubercle-bacilli in the lesions, both *in situ* and by animal-inoculation, in at least a few instances.] Even in lupus vulgaris it had been a puzzle why the bacilli were so much more difficult to demonstrate than in ulcers or in lesions of internal organs, and it was thought that infection with an attenuated strain might be the secret. But there are many instances where lupus has been known to be contracted from individuals dying of virulent pulmonary tuberculosis. On the other hand, there is now agreement among most researchers that the majority of strains derived from lupous tissue are attenuated (Ledermann) and give rise to a special form of tuberculosis when inoculated into guinea-pigs (Stanziale). Sometimes direct culture from lupous material is positive, whilst guinea-pig inoculation is negative. It appears, therefore, that the skin-reaction which we call lupus vulgaris has the power of attenuating tubercle-bacilli. Similarly, Griffith found that in about 12% of cases of colliquative tuberculosis the bacilli are attenuated, whilst, according to Burnet, strains obtained from internal organs very rarely show any attenuation. Now it would not be inherently improbable if, under certain circumstances to be discussed later, the lesions of exanthematic forms had in a still higher degree this power of attenuating (or killing) the bacilli.

Wolff-Eisner was the first to grasp that the phenomena of the "tuberculides" had something to do with the immunity-process, and this idea led Jadassohn in 1913 to conclude that the scarcity of bacilli was due to their destruction in the lesions themselves. He explained that the arrival of live bacilli (not necessarily attenuated or dead) in the skin of a subject in a state of intense *allergy* sets up a violent reaction, sometimes leading to

necrosis, which rapidly kills them. This conception is still very widely entertained, but we shall see that it has to be considerably modified as well as amplified in the light of subsequent knowledge.

Quite a different explanation is at present favoured by many French authorities, who attribute tuberculides to the *filter-passing form of the tubercle-bacillus* (Ravaut, Valtis and de Blasio, 1932). This suggestion was first made by Darier in 1926. If substantiated it would certainly explain the association with frankly tuberculous manifestations, the paucity or absence of bacilli in the lesions and the inconstancy and irregularity of the results of guinea-pig inoculation. This will be discussed again later.

Some consideration must now be given to the various *criteria* by which we judge whether any particular skin-manifestation is, in fact, tuberculous.

Association with Tuberculosis. It was actually through association that the eruptions under discussion were first attributed to tuberculosis. But this criterion could never have the value of proof in view of the very great frequency of some degree of tuberculosis at any age after early childhood. It would only have significance if the particular dermatosis occurred *exclusively* in proved tuberculous subjects; but when statistics are examined it is found that the evidence is often only a matter of impression. All the varieties of eruption are occasionally seen without any accompanying evidence of tuberculosis, either past, present or in the subsequent history. Goeckermann in 1929 estimated that 84% of patients with tuberculides, under which term he included Tb. lichenoides, Tb. papulonecrotica and Tb. indurativa, presented manifest signs of tuberculosis, mostly glandular; whereas such signs were only found in 32% of patients with other dermatoses. But as regards the lungs, Martenstein found that out of 1,032 cases of cutaneous tuberculosis as many as 822 were radiologically normal or merely had some thickening at the hylum and the usual bronchial shadows; 157 had infiltrative and 53 florid tuberculosis.

Very similar, if not identical, eruptions sometimes appear to be caused by some other infection, such as leprosy, syphilis or dermatophytosis.

Tinea versicolor is a good example of a disease which, through its association, used to be considered tuberculous, but which is now known to have its own independent ætiology.

Histological Structure. The perfect classical tubercle is rare in any form of cutaneous tuberculosis, though it is approximated in the local progressive forms and in some phases of the exanthematic forms. But even perfect histological tubercles can also be seen in syphilis as well as in other chronic infections, such as sporotrichosis. Rather more atypical tubercles can be imitated by foreign-body reactions; among which we may include reactions to pathological autogenous (*e.g.*, lipoid) infiltrates. Conversely, it is known from experimental tuberculosis that the reaction sometimes has the features of an ordinary acute inflammation. I have seen tubercle-bacilli in the skin without any local histological reaction. The more precise significance of these variations will be dealt with in the section on allergy.

Demonstration of Infective Agent. DIRECT DEMONSTRATION IN LESIONS. This is the most cogent of all the criteria, but it is essential that the bacilli should be actually within the histologically diseased tissue and not simply in superficial excretions or scabs. Smear-preparations of pus are particularly unreliable, in view of such facts as the finding by Schwabacher of numerous acid-fast bacilli, morphologically indistinguishable from tubercle, in the slime of every one of 56 cold water taps in constant use. In various pathological processes similar bacilli have been recognised for many years (Preis), especially in such lesions as acne conglobata. Gray and Okell found some in a direct smear of the pus in 1 case of acne conglobata and in 1 of acne vulgaris, but they could not be grown on the usual media and did not tuberculise guinea-pigs. In 1930 Ramel found acid-fast bacilli microscopically in the pus of about half of a series of cases of ordinary acne. Such bacilli generally lose their acid-fastness in histological sections, in which Koch's bacilli can scarcely be confused with any except Hansen's. But strictly all such findings should be confirmed by animal-inoculation.

Conversely, in a patient with internal tuberculosis I have seen typical tubercle-bacilli in histological sections of a portion of the

skin which showed no clinical or histological changes other than pigmentation. The presence, therefore, of tubercle-bacilli in a skin-lesion of a patient with active internal tuberculosis, whose skin is almost sure to be receiving bacilli from time to time, does not absolutely prove that that lesion is caused by them. Volk has pointed out that skin-lesions due to other causes may favour the deposition of bacilli in them, and has demonstrated this in furuncles. On the other hand, it is quite clear from one's experience with syphilitic gummata that it would not be justifiable to deny the tuberculous ætiology of a lesion on the strength of the failure to demonstrate tubercle-bacilli in it.

CULTURES. In 1931 Löwenstein made the startling announcement that by his method of culture live tubercle-bacilli could be demonstrated in the blood of the majority of patients with any tuberculous focus. He and Kren obtained positive blood-cultures in Tb. indurativa in about 60% of cases, in Tb. papulonecrotica in 100%, in lupus vulgaris in 50% and in lupus erythematosus in about 60%. Later he reported a large percentage of positive results in diseases not suspected of any tuberculous connection. Attempts on the part of others to confirm his results have mostly failed (Wilson, Okell, Kolle). Münster-Frank, keeping closely to Löwenstein's technique, obtained no positive results in 260 cultures from the circulating blood of cases with mild and severe tuberculosis of the lungs, bones, joints, glands and skin. She emphasises that in any case microscopic diagnosis alone is inadequate. Any acid-fast bacilli grown can only be proved to be tubercle-bacilli by animal inoculation. Bonnet and Le Gros found bacillemia very rare, even in internal tuberculosis manifesting a fresh exacerbation. Okell examined some cases of active open pulmonary tuberculosis and also some of erythema nodosum, lupus erythematosus, erythema multiforme, acne conglobata and nodular acne vulgaris for the presence of tubercle-bacilli in the blood. But all his attempts at culture or guinea-pig inoculation were negative. Material taken from the skin-lesions themselves also gave negative results. On the other hand, in 2 out of 19 cases of ordinary acne, acid-fast bacilli (not proved to be tubercle) were grown from

comedos by Schwabacher. In a special report of the Medical Research Council, Wilson concludes that bacillemia of an intensity to be detectable by our present methods of examination is, except as a transitory phenomenon, rarely present in tuberculosis until the disease has assumed a more or less acute phase accompanied by extensive lesions. It is, however, generally agreed that Löwenstein's medium is a pre-eminently good one for the primary isolation and growth of the tubercle-bacillus.

In spite of the difficulty of demonstrating bacillemia, it seems certain, in view of the not very rare finding of bacilli in exanthematic lesions, even in the absence of gross tuberculous manifestations, that little showers of bacilli must take place into the blood-stream from time to time. Baemeister has reported such showers of virulent bacilli after diagnostic tuberculin injections.

Animal Inoculation. In addition to the undisputed positive guinea-pig inoculations in a small proportion of cases from the lesions of all the dermatoses in the table, Ramel (1929) reported the successful tuberculisation of guinea-pigs with the blood or the lesion of the majority of cases of erythema multiforme, though tubercle-bacilli could not be seen in the injected material. But the first guinea-pigs injected throve normally and, when killed after six months, only revealed slight adenitis, enlargement and fatty changes of the liver, splenic enlargement and mottling, with some fibrosis, of the lungs. The affected organs were removed, macerated and injected into other guinea-pigs. This process was repeated, and it was only after the third or fourth passage that signs of tuberculosis were produced, which on still further passage was rapidly fatal. He concluded that erythema multiforme is due to a bacillemia of organisms in a peculiarly attenuated state. His experiments have been repeated by Percival and Gibson and by Hallam and Edington with entirely negative results. Wood made some very thorough investigations on the same lines in cases of erythema multiforme, erythema nodosum, lupus erythematosus, chronic nodular acne, erythema induratum and normal subjects, over 200 guinea-pigs being used. In no case were tubercle-bacilli or any other evidence of tuberculous infection detected.

Much hinges on the correct recognition of inoculation-tuberculosis in guinea-pigs. Wilson mentions as insufficient grounds for its diagnosis the microscopical demonstration of acid-fast bacilli in the viscera without any macroscopic lesions; the presence of bacilli in the local lesion or regional lymphatic glands without any other evidence of disease; the presence of macroscopic lesions due either to spontaneous tuberculosis or to Salmonella, Pasteurella, Brucella or pyogenic infections; or the occurrence of a reaction to tuberculin in an animal found at post-mortem to show no signs of tuberculosis.

THE FILTER-PASSING FORM OF THE TUBERCLE-BACILLUS. Inoculation of filtrates of tuberculous skin-lesions have not given convincing results. Ravaut, Valtis and Guerra (1931), by the inoculation of guinea-pigs, either with tissue from the lesions or with the blood of patients with tuberculides, obtained manifestations identical with those attributed to the filtrable tuberculous virus. Nicolau and Blumenthal (1932), in 17 cases of frank tuberculosis of the skin, studied the effect of injecting a filtrate of the diseased tissue. In 13 of them the guinea-pigs remained well; 1 animal showed some enlargement of the inguinal glands which, when injected into a second animal, caused fatal visceral tuberculosis. In 3 cases only was there a direct positive result, the animals dying and revealing at autopsy caseating peribronchial glands with acid-fast bacilli. The authors conclude that filtrable tuberculous virus is sometimes obtainable from skin-lesions.

Van Beneden denies that the pathological changes occurring in guinea-pigs after inoculation with filtrates of tuberculous material are merely the result of the passage of very small numbers of bacilli through the filter, as suggested by Schmidt. According to his observations the inoculation of minute doses of virulent bacilli produces the same type of lesions as larger doses, whilst animals inoculated with filtrate react quite differently.

But Flarer's experiments in 1929 throw great doubt on the theory. He compared the effects of filtered and unfiltered extract of tuberculous skin-lesions. The unfiltered extract produced caseating lesions of the proximal glands and also distal lesions in

the glands, spleen and lungs. The latter were ordinary inflammations, in which it was impossible to demonstrate tubercle-bacilli, either by direct examination, by cultures or by inoculation. With the filtered extract he obtained exclusively lesions of this second type; moreover, the animals did not become sensitive to tuberculin. Further, Leigheb, in a series of control-experiments with the blood of patients apparently free from tubercle, obtained in all cases similar results to those attributed to the ultravirus. Volk (1933), as a result of numerous attempts to produce tuberculosis by injection of a filtrate of tissue and also of cultures, all of which, with one exception, were negative, and after a survey of recent literature, finds himself unable at present to accept the proof of the existence of the filter-passing form.

Whether this is true or not, perhaps we ought not to consider any animal inoculation tests as negative without the performance of passage through a series of animals. But this method needs extremely careful controls, such as the serial inoculation with portions of the organs of guinea-pigs inoculated with non-tuberculous human tissue.

Biological Reactions. Sipos has found that, if a cantharides-blister is raised on the skin of a patient with cutaneous tuberculosis and its contents are injected into the skin of another subject of cutaneous tuberculosis, there develops, in the majority of cases, a prolonged inflammatory reaction. This is not obtained in clinically non-tuberculous individuals and only rarely, and then only very weakly, in persons suffering from tuberculosis of internal organs. The test is, therefore, thought to be of diagnostic value as a sign of tuberculosis of the skin. It is interesting that he found it positive in 9 cases of lupus erythematosus (the total number tested is not given).

The most important biological test remains the tuberculin-reaction in all its varieties. From the point of view of determining whether any individual cutaneous disorder is tuberculous, the mere presence of a positive tuberculin-reaction has, in view of the great frequency of some degree of infection, much less value even than a positive Wassermann test would have in proving its syphilitic character. Moreover, we are ignorant how long

sensitiveness to tuberculin can survive the termination of a tuberculous infection. Conversely, it will be shown how, under certain circumstances, a completely negative response can actually be evidence in favour of tuberculosis. Tuberculin-sensitivity is an exceedingly obscure phenomenon and will be studied in its relationship to other allergic phenomena in the ensuing section.

Tuberculous Allergy. Although the importance of allergy in tuberculosis has only been fully appreciated recently, its first experimental demonstration was made by Koch in guinea-pigs in 1891. His classical experiment, which served to show the different effects produced by the inoculation of living tubercle-bacilli into the skin of already tuberculised, as compared with normal, animals is now generally referred to as "Koch's elementary experiment," and its result is known as "Koch's phenomenon." This experimental work was resumed and amplified in 1906 by Lewandowsky. Arguments based on Koch's phenomenon so often reveal an inadequate knowledge of these fundamental experiments, that I must be excused if I remind my readers of the essential facts, as described by Lewandowsky.

Experimental Tuberculosis in Animals. If normal guinea-pigs are inoculated with living tubercle-bacilli, there develops, after about 12 days, a hard nodule which soon ulcerates. The tuberculous process regularly progresses further and soon involves the regional lymph-glands. Histologically there is at first an accumulation of polynuclear leucocytes. From the third day large mononuclears are seen, and by the end of the first week they form the majority of the cells. These phagocytose both bacilli and leucocytes. After 14 days the base of the ulcer begins to take on a tubercular structure, in which the number of bacilli diminishes. Apparently-healed primary-inoculation-ulcers, which appear clinically as fine red scars, contain histologically tubercular tissue and virulent bacilli. Later, when the ulcer once more extends and deepens, the histology becomes less specific and the number of bacilli increases. This process is called the primary complex.

Now if, not less than 4 weeks after a guinea-pig has been cutaneously or otherwise tuberculised, fresh tubercle-bacilli are

inoculated into a scarified area, there ensue at this site intense inflammation and œdema, and then necrosis and crust-formation. The crust, and with it most of the bacilli, is eventually cast off. The process does not spread further and often heals up by the fifth day without leaving any active disease. This second type of reaction has so far only been observed in already tuberculised animals and must therefore be the result of the primary complex. But in the majority of cases healing is not so complete, and from the second week onwards there gradually develops a fairly sharply demarcated tubercular infiltrate of epithelioid and giant cells, in which, up till the third week, a few tubercle-bacilli can be seen microscopically and confirmed by inoculation. But that this subsequent tubercular infiltrate is not due to a multiplication of bacilli is proved by the fact that in parallel experiments, using dead bacilli for the re-inoculation, a similar infiltrate develops at the same period. After 6 or 8 weeks this infiltrate is resorbed completely, and no more bacilli can be seen. Exceptionally there is a later increase of bacilli and a re-outbreak of the lesion. Further re-inoculations in the same animal have the same results. We may summarise by saying that the response to the re-inoculation represents a great speeding-up of the processes seen in the primary complex, an increase in its defensive efficacy and an intensification of its first phase.

Lewandowsky, and later Tanimura, Baba and Tagikawa, have also studied the results of a *hæmatogenous* infection. If living tubercle-bacilli are injected intracordially into healthy guinea-pigs, there develops on the abdomen a squamous and papulo-squamous dermatitis, presenting microscopically ordinary inflammation and countless bacilli. Killed bacilli, on the other hand, produce no changes. But if the guinea-pigs have been previously injected intracutaneously with living tubercle-bacilli, then small endocardiac doses of either living or killed bacilli lead to papulo-squamous and papulo-pustular lesions, which microscopically present at first ordinary inflammation with copious bacilli, whilst 14 days later they have a tubercular structure with scanty bacilli.

It appears to be a general biological law that where bacteria multiply freely the reaction is that of ordinary inflammation, but

where bacteria, under the influence of antibodies, slowly disintegrate there arise tubercular structures. In animal experiments it is often found that while the primary ulcer still persists and contains bacilli, new inoculations with large quantities of bacilli will not take. Lewandowsky has excised such primary ulcers and inoculated the triturated tissue into other parts of the skin. The animals reacted in the same way as if foreign bacilli had been inoculated, namely, with an early abortive reaction and disappearance of the bacilli. This shows that other parts of the skin become allergic towards the bacilli still present in a primary focus.

In guinea-pigs whose lymph-glands have been removed Martenstein and Hahn found that a single intracutaneous injection of bacilli was followed, first, by a primary lesion and, from 1½ to 8 weeks later, by disseminated, hempseed-sized lesions, the tuberculous nature of which was established by the demonstration of bacilli. The histology of these tuberculides varied just as it does in spontaneous human tuberculides. Sometimes there were typical tubercles with central necrosis, sometimes more ordinary inflammatory changes with a few giant-cells and sub-epidermal pustule-formation, and sometimes the infiltration surrounded the follicles, as in Tb. lichenoides. It was only in a small proportion of these lesions that bacilli could be found, whereas they could be regularly demonstrated in the primary lesion even 60 days after its appearance.

The above experiments all refer to guinea-pigs, whose skin and other organs are much more sensitive to tuberculous infection than the human. The skin of rabbits resembles the human more closely in being more resistant. In them *primary* cutaneous inoculations with living bacilli can produce patches like lupus, but they generally heal after some weeks. In their neighbourhood there sometimes develops a lichenoid rash. Inoculation of the skin of the ear can produce hard papules with keratoses resembling Tb. verrucosa. In 1929 Lewandowsky and Fischl inoculated rabbits subcutaneously with living bacilli, and subsequently injected the same strain into a vein of the ear, which had been ligatured and cut. There developed in the territory of the injected vein lesions which, clinically and histologically, resembled tubercu-

lides; they disappeared in a few weeks, the animals remaining alive. They concluded that tuberculides are the result of a hæmatogenous dissemination in subjects already tuberculous. Although most of the forms of human skin-tuberculosis can be experimentally imitated by injecting bacilli into the skin of *normal* animals, especially the rabbit and ape, it is only after some weeks that the lesions assume a typical tubercular character, clinically and histologically. At first there is ordinary inflammation, such as might follow the introduction of a foreign body. As the histology becomes more tubercular, the bacilli become fewer.

It is very important to realise that attempts to produce even relative immunity by the injection of dead bacilli have failed.

TUBERCULIN. Old tuberculin is not toxic and (with certain possible exceptions) produces no reaction in a non-tuberculous subject. Moreover, it cannot act as an antigen; it cannot sensitise against itself. Sensitiveness to tuberculin results only from infection or from inoculation with living or dead bacilli, the protein fraction of which is thought by Albert-Weil and by Seibert and Munday to be concerned in its production. Tuberculin behaves, in fact, as a *hapten*, and the specific moiety is unlikely to be protein. But though tuberculin cannot sensitise against itself, a tuberculin-injection which at the time causes no local reaction may, in a tuberculous individual, reawaken sensitiveness, as shown by a second injection. Moreover, sensitisation may take place towards non-specific constituents of the medium. Such non-specific reactions cannot be distinguished with certainty by their actual characters from specific ones, but can and should be excluded by a proper control consisting of non-inoculated medium.

Seibert and her co-workers have recently put on the market a diagnostic preparation called *purified protein derivative* (*P.P.D.*), which eliminates such non-specific reactions. Moreover, old tuberculins vary according to the media and the strains used, so that results obtained with different preparations are not strictly comparable. The specific reacting substance is produced by most, if not all, strains, but in varying quantities. It has a low molecular weight and has been isolated by Seibert. The potency of a

given weight of the final product is constant. It is prepared by a uniform method from a uniform medium, free from protein, by the growth thereon of known strains. The minute quantities necessary for individual testing are distributed in tablets, together with a diluent of constant character. It is non-antigenic in that it does not sensitise or lead to antibody-production. It is recommended that the initial dose be 0·00002 mgm.; if in 48 hours there is no reaction, a second dose is given in the other forearm of 0·005 mgm. The solutions must be fresh. The first dose is equivalent roughly to 0·002–0·01 mgm. of Koch's old tuberculin and the second dose to about 1 mgm. The first dose, therefore, corresponds roughly to a dilution of old tuberculin of 1 in 50,000 and the second to 1 in 200. The second dose never gives inconveniently severe reactions in patients who have responded negatively to the first.

In sensitised persons repeated injections of tuberculin can bring about some diminution of reactivity (Courmont), but it is seldom that even a long course can produce a high degree of tolerance. On the other hand, it appears that even absolute tolerance can develop spontaneously in man. The reactivity is increased by a sub-erythema and decreased by an erythema dose of ultra-violet rays (Volk), and is also influenced by the numerous factors discussed in the previous chapter.

The action of tuberculin is closely similar to that of dead bacilli. Attempts to produce immunity to living bacilli by means of its injection have failed.

Sensitisation to tuberculin (one of the first phenomena to which v. Pirquet applied the term "allergy") has naturally been attributed to antibodies; but these are very difficult to demonstrate. Passive transmission of tuberculin-sensitiveness has hitherto failed. It is only quite lately that Lehner and Rajka have reported success with serum from a highly sensitive patient. Otherwise it is only the sensitiveness to bacterial protein that has been successfully transmitted. Moreover, the tissue-reaction to tuberculin differs from the *classical* anaphylactic reaction, in which there is ordinary inflammation and no tubercular structure, and its latent period is longer. Now we have seen that in Koch's

basic experiment prior infection with tuberculosis leads to a *hastening* of the reaction to a second inoculation; but this hyperergic response is not immediate, because the allergen, namely, tubercle-bacilli, is with difficulty dissolved and absorbed. A further hastening is achieved by injecting killed bacilli. The latent period is still shorter if old tuberculin is used. Now Kallos and Nathan have shown that in actively tuberculous subjects a real *immediate* reaction can be brought about if the allergen is presented in a really soluble form, not bound to protein denatured by previous heating. They have managed to prepare such a substance and call it *beta-tuberculin*. This seems to represent the purest form of the hapten of tubercle-bacilli and is completely protein-free. Its action on the skin is about 100 times as strong as that of old tuberculin. It has the advantage of keeping indefinitely. Within a few minutes of the intracutaneous injection of 0·0001 mgm. the reaction begins and it reaches its maximum in about 24 hours. Beta-tuberculin is also capable of making the uterus of tuberculous guinea-pigs contract and of specifically desensitising it. The regular demonstration of organ-anaphylaxis proves the existence of some kind of fixed antibodies as the basis of the tuberculin-reaction. This is further shown by the fact that tissue-cultures of non-tuberculous tissue from tuberculous animals exhibit a strong allergy towards tuberculin (Aronson).

Histologically the reaction to old tuberculin resembles the effects of the injection of living or dead bacilli in infected animals. The reaction is often isomorphic, reproducing the lesions of the patient, taking the lichenoid, papulonecrotic or indurative form. But it also depends on the technique, so that in the same patient one may obtain the indurative form with an intracutaneous test and the lichenoid with a patch-test. Kitamura and Tasaki have shown that not only in intracutaneous but even in patch-tests a tubercular structure is always formed in the cutis or subcutis, and that, without pathological changes there, no epidermal changes are observed. The primary damage is in the endothelial cells of the capillaries, with which the giant cells seem to be intimately connected. It appears then that the characteristic

tubercular granulation-tissue is the result of the interaction of allergen and cell-fixed antibodies. Nevertheless, the specificity of a tuberculin-reaction cannot be gauged by its histological character, and it is interesting that in a case of Boeck's lupoid Volk found that injection into the skin of Indian ink produced, instead of the usual foreign-body reaction, a characteristic lupoid formation. This resembles Köbner's phenomenon in psoriasis or lichen planus, in which lesions typical of the disease appear at sites of trauma.

The intensity occasionally shows the paradox of being greater with weaker than with stronger doses. Sahli seeks to explain these various phenomena by the hypothesis that in infected individuals the cells acquire the power (possibly resident in cell-fixed antibodies) of chemically disintegrating tuberculin, whereby there arises a toxic body called *tuberculopyrin*, the actual cause of the inflammatory reaction. In patients progressing favourably, or who have been successfully treated, the tuberculin-test is often negative, owing, according to this hypothesis, to the tuberculin being so rapidly destroyed by these chemolytic antibodies that the tuberculopyrin is immediately further broken down into non-poisonous substances. This would represent an acquired immunity or "positive anergy." If the antibodies are mainly manufactured in the tuberculous lesions themselves, we have an explanation of focal reactions. If there are no antibodies, through absence of infection or through intercurrent troubles, such as measles, or in the advanced stages of phthisis, there is no reaction because the tuberculin is not broken down. This represents "negative anergy." So far it has not proved possible to produce tuberculopyrin in the test-tube.

Some ill-defined substances have been found in the tissues which, when mixed with tuberculin, diminish or enhance its action. The name *anticutine* was given in 1908 by Pickert and Löwenstein to a substance which weakens it. It has been demonstrated in the serum of tuberculous individuals, whether they have received tuberculin or not. Volk and Löwenstein have found it in lupus patches approaching cure. But it is not always present in tuberculous patients, whilst it can occasionally be found in

clinically normal persons. The name *procutine* was applied by Fellner to a hypothetical antibody, produced, as he thought, only in the skin, which increases the action of tuberculin. Such a substance has also been found in the serum. In 1923 Martenstein and Schapiro showed that, whereas the skin of normal guinea-pigs does not react either to tuberculin or to skin-extract of a tuberculous animal or to its serum, it does react to a mixture of tuberculin and the skin-extract or serum. This supports Sahli's hypothesis, for it shows that tuberculin is rendered toxic even to the skin of a non-tuberculous animal by some substances elaborated by an infected one.

W. Jadassohn has found that if tuberculin, when mixed with serum (active or inactivated), even of tuberculin-negative persons, is left for 1–24 hours at room-temperature, its action may be increased; though immediate injection of the mixture reveals a weakening. The strengthening substance he identifies with Fellner's procutine and also with Sahli's chemolysin. Anticutine, on the other hand, behaves more like an amboceptor, disappearing if the serum is inactivated. Volk has found that occasionally the serum even of tuberculin-negative *children* contains procutine. It is, therefore, doubtful whether either anticutine or procutine is specific.

The sites of former tuberculin-tests, like actual tuberculous foci, may light up on the subsequent introduction of tuberculin. But this is not absolutely specific; for tuberculin-inoculation-sites have been observed to light up on the injection of egg-white, various bacteria or autogenous serum. Conversely, old depots of colon-bacilli or milk can be lit up by the subsequent injection of tuberculin (Adler).

As regards the *specificity* of the tuberculin-reaction itself, Jadassohn has shown that with strong doses one can obtain positive results in other infections, such as leprosy, actinomycosis and syphilis. Nicolas and Favre actually obtained strong positive reactions to high dilutions in 93% of apparently non-tuberculous syphilitics. Their figures for non-syphilitics are not given.

Wolff-Eisner has emphasised the diagnostic importance of the test giving a stronger reaction within the diseased area

than at a distance. Doutrelepont and Nagelschmidt have found big differences; the inflammation in lupous tissue starts much more rapidly and the infiltration and œdema are more intense, even leading to ulceration. But even this must be interpreted with care, for Jadassohn has met with similar behaviour in lichenoid syphilis. It appears to be especially those syphilitic lesions with tuberculoid histology that react to tuberculin. In primary tuberculosis of the skin the test may be positive in its neighbourhood while still negative at a distance. But a failure to find any difference between the reactivity in the region of the disease and at a distance cannot be taken as evidence against its being tuberculous (Pautrier).

Nathan and Kallos (1932) have investigated the occurrence of *epidermal* sensitisation in cutaneous tuberculosis, by means of patch-tests with old tuberculin. The patches are removed after 24 hours, but it is generally another 24 hours before the reaction develops and sometimes it is delayed for 5 days. It consists of redness, swelling and blisters or papules. It lasts from 4 to 10 days and is accompanied by itching. The histology is that of eczema. Subsequent injections of old tuberculin light up the sites of the eczematoid reactions, which have subsided. Konrad has shown that at these sites there has meanwhile taken place the formation of specific granulation-tissue. Such lighting-up occurs even at the sites of subliminal, intracutaneous or epidermal inoculations of tuberculin, which, at the time, produced no clinical manifestation. Nathan and Kallos have found that their patch-test is quite negative in cases of tuberculosis not involving the skin and also in non-tuberculous persons. On the other hand, they found it positive in 24 out of 28 cases of cutaneous tuberculosis, including lupus, Tb. colliquativa, Tb. verrucosa, Tb. ulcerosa, and also lupus erythematosus. The test should, therefore, be of great value in deciding whether any particular skin-disease is tuberculous. Konrad, who has tested the method in a much larger number of cases, supports the conclusions of Nathan and Kallos. The epidermal eczematoid test does not run parallel in intensity with that of the intracutaneous reaction.

Now, whilst the epidermal test is positive in cutaneous

tuberculosis and negative in internal tuberculosis, the immediate urticarial response to intracutaneous beta-tuberculin, which is positive in active pulmonary tuberculosis, was not obtained in Nathan and Kallos's cases of tuberculosis of the skin. This curious antithesis has not been adequately explained ; but there is a good deal of other evidence that tuberculosis of the skin gives rise to somewhat different antibodies from those elaborated by that of other organs. Nathan and Kallos's observations are, however, disputed by Bonnevie ; according to him responsiveness to epidermal tallies with responsiveness to intracutaneous tuberculin, and does not represent a special eczematous form peculiar to cutaneous tuberculosis. He asserts that the epidermal changes are secondary to a typical reaction in the cutis. The test does, however, teach us that tuberculin can diffuse through the epidermis without scarification.

In trying to form an idea of the state of allergy usually accompanying any particular type of eruption, it is perfectly useless to record the mere presence or absence of a positive tuberculin-reaction. One must at least know the degree of sensitiveness to various dilutions. The only systematic investigations of this sort known to me are those of Martenstein and Noll (1929), and their results are rather surprising. They used freshly-made dilutions ranging from 1 in 1,000 to 1 in 1,000,000. In the localised progressive group, which included lupus vulgaris and verrucose and colliquative tuberculosis, three-quarters of the cases were positive to a dilution of 1 in 100,000, and half of them even to 1 in 1,000,000. Now it was found that in the tuberculides, which included Tb. lichenoides, Tb. indurativa and Tb. papulonecrotica, the sensitiveness to tuberculin was actually less; only about half reacting to 1 in 100,000, and only a quarter to 1 in 1,000,000. Fully two-thirds only reacted to 1 in 5,000, whilst in lupus vulgaris it was not more than a quarter that required such a strong concentration. It had hitherto been thought that a high degree of tuberculin-sensitiveness was an essential characteristic of "tuberculides." The "sarcoid" group showed still lower reactivity, even below that of apparently non-tuberculous controls. Thus, according to this investigation, the tuberculides

must be placed between localised progressive tuberculosis and lupoid of Boeck, as regards their sensitiveness to tuberculin. Now it does not necessarily follow that the allergy in the tuberculides is less than in lupus. It is necessary to distinguish between the obvious clinical response to tuberculin, immunity to tuberculin and immunity to living bacilli. It is probable that in tuberculides, in contrast with localised progressive forms, the acme of fully developed tuberculin-sensitiveness has already been passed, and there are the beginnings of the specific or positive anergy which we shall see to be a characteristic of lupoids. The conception of specific anergy is that substances have been elaborated in adequate quantity to break down the tuberculin rapidly past the toxic tuberculopyrin stage and so neutralise it.

In all the varieties of cutaneous tuberculosis the degree of tuberculin-sensitiveness is far from constant. Thus, of Martenstein and Noll's cases of Bazin's disease, 6% were negative to 1 in 1,000, whilst in a typical case of my own an enormous reaction with severe necrosis was obtained with a dilution of 1 in 20,000,000.

Immunity. The relationship between tuberculin-sensitiveness and immunity is very obscure. Van Beneden has shown that after subcutaneous injection of B.C.G. into guinea-pigs a considerable degree of tuberculin-sensitiveness develops, but that the resistance of the animals to further inoculation with virulent bacilli is not raised. If, on the other hand, the B.C.G. is introduced intracordially there is a less durable tuberculin-sensitiveness but a significant increase in immunity. The latter might be explained by positive anergy. Similarly Sewall, de Savitsch and Butler, who superinfected guinea-pigs at varying times after the first infection, obtained results suggesting that immunity is more or less inversely proportional to tuberculin-sensitiveness, and that the latter gradually passes into the former. But, on the other hand, we sometimes see patients developing a considerable degree of tolerance to tuberculin, after injections of it, while the tuberculous infection still progresses; in others the disease progresses in the presence of a high degree of tuberculin-sensitiveness; in others again the disease improves whilst the tuberculin-titre remains the same. Moreover, injections of dead bacilli

bring about a pronounced tuberculin-sensitiveness but only trifling immunity. That one can make no *general* prognosis from the sensitiveness of the skin to tuberculin is also shown by the fact that intracutaneous and subcutaneous titres by no means run parallel. Even different parts of the skin may respond very differently.

A high degree of immunity is not accompanied by the presence of a large amount of antibodies of any kind in the serum. There has been just as little success in transferring immunity as in transferring tuberculin-sensitiveness. All modern work points to both of them being functions of the tissue-cells.

The progress of allergisation in man is much more irregular than in syphilis. Histologically, normergy, as exhibited by the normal person, consists of a short exudative stage followed by a productive one. Hyperergy (Rössle) consists in a very strong exudative stage which can lead to softening and shedding of the tissue. In positive anergy, a relative immunity, the exudative phase is only weakly developed whilst productive tissue-changes predominate. Negative anergy is associated with the relative failure of the cellular defence-function.

Many so-called *primary complexes* are probably not true ones but really superinfections. But there appears little doubt that a primary tuberculous complex does occur in the skin. The cases of primary complex observed by Bruusgaard fall within the age-period of 2 to 8 years. Rotnes has reported a case in a woman aged 30 years. In adults it seldom takes such a dangerous or generalised course as in babies (*e.g.*, following circumcision). This may be a question of virulence ; but more probably it reflects either a general non-specific increase in resistance with age or the more rapid and efficient production of specific defence-forces. The baby's skin behaves more like the guinea-pig's and the adult's more like the rabbit's. The primary complex consists essentially of a sore and a pronounced swelling with caseation of the regional glands, the spread being often marked by obvious lymphangitis. The sore may be comparatively inconspicuous. When typical it is sharply circumscribed, raised and of rubbery consistency and develops a central necrosis. Microscopical examination of

the sore and the glandular tissue reveals typical tubercles and numerous bacilli. The primary sore generally heals within a few months, but often the healing is incomplete and the infection continues in the form of lupus, the explanation being that the necessary allergy can develop in the infected site very rapidly. In a case of this type described by Bezecny a positive epidermal tuberculin-reaction of Nathan-Kallos developed within 4 weeks of the appearance of the primary sore. Sometimes the process is so mild as to be unable to sensitise or immunise the rest of the skin or other parts of the body. But generally it leads to a widespread allergisation, the tuberculin-reaction very soon becoming strongly positive. Why, in spite of this, does the primary lesion often not heal? W. Jadassohn ascribes this to adaptation of the primary infective agent. That such an adaptation does, in fact, occur has been shown by Kallos and Nathan in 1933; they demonstrated that the blood-serum of patients suffering from cutaneous tuberculosis contains a substance which can damage laboratory strains of tubercle-bacilli but not autogenous bacilli cultured from the lesions. [They further found that this substance was only present in subjects of *cutaneous* tuberculosis, proving that such patients are immunologically in a different state from other tuberculous individuals.] But this interesting adaptation is not enough to explain the phenomenon, for we have seen that Lewandowsky was able to demonstrate that Koch's phenomenon can be obtained, even if material from the primary lesion is used for the second inoculation. It is, therefore, clear that the tissues around the primary infection are in a less resistant state than other parts of the skin.

The beginning of the secondary period can be marked by erythema nodosum or other exanthems which rapidly disappear. Although the tuberculin-sensitiveness is now usually very pronounced, yet other persistent forms can ensue, such as lupus, Tb. colliquativa and indurativa. Subsequent stages cannot be clearly distinguished.

The post-primary eruptions arise from existing foci, either by way of the blood or by direct contact. They may also arise by exogenous superinfection. The hæmatogenous forms are prone

to occur either in the first two decades or else late in life. *True miliary tuberculosis*, while not uncommon in early childhood, is very rare in adults. The lesions are quite untypical clinically and histologically, but contain large numbers of bacilli. In contrast with it *post-exanthematic cutaneous tuberculoses* have a relatively small tendency to progress. They seem to arise from the dissemination of moderate numbers of bacilli in the presence of moderate amounts of antibodies. During measles the degree of immunity is usually temporarily lowered, but it rises again afterwards. The lesions may assume not only a lichenoid, papulonecrotic or lupous form, but even that of Tb. verrucosa or subcutaneous gummata. The most typical expressions of a *post-primary cutaneous exogenous infection* are Tb. verrucosa and lupus vulgaris. The *verrucose* form arises almost exclusively in middle life and, in contradistinction to all other forms, it is commoner in males, probably for occupational reasons, which also explain its localisation, which in turn may account partly for the tendency to hyperkeratosis. But verrucous lesions *can* occur on any part of the skin ; both the verrucous and lupous forms can also be endogenous.

The first general eruption may appear almost immediately after the primary complex or only after many years. The state of immunity fluctuates and the different tissues may, at the same time, be in different stages, so that the disease may be progressive in one organ while it is healing in another. Even in the skin alone lesions of different types may co-exist. Thus in 1929 Gaté and Rousset reported the co-existence in the same patient of gummatous, ulcerative, papulonecrotic and lupoid lesions. This extensive involvement of the skin did not prevent her subsequently dying of tuberculous meningitis. Even disseminated miliary tuberculosis in children can merge into the papulonecrotic form (Leiner). But a commoner transition is with lupus. Such co-existence in the same patient shows that the explanation of the different forms of skin-tuberculosis cannot reside merely in the state of *general* allergy.

Though tuberculides are usually associated with a relatively benign internal infection, they may, nevertheless, in early child-

hood have a bad prognosis; for though such an eruption in the skin is harmless, a corresponding one in the meninges will probably be fatal. The lichenoid form is much more frequently associated with obvious tuberculous manifestations elsewhere than the papulonecrotic or indurative. In cases of the latter two forms that Adamson has followed up there have been intermittent repetitions which eventually ceased, but never any serious systemic symptoms.

The irregularity of the histological structure of tuberculides depends on their stage. In the early stage there are ordinary inflammatory changes, sometimes with necrosis. At a later stage there is a more tubercular structure. But if the lesion is involuting there is again a more unspecific granulation-tissue. These are just the changes one finds in animal-experiments in reactions to hæmatogenous and exogenous superinfection.

Modern knowledge tends to break down the distinction between tuberculides and other forms of cutaneous tuberculosis; they are transitional between the localised progressive forms, due to infection of an allergic soil, and the absolutely anergic lupoids (Jadassohn).

Other Factors. Though many investigators ascribe to these specific immunological processes which are undeniably consequent upon tuberculous infection, the decisive *rôle* governing the course of tuberculous disease, others think that the *natural non-specific resistance* of the body is of greater importance. We have seen that *age*, at any rate, has a considerable influence independently of allergy. The papulonecrotic and indurative forms occur especially in patients with *languid peripheral circulation*, which perhaps favours the holding-up in the capillaries of bacilli that have escaped into the blood-stream. As regards the route or mode of infection, there is none that always produces the same clinical picture, nor are any of the main clinical forms brought about exclusively by one mode of infection.

Adamson points out how comparatively *rare* the tuberculides are, even in persons with manifest tuberculosis of the glands or other organs. There are various possible explanations. Though bacilli occasionally reach the skin, the products of their destruction

may be neutralised by a high content of anticutine. There must, further, be individual differences in sensitiveness to the toxin, as is known in the case of other defined substances. Probably most cases of the tuberculides pass unnoticed owing to their inconspicuousness. Their recognition may be of great value, as they are often the first sign pointing to tuberculosis of other organs.

Tuberculosis Lichenoides. Pautrier and Marfan think that an atypical form of this is represented by the pityriasis simplex of the face and scalp. The nearer the lesions of the trunk are traced towards the neck the fainter and flatter they become. In 1930 Nicolas, Massia and Michel described a case in which the lesions resembled typical lichen planus papules, but without Wickham's sign. There were even punctate keratomas on the soles. In 1925 Herxheimer and Martin had also reported a tuberculide remarkably similar to circinate or annular lichen planus with central atrophy.

Lupoids. An excellent clinical and histological description of these curious granulomata was made by Boeck in 1897. There may be just a solitary lesion or large numbers, and they can take the shape of either papules, nodes or infiltrated plaques. The first form consists of an exanthem of hemispherical papules of the size of a pin-head to that of a large pea ; it may have a close clinical similarity to lichen planus. All three forms can co-exist. The favourite sites are the face, shoulders and extensor surface of the upper limbs. The lesions can make their appearance slowly or rapidly and have no tendency to caseation or ulceration. After a duration of months or years a nodule frequently involutes, leaving a brownish stain or slight atrophy. Under glass-pressure lupoid is less transparent than lupus and minute greyish-yellow specks can often be detected.

It was these specks that led Boeck to adopt the term "*miliary* lupoid" in preference to sarcoid. Sarcoid is a most inappropriate name, as there is no question of any relationship with sarcoma. "Lupoid" is a great improvement, but "*miliary* lupoid," as applied to the whole group, even the large infiltrated plaques, is again most misleading. It is, however, still used in this sense

by German-speaking authors. Confusion is made worse confounded by Nicolas and Gaté's restriction of the term to the small papular variety (its most natural meaning), whilst Schaumann applies the term "miliary lupoid tuberculide" to the superficial form of Tb. papulonecrotica, even though he expressly states that this has nothing to do with Boeck's disease.

Lupoid Pernio. Boeck himself suggested in 1900 that there was a close relationship between his lupoids and Besnier's lupus pernio, and most writers now agree that the latter is a clinical variant of the same disorder; one sees on diascopy the same fine yellowish powdery stippling.

HISTOLOGY. This is characterised by sharply circumscribed masses of epithelioid cells in the corium. Lymphocytes and giant-cells are scarce and caseation absent. Volk, Sellei and Berger call this the "lupoid allergic reaction-type." A similar structure is sometimes seen in portions of the lesions of indurative tuberculosis, where it is, however, situated in the subcutis. It can also be present in some areas of lupus vulgaris; further, the histology cannot differentiate lupoid with certainty from clinically similar lesions caused by lepra or syphilis. It is, however, characteristic of lupoid that the lesions are *throughout* composed predominantly of epithelioid infiltrate.

TUBERCULIN-REACTION. In whatever way tested, this is absolutely negative in a greater proportion of lupoid patients than of a series of "normal" adult controls. Moreover, this anergy sometimes obtains even if the patients also have sure evidence of tuberculosis elsewhere. For these reasons Jadassohn thinks that this anergy is a specific and positive one; a view which Martenstein considers strengthened by his finding that more lupoid patients have procutine in their serum and more L. pernio patients have anticutine than normal controls. We have, however, seen that procutine and anticutine are not indubitably specific products of tuberculous infection.

ASSOCIATED CONDITIONS. Granulomas of identical histological structure are also found in many other organs. The *lymphatic system*, including the tonsils and spleen, is relatively often attacked. The middle and lower lobes of the *lungs* present skiagraphically a

characteristic "marbling," described by Schaumann in 1914 and by Bittorf and Kuznitzky in 1915. The lung-shadows can disappear contemporaneously with the skin-lesions. Characteristic changes in the *bones* were first described in association with L. pernio by Kreibich in 1904 and with Boeck's lupoid by Morosoff in 1908. They have been noticed more often with L. pernio than with lupoid of Boeck. Jüngling, who has studied this disorder since 1911, calls it "ostitis tuberculosa multiplex cystoides." It generally involves the proximal and middle phalanges of the fingers and toes. Skiagrams show that the granuloma starts from the marrow and causes rarefaction of the bone, which may be either diffuse or form circumscribed round spaces, especially in the heads of the phalanges. Schaumann states that the whole bone-marrow may be affected without the skiagram revealing any change. The soft surrounding tissue may become secondarily involved or the overlying skin may be the seat of an independent L. pernio. Jüngling has not seen it in any other skin-disorder, except one case of exfoliative lupus. There may, however, be no skin-disorder. Schaumann and Jüngling have both shown that the granuloma has a lupoid histology and have both tuberculised guinea-pigs with it. Bursae, tendon-sheaths and internal organs can also be involved. In recent times these peculiar granulomas of internal organs, with or without skin-changes, have been recognised as a particular form of tuberculosis (Askanazy, Melius, and Schürmann and Valenti). Schaumann emphasises the presence of a lymphocytosis of the large type in the blood. This together with the involvement of the lymphatic and hæmatopoietic systems led him in 1914, before he accepted its tuberculous ætiology, to regard the disease as a morbid entity and call it "lymphogranulomatosis benigna." The majority of other investigators find the blood normal.

Co-existence with other forms of tuberculosis, in the skin or elsewhere, is not very uncommon and transitional forms can be met with linking lupoid with Tb. papulonecrotica and with lupus vulgaris. An interesting case was published by me from Jadassohn's Clinic in 1925, in which lupoid became transformed clinically and histologically into a verrucous form of lupus vulgaris. With

this transformation the tuberculin-reaction, which had been negative, became positive. Volk observed the reverse process in a patient with disseminated post-exanthematic lupus, typical both clinically and histologically, whose lesions when seen a few years later were found to have developed the structure of lupoids.

In Kyrle's well-known case the lesions showed an unusually rapid onset and evolution. In very early red spots, which microscopically revealed ordinary inflammation, and even in apparently normal areas of skin he found very numerous acid-fast bacilli; as these became less there was a transformation into epithelioid tissue. In the fully developed lupoid lesions there were no longer any bacilli. A positive tuberculisation of a guinea-pig was obtained by inoculation of the blood. It is curious, however, that it did not follow inoculation of a portion of skin containing numerous bacilli. This suggests that there were in the skin more immune bodies than in the blood and may explain the positive anergy, the tuberculin-reaction being negative. In L. pernio bacilli have so far not been shown with certainty in sections, but there have been a few positive animal-inoculations.

If lupoids are tuberculous, Jadassohn's conception of their positive anergy is a good, though unproved, hypothesis. Yet if positive anergy represents a high degree of immunity it appears to me difficult to explain the long duration of lupoids; for although as regards sensitiveness to tuberculin the tuberculides come between lupus and lupoids, as regards clinical evolution lupoids come between lupus and the tuberculides. But again it must be remembered that immunity to tuberculin is not the same as immunity to living bacilli.

But whereas Jadassohn, Lewandowsky, Volk and Darier look upon lupoid as definitely a form of tuberculosis, Bloch and Pautrier think it is a symptom-complex which can be caused by various agencies. There is good evidence (Tzanck and Pautrier) that, as is also the case with the other tuberculides, indistinguishable lesions can be due to syphilis. Kissmeyer and Nielsen still maintain that lupoid is a morbid entity and consider that it has a closer resemblance to lepra than to tuberculosis, pointing

out the similarity of the bone-changes to those of leprosy as described by Murdock and Hutter.

Schaumann, who now agrees that they are tuberculous, insists that lupoid of Boeck and L. pernio are *always* accompanied by the triad:—(1) insensitiveness to tuberculin, (2) similar granulomatous changes in the tonsils or lymph-glands, and (3) in the bones. This strict conception may be referred to as "Schaumann's Disease."

The *subcutaneous* "*sarcoids*" of Darier-Roussy, as well as those of Darier, are now generally regarded as identical with Tb. indurativa subcutanea (erythema induratum of Bazin). At one end of the scale they have a long duration, do not ulcerate, and exhibit a tubercular histology with sometimes a partial approximation to that of lupoid; and at the other their evolution is more rapid, necrosis and ulceration may develop, and the histology approaches nearer to that of the papulonecrotic form. Any part of the skin can be affected, but, next to the calves, the favourite sites are the scapular region, the costal wall, the flanks and the extensor surface of the limbs.

Gray believes that Darier-Roussy sarcoids are type-reactions which can be produced by a variety of irritants, probably bacterial, acting on a suitable soil. He quotes Guy of Spitzburg as having produced similar lesions by injecting intravenously dead cultures of B. coli.

Tuberculosis Papulonecrotica. The superficial variety of this form has been called, among other names, "follicular lupus," "folliclis," "lupus miliaris disseminatus" and "miliary lupoid tuberculide." The deep variety, often starting subcutaneously, has received, among others, the names "acnitis," "acne cachecticorum" and "acne agminata."

Facial Type. This is not very uncommon but frequently passes unrecognised. It generally attacks young adults, chiefly men between the ages of 20 and 40 years. The lesions are often confined to the face, but not necessarily so, and can be either of the superficial or deep variety or combine the two. They are not always connected with the follicles as implied in Fox's name "follicular lupus" and in "folliclis," nor does the size always correspond with the word "miliary," which appears in the other

names. The superficial variety occurs in crops of discrete papular lesions, which can be as small as a pin-head or as large as a lentil. Sometimes at the summit there is a yellowish scale and the centre

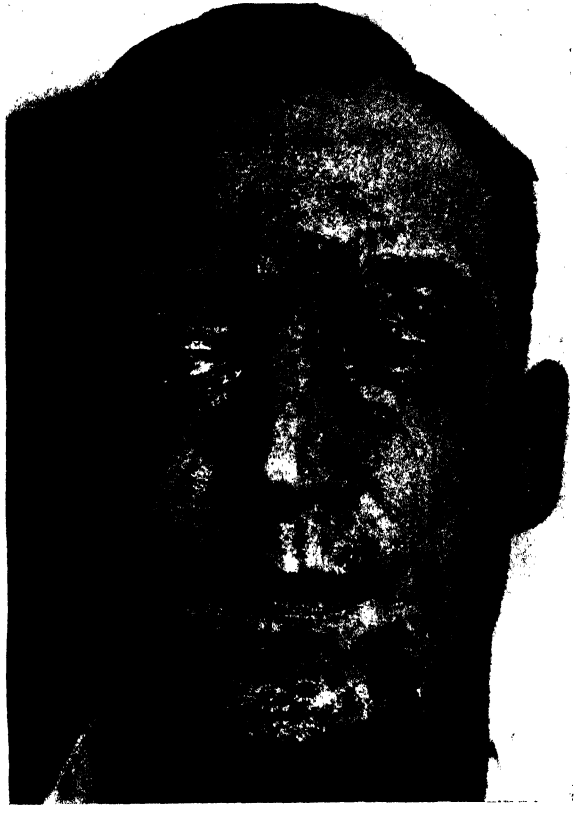


FIG. 16. Tuberculosis papulonecrotica: facial type. (Author's case.)

gives the impression of a beginning pustule, but one can seldom press out pus. They may be closely aggregated but are rarely confluent. The primary lesion may nearly resemble lupus vulgaris, but it shows no tendency to increase in size. In addition to

these superficial lesions there are frequently found deep in the cutis, or even the subcutis, hard nodules which gradually approach the surface, causing there a slight bluish-red discoloration and occasionally ulceration. The disorder sometimes disappears quite quickly, either spontaneously or through treatment, whilst in other cases it lasts months or years. Involution and the appearance of new crops can alternate.

Mostly the face is symmetrically attacked over its whole surface. It is often stated that "acne agminata" of Crocker is distinguished by its peculiar distribution around the orbits and in the central part of the face and the fact that the papules do not ulcerate; but in Crocker's own description lesions were present, in addition, on the chin, cheeks, brows, temples and sides of the face. Moreover, he says, "a large proportion contained pus even when they appeared to be solid." Figs. 16 and 17 illustrate the superficial variety in opposite distributions; but the lesions themselves were quite similar. Fig. 18 shows the lesions of "M.M." in greater detail.

The *histology* generally resembles that of lupus. Often there is a more perfect tubercular structure with central caseation than in any other cutaneous eruption (Arndt). There is seldom any evidence of superficial pustule-formation. Schaumann found that sections from lesions in the same patient may show either sharply demarcated masses of epithelioid cells, with complete absence of necrosis and only a few lymphocytes (lupoid type of reaction), or typical tubercles including central caseation. The *tuberculin reaction* is sometimes strongly positive but by no means always (Jadassohn, Peck). In one of my cases (Fig. 16) it was quite negative to 1 in 1,000 even when performed on the face and in spite of the fact that microscopically the lesions had a frankly tubercular structure.

Its association with tuberculosis elsewhere is very irregular; sometimes there are no clinical traces and the patient is in good general health; but occasionally there is manifest, or even advanced, tuberculosis. Schaumann has not found it accompanied by pulmonary, lymphatic or other changes characteristic of lupoid.

Schaumann and Pautrier think it is always tuberculous; but,

in spite of the typical histology, its tuberculous ætiology is difficult to demonstrate. Bacilli are very rarely seen in sections, though

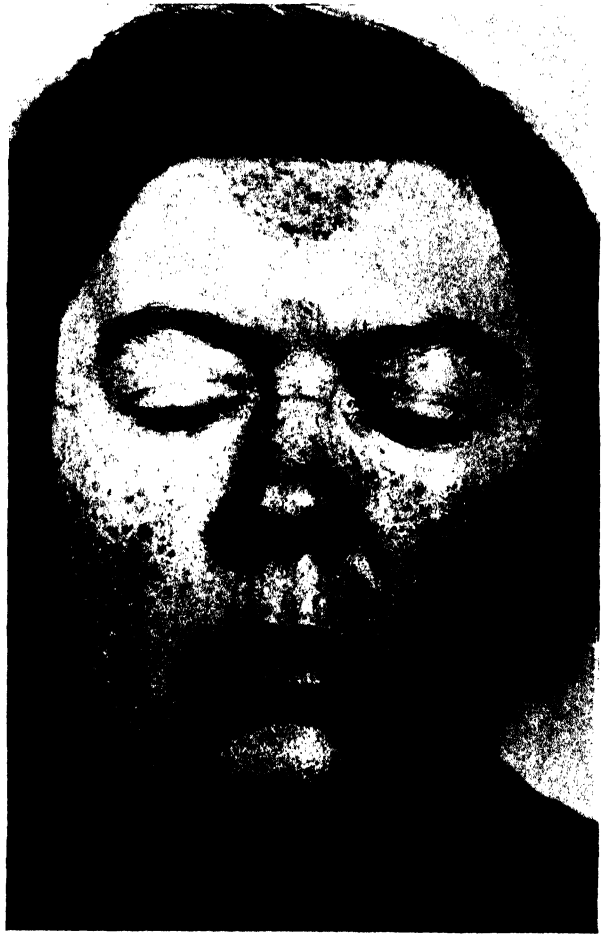


FIG. 17. Tuberculosis papulonecrotica: facial type. ("M.M.," Author's case.)

recently positive findings have been reported by Tanimura and other Japanese authors. Animal-inoculation has also been rarely

positive (Jacquet). In view of this and its very irregular relationship to the tuberculin-reaction and to tuberculosis elsewhere, it is by no means certain that the disease is always of tuberculous origin. If it is tuberculous it appears to me to be a link between

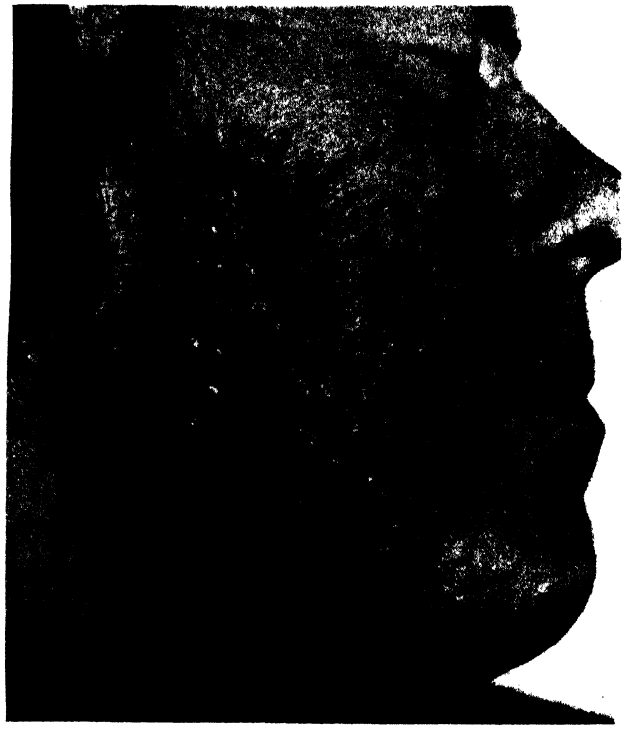


FIG. 18.—Tuberculosis papulonecrotica: facial type. ("M.M.," Author's case.)

Tb. papulonecrotica and lupoid, though it is more usual to place it between the tuberculides and lupus vulgaris (Volk, Nicolas and Gaté).

The vascular dilatation, which often accompanies the eruption, and the little yellow centres of the lesions often lead to a mistaken diagnosis of rosacea. Lewandowsky called this variety "rosaceous

tuberculide." But it rarely affects exclusively the centre of the face, the favourite positions being the sides of the cheeks, forehead, chin and neck (see Fig. 19). The papules differ from those



FIG. 19.—Rosacea-like tuberculide. (J. Schaumann, "Tuberculides, nature et traitement," 1926.)

complicating rosacea in being more brownish or bluish and translucent. MacKee and Sulzberger draw a distinction between rosaceous tuberculide and lupus miliaris faciei and state that in the former the tuberculin-reaction is strongly positive and in the latter generally negative. It can also be confused with acne

vulgaris and papular syphilis. The nodules are softer than in acne, there is seldom any pus, and there are no comedos. Differentiation by histological examination is not too simple, for in some instances of indurated acne and rosacea one may find granulation-tissue with epithelioid and giant cells, though it lacks the typical tubercular arrangement. Further, the conditions may be combined, and it is not impossible that rosacea and acne vulgaris lesions occasionally determine the deposition of tubercle-bacilli, as Volk has demonstrated in furuncles.

Erythema Nodosum. The ætiological connection between erythema nodosum and tuberculosis has recently received growing attention. According to Rotnes the view is gaining more and more ground in Norway that it is essentially a tuberculous manifestation. He describes a family-epidemic, in which four sisters developed it within 5 weeks and all appeared to have acquired tuberculosis from a known source. None had sore throats or other infective symptoms. Cruise investigated a series of cases occurring among nurses. One-third developed definite signs or suspicious symptoms of tuberculosis, either at the time of the eruption or within six months. Over 50% of the nurses affiliated to an institution for the treatment of tuberculosis got erythema nodosum. Ustvedt and Johannessen reviewed nearly 300 cases observed in the medical department of the hospital at Oslo. More than 15% later became ill with tuberculosis and 4·5% died of it. (These figures agree exactly with those of Symes in England.) The great majority of those who developed the disease did so within the first year. They think this points to erythema nodosum being definitely a sensitisation-phenomenon towards tubercle; for, if it were merely a symptom of inherited diminished resistance, the cases of severe illness or death after it would be distributed over many years, as they are after pleurisy. The authors came to the definite conclusion that persons who have had erythema nodosum have a greater probability of becoming ill with tuberculosis than those who have not. Of Forman and Whitwell's cases about 12% got tuberculous manifestations within 2 years; 6% developed indisputable progressive tuberculosis. But the figures of other observers are less suggestive.

Demiévelle, out of 300 cases, found that only about 5% developed any signs of tuberculosis, and Färber and Boddin and also Gueissaz dismiss it as a cause.

It is thought to occur either after the end of the incubation-period, when allergy has developed, or else when there is an activation of a latent focus. In Rotnes' case, in which it followed an apparently primary tuberculous chancre, the tuberculin-reaction was strongly positive at the height of the eruption. Ranke's theory, which is supported by Ernberg, Kundratitz, and Forman and Whitwell, is that it is a manifestation of the secondary stage. But this is by no means necessarily the case; for while Staehelin (1930) stresses its frequent occurrence in miliary tuberculosis, it has also been observed together with lupus vulgaris and Tb. colliquativa, lichenoides and papulonecrotica, and finally Volk has observed it in a child with fibrous tuberculosis of the lungs, infected hylar glands and tuberculosis of the bone, whose general health was good.

The upholders of the tuberculous ætiology further maintain that it depends on a high degree of allergy as indicated by a strongly positive tuberculin-reaction. Many observers agree that this is positive in 85–100%. Collis's figure is 70%. In a small series of cases in children Forman found 92% positive to tuberculin 1 in 5,000. This figure may be rather high, as reactions consisting solely of an erythema over 10 mm. in diameter were counted as positive, and they were not compared by the same observer with the responses of normal children. In any case, even when tuberculosis is present, erythema nodosum does not seem to *require* a high degree of tuberculin-sensitiveness. This is illustrated by Gordon's case, in which a young child developed a primary tuberculous complex: a week later typical erythema nodosum developed, but the tuberculin-reaction only became positive a considerable time after this had completely disappeared. Moreover, Volk states, and I have confirmed it, that a patient with erythema nodosum often shows a strikingly raised non-specific reactivity to many substances, such as broth, horse-serum and bacterial suspensions. It must be admitted that tuberculous subjects also show some degree of raised non-specific

reactivity (Hart), but I have not seen it so pronounced as in erythema nodosum.

Jadassohn and Wiborg (1929) think that erythema nodosum may favour the spread of tuberculosis in the same way as can measles. Forman and Whitwell object that the effects are not comparable; because measles depresses tuberculin-sensitiveness, whilst this is exalted in erythema nodosum. But this objection is countered by several reports of erythema nodosum itself immediately following measles.

It is hardly justifiable to compare an erythema nodosum lesion with Koch's phenomenon. The skin-lesions which follow intravascular inoculation of already infected guinea-pigs show a tubercular structure and never resemble erythema nodosum. Even the lesion following a cutaneous reinoculation usually develops some tubercular histology after the acute phase.

Bacilli have never been found in the lesions except by Landouzy and Gutmann in one case each (but they were clinically atypical and the bacilli were not found in the infiltrate but in the lumen of a vein) and by Koike in two cases. Animal-inoculation with tissue from a node has always been negative except in one case of Koike's. This is strongly against its being analogous to a syphilitic "secondary."

The occasional transition of erythema nodosum lesions into "lupus follicularis acutus" (Fantl) or Tb. indurativa (Forman and Whitwell) could be due to the lesions favouring the deposition and the multiplication of bacilli in the damaged sites.

On the whole, the evidence seems to me to suggest that tuberculosis, especially a recent massive infection, strongly favours the occurrence of erythema nodosum, which is, however, probably not itself a tuberculous manifestation. It should always prompt careful watching for tuberculosis but does not justify a bad prognosis. Collis, from his careful study of a small series of cases in children, thinks that the disease is caused by a soluble toxin (an acceptable theory in view of the ability of some drugs to cause rather similar lesions), derived in some cases from the tubercle-bacillus and in others from the hæmolytic streptococcus. He considers that all his cases fitted clearly into one or

the other of these groups, which differ slightly in their clinical aspects, the nodes in tuberculous cases being relatively small, numerous and of light red colour. His opinion is based partly on intracutaneous tests with tuberculin and hæmolytic streptococcal endotoxin, but he did not apparently test the skin with any other allergens. Of cases occurring in children under the age of 15 years a much larger proportion have signs of active tuberculosis than in adults over the age of 20.

A view widely held on the Continent is that it represents an allergic type-reaction to the products of tubercle, streptococcus, lymphogranuloma inguinale, soft sore, syphilis, trichophyton, staphylococcus or the bacillus crassus.

Treatment

Preventive treatment is too wide a subject to be considered here, but it is interesting to note that in babies vaccinated with B.C.G. colliquative and lichenoid tuberculosis have been observed, but they heal with unusual rapidity (Marfan).

General Treatment. DIET. There is no doubt that some striking results have been obtained with Gerson's salt-free diet, as well as with the Sauerbruch and Herrmannsdorfer salt-poor diet, and with the sort of compromise between the two, known as the "S.H.G. diet." The essentials of this are :—(1) Virtual exclusion of sodium chloride and plentiful supply of other minerals. These can be conveniently given in the form of compound syrup of hypophosphites B.P.C., which contains calcium, manganese, potassium, iron and phosphorus, but no sodium. Restriction of water. (2) A large percentage of uncooked fresh vegetables and fruit and their juices. Also raw eggs and milk and the juice and scrapings of raw meat. All necessary cooking to be as short as possible. (3) Cod-liver oil. (4) Restriction of meat. (5) High proportion of fat and protein and low proportion of carbohydrate.

The Cl ion does not seem to be the injurious part of common salt, as the good effects of the diet can still be obtained if it is combined with potassium, magnesium or calcium instead of sodium (Mettenleiter). If, then, sodium is the objectionable ion, it seems

inappropriate that the salt-substitute " selarom " consists to the extent of 98% of sodium formoxyl. It is, nevertheless, said not to impair the efficacy of the *régime*. Herrmannsdorfer's original diet, as opposed to Gerson's, was thought to be acidifying. This, however, has been denied by van Noorden and several other authorities, who consider that in any case the acid-base relation is of no importance. Bauer draws attention to the serious symptoms resembling uræmic coma which may be produced by excessive limitation of chloride; about 4 gm. of table-salt and 600 gm. of meat a week are now allowed, which maintain a neutral balance. Experimentally this diet increases the reactivity of the skin to irritants and dehydrates it.

Dörffel has noted that the improvement, which is generally preceded by a short exacerbation, may cease for a few weeks and then begin again suddenly. An entire lupus patch may heal completely within 6–18 months. Sometimes a sudden change from the Herrmannsdorfer diet to an alkalising milk and vegetable one hastens the improvement. Fasting-days have been similarly interpolated by others with the idea of producing a metabolic shock. Bacteriological examinations showed that the tubercle-bacilli disappear.

Blumenthal thinks the S.H.G. *régime* is capable by itself of healing cutaneous tuberculosis. Wichmann has noticed indisputable improvement, and even complete histological cure, but also occasional aggravation. Jesionek actually states that he gets as good results with the diet alone, even without extra minerals and cod-liver oil, as in conjunction with light. Dundas-Grant has had conspicuous success in tuberculosis of the nose and larynx.

Lomholt attaches value to vitamins, but has not seen any advantage from restriction of salt. Manca Pastorino found that if guinea-pigs are given irradiated ergosterol by mouth, the skin-manifestations following inoculation with tubercle-bacilli run a milder course than in controls. He demonstrated histologically the presence of calcium in the lesions of the treated animals and its absence in those of the controls. But caution must be exercised in giving irradiated ergosterol, as it can produce calcification in

the walls of the renal tubules and blood-vessels (De Savitsch). According to Fraser the dose should not exceed 15 m. daily.

A series of cases of cutaneous tuberculosis, including tuberculides, treated with cod-liver oil and salt-free diet by Kitamura and Tasaki, were shown to acquire thereby an anergic condition of the skin, which seemed to favour clinical improvement.

It is still not certain which are the most important elements in the S.H.G. diet. The majority of authorities accept its useful adjuvant action, but find that other methods are generally required in addition. It appears to be of most value in the ulcerated and hypertrophic forms of lupus and least useful in Tb. colliquativa and verrucosa.

Tuberculin. Tuberculin having in early days caused some disasters was for a time abandoned. It has, nevertheless, been extensively and successfully employed by Walker, Darier, Covisa and others. The technique finally adopted by Walker was to inject P.T.O. subcutaneously every third day in increasing doses. He also used old tuberculin in ointment-form applied to the lesions. Aitken says that Walker's treatment is especially useful in the elephantiasic type. The intracutaneous route is now more commonly adopted. A dose of 0·1 c.c. is given every 3 days, the strength starting with 1 in 10,000 and gradually rising to 1 in 500. After about ten injections a few weeks' or months' interval are allowed. Darier and Nicolas and Gaté think it especially efficacious in the exanthematic forms, particularly Tb. indurativa, but that it is also useful in lupus. Volk recommends it for lupoid, and MacKee and Sulzberger for rosacea-like tuberculide. As we have seen that tuberculin cannot produce immunity, no attempt should be made to reach very high doses with such an object in view; this also applies to B.E. It probably acts by stimulating slight beneficial focal reactions. Semon and Burnell-Jones have had success in chronic ulcerating lesions, which had resisted all other recognised methods.

Drugs. In addition to the well-established remedies, such as calcium, arsenic and iodine (the latter especially recommended by Adamson), the following have recently come into favour :—

Neoarsphenamine is recommended for tuberculides by

Schaumann, and Darier and Pautrier consider it, in combination with intracutaneous tuberculin, to be the best available treatment. When the results are very striking the possibility of a syphilitic ætiology must be borne in mind. Volk has found it useful for Boeck's lupoid. In lupoid pernio large doses of *sodium cacodylate* sometimes succeed when neoarsphenamine has failed (Hudelo, Montlaur and Leforestier).

Gold. Whitehouse and Bechet advocate gold for Tb. papulonecrotica and indurativa. Barber and also MacKee and Sulzberger have used it successfully in the rosacea-like tuberculide. Pooman reports complete healing of 3 out of 4 cases of lupus vulgaris with solganal. But most authorities find it a very uncertain remedy in frank tuberculosis of the skin, and Hudelo and Rabut have met with acute exacerbations, meningitis and acute miliary dissemination during its use.

Bismuth is reported by Nicolas and Gaté to be successful in papulonecrotic forms, and by Zurhelle, Pond and McKenna in lupus.

Chaulmoogra and Cod-liver Oil Derivatives. After the results obtained by several authors in the treatment of tuberculosis by anti-leprous chemotherapy (Rogers, 1921), chaulmoogra preparations have been used for tuberculides too. Thus Aronstam saw good effects from the ethyl-esters. Schaumann's experience with them has been disappointing. Gray has introduced sodium morrhuate for Boeck's lupoid. It is given intramuscularly or intravenously in a 3% aqueous solution in doses from ½ c.c. to 2 c.c., once or twice a week, and has sometimes proved very effective.

IRRADIATION. Statistics show that involvement of the skin has an important immunising effect on the body as a whole, and therapeutic experience has proved the importance of an actively functioning skin in the non-specific, as well as the specific processes leading to the cure of tuberculosis. The great efficacy of general carbon arc light baths is now universally accepted. In order to stimulate and not paralyse the beneficial activities of the skin, the dose should not be greater than to produce a faint erythema. Thus Ravaut and Desbucquois in 1929 reported the case of a young

girl, already the subject of tuberculous glands, who, after a sunstroke, suffered an explosion of lichenoid, papulonecrotic and lupoid pernio lesions on the areas exposed to the sun. This shows that, though the local doses for the progressive forms can scarcely be too high, an excessive dose over a wide area of unaffected skin may predispose it to the exanthematic forms.

Local Treatment. IRRADIATION. Details of these methods will be given in Chapter XIII.

Ultra-violet Rays. For lupus vulgaris, especially the flat, non-ulcerated circumscribed patches, the *Finsen* treatment is still held in highest esteem by most writers, but Jesionek still prefers the *Kromayer Lamp* with compression. Volk has found that when patches of lupus do not react well to light they can be made very responsive by the intracutaneous injection in their neighbourhood of small quantities of B.C.G. This seems specific, as the effect could not be achieved by the injection of other proteins. Ultra-violet rays are also indicated in Tb. colliquativa and the facial type of Tb. papulonecrotica. Whilst Schaumann appears satisfied with the effect of Finsen in lupoid pernio, the typical lupoid of Boeck is, according to Volk, very resistant to light.

Borderline rays are recommended for lupus by Samek and by Schreus, who points out their advantage in not producing an inflammatory reaction. Spiethoff considers them the method of choice, in that they bring about cure in the shortest time and at relatively small cost.

X-rays are condemned by the great majority of authors. But for verrucous forms Nicolas and Gaté consider them the best treatment if Coste's technique is used. This should not be preceded by scraping or any surgical intervention. After some weeks or several months a perfect scar and definite cure are obtained. Subsequent pulmonary and visceral manifestations have never been observed except in individuals already showing progressive tuberculosis. These opinions are based on 42 cases. They also recommend this method for epithelioma complicating lupus. Hoede thinks that the bad effects of X-rays reported in the past have been due to lack of experience in dosage, and he himself warns against the use of large doses for areas already irradiated,

very extensive lesions and parts of the skin which lie close to bones, tendons or cartilage. At the Tübingen Clinic, out of nearly 500 cases of lupus, nearly 400 were treated with X-rays, 1 skin-unit repeated 3 or 4 times over a period of 2 years. The percentage developing secondary carcinoma was just the same in these cases as in those that had received no X-rays, namely, 2·6% (Koch and Birkenmaier). Volk considers small doses useful for hypertrophic and ulcerated lupus, for patches connected with glandular or osseous tuberculosis and Tb. colliquativa, as a preliminary to Finsen.

Radium was advised for lupus in 1926 by Noguer-Moré, and has been found suitable for the exuberant forms in a dosage of 200–300 microcuries per square centimetre. According to Degrais and Bellot it should be unfiltered for the exuberant and filtered for the deep forms, whether ulcerated or not. Behoegel (1930) has used radium-needles hypodermically with success.

Excision. This is still preferred by Darier, Reyn (1930) and Volk for verrucose forms, if the lesions are discrete; but Moutot, who was once a convinced upholder of excision, has reported that all those patients whose subsequent history he followed up died some months or a few years afterwards of pulmonary tuberculosis. For little defined non-softened gummata and for small isolated foci of lupus it appears to be safe and is recommended by Nicolas and Gaté and also Volk, especially for areas other than the face.

Excision can also be performed by means of the cutting current, using a wire-loop, which is found particularly useful by Wucherpfennig for lupus in the neighbourhood of orifices or on the eyelids; it would also be suitable for a primary tuberculous chancre in the absence of any other sign of tuberculosis.

Electro-coagulation. This finds its chief indication in isolated nodules persisting in firm scars, or as a rapid method for larger patches on covered parts of the body. It has been chiefly advocated by Ravaut. The diathermy-needle is inserted into each nodule to a depth of about 4 mm. The current is stopped as soon as the characteristic luminosity is seen inside the nodule. For massive coagulation of large plaques a surface-applicator is kept in place till the tissue turns white. It is generally necessary

to repeat the process at intervals of 3 weeks. It would also be a proper treatment for a primary sore.

CO_2 Snow. Freezing is, in my experience, one of the best methods for the verrucous forms and also for lupus vulgaris. It has the advantages over light of being much more rapidly administered and of producing deeper reactions. It is, therefore, specially useful where scarring is present. It is claimed as a special virtue of light that it acts selectively on diseased tissue and therefore causes minimal scarring. But we have seen in Chapter I. that freezing strong enough to cause a conspicuous wheal produces no damage, even to the most superficial capillaries. It is probably only a matter of dosage, freezing being a more potent agent than ultra-violet rays. Though the naked pencils are quite adequate, the cryocautery of Lortat-Jacob has the advantage of providing applicators in a large number of shapes, which do not become deformed during the operation, and also of registering the pressure exerted. An average exposure would be 20 seconds with a pressure of 1½ kg. With the naked pencils I use about 45 seconds in scarred lupus : less is required in the absence of scarring.

Chemical Caustics. *Pyrogallic acid* is still largely employed in lupus vulgaris in addition to light, often in the form of 10% ointment. For all ulcerated forms Nicolas and Gaté are very enthusiastic as to the efficacy of *zinc chloride* when used according to the following technique. They prefer it, too, for the tumid, vegetating and exuberant forms of lupus vulgaris, following scarification. According to the technique arrived at in 1926 by Nicolas and Pillon, a tampon soaked in zinc chloride 3 gm., 80% alcohol to 10 gm. is pressed on the ulcerated surface until the lesion has turned white ; it is then dressed with tincture of iodine. This process is repeated every 3 weeks, and during the intervals a daily dressing of tincture of iodine 5 gm., 50% alcohol 45 gm. is used.

Liquid acid nitrate of mercury B.P.C. is still the best application for isolated nodules of lupus in scar-tissue when a diathermy machine is not handy. It must be driven well into the nodules with a match-stick (Adamson).

Intracutaneous Injection of Hydnocarpates and Mor-

RHUATES. By this method Rogers has reported relatively rapid healing of an extensive case of lupus which had resisted a long course of Finsen. He started by injecting a few drops of ethyl-ester-morrhuate intracutaneously at several neighbouring points at the edge of the lesion; different areas being dealt with each week. There was definite local improvement within 2–3 weeks. He then substituted the ethyl-ester-hydnocarpate combined with 4% of creosote. This acted more rapidly but led to some softening and ulceration in adjacent areas. Subsequent courses of the two esters were alternated. Muende has had good results in adults, though not in children, with creosoted moogrol, but it causes painful local reactions. Burgess recommends phenylethyl hydnocarpate, suggested by Cochrane, as it causes less pain and leaves very little scarring. About 0·1 c.c. is introduced at each point and not more than 5 c.c. should be given at one session.

Bibliography

ADAMSON, H. G. "Tuberculides of the Skin and their Treatment," *8th Internat. Cong. of Derm. and Syph.*, Copenhagen, 1930, 312.

AITKEN, R. "The Tuberculin Treatment of Lupus Vulgaris," *Brit. Journ. Derm.*, 1934, **46**, 207.

BARBER, H. W. "Two Cases of Rosaceous Tuberculide," *Proc. Roy. Soc. Med.*, 1934, **27**, 1362.

BONNEVIE, P. "Beitrag zur Methodik der Tuberkulinprobe," *Hosp. Tid.* (Danish), 1934, 1293 (*Abs. Zbl. Hautkrank.*, 1935, **50**, 676).

BRUUSGAARD, E. "So-called 'Primary Complex' of Tuberculosis of the Skin," *Brit. Journ. Derm.*, 1934, **46**, 113.

BURGESS, N. "A Note on a New Method of Treatment for Lupus Vulgaris by Intradermal Injection of Phenylethyl Hydnocarpate," *9th Internat. Derm. Cong. Budapest*, 1935, 419.

COLLIS, W. R. F. "A New Conception of the Ætiology of Erythema Nodosum," *Quart. Journ. Med.*, 1932, **1**, 141.

CRUISE, J. T. "Erythema Nodosum in Undergraduate Nurses and its Relationship to Tuberculosis," *Canad. Med. Assoc. Journ.*, 1932, **27**, 603 (*Abs. Brit. Journ. Derm.*, 1934, **46**, 41).

DÖRFFEL, J. "Clinical, Experimental and Chemical Studies on the Influence of Diet on Inflammatory Processes in Healthy and Diseased Skin," *Arch. für Derm. u. Syph.*, 1931, **162**, 621.

DUNDAS-GRANT, J. "Diet in the Treatment of Lupus," *Practitioner*, 1934, **132**, 101.

FORMAN, L., and WHITWELL, G. P. B. "Preliminary Observations on Erythema Nodosum," *Guy's Hospital Report*, 1934, **2**, 213.

GOLDSMITH, W. N. "Ueber circinaer-verrucöse Umwandlung bei einem Sarcoid Boeck und eine aehnliche Form bei Lupus Vulgaris," *Arch. f. Derm. u. Syph.*, 1925, **149**, 2.

GORDON, H. "A Case of Tuberculous Infection with Erythema Nodosum," *Brit. Journ. Derm. and Syph.*, 1933, **45**, 69.

GRAY, A. M. H. "On Darier-Roussy Sarcoids," *Brit. Journ. Derm. and Syph.*, 1935, **47**, 171.

HALLAM, R., and EDINGTON, J. W. "An Investigation of the Alleged Tuberculous Ætiology of Erythema Exudativum Multiforme (Hebra)," *Brit. Journ. Derm. and Syph.*, 1933, **45**, 133.

HART, P. D'ARCY. "The Value of Tuberculin Tests in Man," *Med. Res. Counc. Special Report*, No. 164, London, 1932.

JADASSOHN, W. "Beeinflussung der Tuberkulinreaktion durch Serum," *Klin. Woch.*, 1925, **4**, 1964 (*cit.* Volk).

JÜNGLING, O. "Ueber Ostitis tuberculosa multiplex cystoides, zugleich ein Beitrag zur Lehre von den Tuberkuliden des Knochens," *Bruns' Beiträge z. klin. Chir.*, 1928, **143**, 401.

KALLÓS, P., and KALLÓS-DEFFNER, L. "Ueber Allergie- und Immunitätsverhältnisse bei Hauttuberkulose," *Zbl. Hautkrank.*, 1933, **46**, 273.

KISSMEYER, A. "La Maladie de Boeck," Copenhagen; Levin and Munksgaarv, 1932 (*Abs. Brit. Journ. Derm.*, 1932, **44**, 295).

KITAMURA, S., and TASAKI, K. "Tuberkulinallergie und Hauttuberkulose," *Jap. Journ. Derm.*, 1934, **35**, 18 (*Abs. Zbl. Hautkrank.*, 1934, **48**, 322).

KOCH, F., and BIRKENMAIER, O. "Is the X-ray Treatment of Lupus Vulgaris Justifiable?" *Derm. Woch.*, 1934, **98**, 210 (*Abs. Brit. Journ. Derm.*, 1934, **46**, 297).

KYRLE, J. "Die Anfangsstadien des Boeckschen Lupoids; Beitrag zur Frage der tuberkulösen Aetiologie dieser Dermatose," *Arch. f. Derm. u. Syph.*, 1921, **131**, 33.

LEDERMANN, K. G. "Die Tuberkelbazillentypen bei der Hauttuberkulose," *Med. Klinik.*, 1932, **28**, 51.

MACKEE, G. M., and SULZBERGER, M. B. "Rosacea-like Tuberculide of Lewandowsky," *Archives of Derm. and Syph.*, 1935, **31**, 159.

MANCA PASTORINO, V. "L'azione dell'ergosterolo irradiato sulle tuberculosi cutane sperimentali," *Pubbl. in onore Umberto Mantegazza*, 1933, 281 (*Abs. Zbl. Hautkrank.*, 1934, **47**, 603).

MARTENSTEIN, H., and NOLL, R. "Statistische Untersuchungen ueber die Tuberkulinreaktion," *Arch. für Derm. u. Syph.*, 1929, **158**, 409.

NICOLAS, J., and GATÉ, J. "Tuberculose cutanée et les Tuberculides," Paris, 1934.

PERCIVAL, G. H., and GIBSON, H. J. "Observations on the Ætiology of Erythema Exudativum Multiforme," *Brit. Journ. Derm. and Syph.*, 1931, **43**, 329.

ROGERS, L. "The Use of Hydnocarpates and Morrhuates intradermally in Lupus Vulgaris," *Brit. Med. Journ.*, 1933, **1**, 47.

ROTNES, P. L. "A Family Epidemic of Erythema Nodosum," *Derm. Zeitschr.*, 1933, **67**, 259 (*Abs. Brit. Journ. Derm.*, 1934, **46**, 294).

SAVAGE, W. G. "The Mitchell Lecture on Human Tuberculosis of Bovine Origin," *Brit. Med. Journ.*, 1933, **2**, 905.

SCHAUMANN, J. "Tuberculides, nature et traitement," *Rapport IIIe Cong. Derm. et Syph. de lang. franc.*, Bruxelles-Anvers, 1926.

SEIBERT, F. B., ARONSON, J. D., REICHEL, J., CLARK, L. T., and LONG, E. R. "Purified Protein Derivative," *Suppl. Amer. Rev. of Tuberculosis*, 1934, **30**, 707.

SEMON, H., and BURNELL-JONES, H. X. "Tuberculin in the Treatment of Cutaneous Tuberculosis," *Brit. Journ. Derm.*, 1934, **46**, 544.

SIPOS, K. "Versuche mit dem Inhalt der bei Hauttuberkulose entstandenen Blasen," *Orv. Hetil*, 1934, 241 (*Abs. Zbl. Hautkrank.*, 1934, **48**, 323).

SPIETHOFF, B. "Grenzstrahlen bei Hauttuberkulose," *Strahlenther.*, 1933, **48**, 685 (*Abs. Zbl. Hautkrank.*, 1934, **47**, 720).

TANIMURA, C., BABA, T., and TAGIKAWA, K. "Experimentelle Untersuchung ueber die Pathogenese der sogenannten 'Tuberkulide,'" *Acta Dermat.* (Kyoto), 1929, **14**, 190, and German summary, 207.

USTVEDT, H. J., and JOHANNESSEN, A. S. "Erythème Noueux et Tuberculose Ultérieure," *Acta Med. Scand.*, 1933, **80**, 262 (*Abs. Zbl. Hautkrank.*, 1934, **47**, 721).

VOLK, R. "Tuberkulose der Haut," *Jadassohn's Handbuch der Haut-u. Geschlechtskr.*," 1931, **10/1**, 1.

WILSON, G. S., SCHWABACHER, H., OKELL, C. C., and WOOD, E. A. "Tuberculous Bacillæmia," *Med. Res. Counc. Special Report*, No. 182, London, 1933.

WUCHERPFENNIG, V. "Operative Therapie des Lupus," *Strahlenther.*, 1933, **48**, 698 (*Abs. Zbl. Hautkrank.*, 1934, **47**, 719).

CHAPTER IX

LUPUS ERYTHEMATOSUS

Clinical Features

WISE (1931) differentiates the following clinical types of lupus erythematosus ("l.e.") :—(1) *chronic fixed discoid*, most often affecting the nose, cheeks, ears and scalp; (2) *chronic disseminated* (sometimes discoid), most often affecting the same regions with the addition of the thorax, upper limbs and palms; (3) *subacute and acute disseminated*, not accompanied by grave systemic symptoms; (4) *acute disseminated febrile*, attacking the whole body-surface, including the mucosæ, and frequently ending in death.

The acute form can begin as such, when it has a very bad prognosis, or it can supervene on a chronic variety. But there is such a complete series of gradations between the most acute and chronic forms, that it is now generally accepted that they represent a single disease.

In addition to the established clinical features adequately described in the text-books, Gougerot, Burnier and Eliascheff have recently described a form which they call "*lupus erythematodes tumidus*." Sometimes it begins in this form and sometimes it develops from a typical chronic form. It is of red-violet colour, raised and papular, well demarcated and of soft consistency. The epidermis appears normal or a little thickened, and follicular hyperkeratosis is not clinically recognisable but is present histologically. In older lesions the centre flattens without completely healing. Histology shows the characteristics of l.e. in an early stage with the addition of œdema and vascular congestion. Guinea-pig-inoculation in one case produced tuberculosis from which bacilli of the human type were recovered.

In 1925 *Senear and Usher* described a group of cases of pemphigus with relatively benign course, in which the bullous eruption was associated with evanescent or rapidly changing lesions resembling l.e. or seborrhœic dermatitis. Since then quite a large number of such combinations have been recorded, chiefly in America. The l.e. lesions, which are either typical or resemble inflamed seborrhœic dermatitis, generally involve the scalp and face; the bullous lesions attack the trunk, especially the seborrhœic areas, and sometimes develop into crusted keratotic papules. Senear and Usher thought the cases represented a syndrome, combining disseminate l.e. and pemphigus, due to some toxin. Gilman thinks it a distinct clinical entity. Wise, however, points out that the last two types of his clinical classification of l.e. can simulate at different stages pemphigus, impetigo contagiosa, erysipelas, erythema multiforme, seborrhœic dermatitis and, less often, dermatitis herpetiformis, lichen scrofulosorum and purpura. He estimates that pemphigoid lesions occur in about 35% of cases of the acute febrile form, though in the chronic discoid they are rare. He thinks some of the cases of Senear-Usher syndrome are l.e. with bullæ, showing throughout its characteristic histological structure; and that others are benign pemphigus, in which none of the lesions truly resemble l.e. He neither accepts the view that the two diseases coexist, nor that a transition from one to the other occurs.

Histology

Goeckerman and Montgomery (1932), from a study of 25 cases of the discoid and 18 of the disseminated type, convinced themselves that the usually recognised histological changes are invariably present and distinctive. They are the same in all types, only varying in degree. These changes are summarised as follows:— dilatation of superficial capillaries and lymphatics; perivascular lymphocytic infiltration in the upper layer of the corium; hyperkeratosis; thickening of stratum granulosum; keratotic plugging of hair-follicles and sweat-ducts, and also of other parts of the epidermis; areas of acanthosis and of atrophy of the epidermis and colliquative degeneration of the basal layer. In the stage of

involution there are small hæmorrhages and atrophy, both of the connective tissue and of the walls of the follicles. The stratum spinosum is disintegrated and the stratum granulosum absent. Keratotic rings persist round the pilo-sebaceous and sweat-orifices.

There are never any of the changes characteristically associated with tuberculosis.

Ætiology

General Factors. 507 cases were investigated from this point of view between the years 1920–27 by Freund. There were 3 *women* to 1 man and the chief *age-period* was 30–50 years. The influence of outdoor or indoor work, exposure to cold or heat and country or town residence was gauged by comparing the numbers in these various categories with those of psoriasis-patients as controls. There were no marked differences. But the number of l.c. patients, also calculated statistically, rose suddenly in March and reached its maximum in May and June. The control psoriasis-curve remained almost level. Freund thinks this increase at the beginning of spring is certainly due to the increasing intensity of U.V.R., but he noted that the spring-incidence was highest when the preceding winter had been unusually severe. Whether *cold* or *light* is the more effective predisposing factor probably depends upon which does most damage in the particular patient, or area of skin, involved. Cold does more harm where the circulation is poor, while light is more dangerous where the skin is delicate and easily irritated. In the same patient one often observes that the fingers get worse in the winter and the face in spring. MacLeod points out the frequency with which those parts of the skin are attacked that are stretched over bone or cartilage. Gross and Volk have shown in animals that *infection* with tuberculosis, or even intracutaneous injection of killed bacilli, increases the sensitiveness of the skin to light. Other organisms, for example colon bacilli, can have the same effect. Light cannot, however, be an essential cause, in view of the frequent, and sometimes exclusive, localisation on the scalp and covered parts. The disease is, nevertheless, extremely rare in dark races, whether they are affected by tuberculosis or not (Noel).

The *geographical distribution*, especially of the fatal type, is very uneven. The largest number of acute cases are reported from Central Europe. It is remarkable that, while Gawalowski, of Prague, could collect 112 autopsies on cases of acute l.e., in England this is rare (Roxburgh can find records of only 5 cases at St. Bartholomew's since 1906), in spite of the frequency of the chronic form. With the geographical distribution of lupus vulgaris it shows no relationship whatever.

The Tuberculous and Streptococcal Theories. The general character of the disease, its acute and chronic phases and centrifugal spread, leaving behind a cicatricial atrophy, all suggest a local bacterial cause. The symmetry is indicative of the arrival of such bacteria from an internal source. The two bacteria that have been most under suspicion are the tubercle-bacillus and the streptococcus. In neither case is the evidence conclusive. It will be most convenient to consider their claims side by side.

Presence of Bacteria in the Lesions. It has *never* been possible to show tubercle-bacilli in sections by the Ziehl-Neelsen stain. Positive findings have only been reported in the sediment of excised portions treated with antiformin (Arndt, Hidaka, and a few others). This method is not free from pitfalls. Direct cultures from lesions have failed. Inoculation into guinea-pigs caused tuberculosis in about one-sixth of Bloch and Fuchs's cases, but half of these only after passage. Cannon and Ornstein obtained a slightly higher proportion. The uncertainties of this method have been discussed in the previous chapter.

Some very interesting observations were made by Bloch and Fuchs in the attempt to find out whether there were any derivatives of tubercle-bacilli in the lesions. They made an extract from typical lesions, freed it by filtration of all corpuscular elements and injected it intracutaneously into tuberculous subjects. In the majority of cases the result resembled the effect of injecting diluted tuberculin. The sites lit up after subcutaneous injection of tuberculin and microscopically revealed a tuberculoid structure. Similar extracts from normal portions of the same patient's skin produced no reaction or a very much smaller one. This important observation is somewhat weakened by Ehrmann and Falkenstein's

finding that trichophytin, injected as control at the same time as the extract, produced a similar though smaller papule, which also showed a tuberculoid structure. But on the subsequent subcutaneous injection of tuberculin only the sites of the extract and not those of the trichophytin lit up.

These phenomena could be explained and reconciled if there existed a filter-passing form of the tubercle-bacillus, the evidence as to which has been discussed in the foregoing chapter.

As regards streptococci, Headley-Wright obtained these organisms post-mortem from the edge of lesions in a fatal case. Roxburgh also reports that in one fatal case streptococci were seen microscopically in the papillary vessels of a lesion post-mortem. It was, however, noted that there was only slight endothelial reaction, which suggests that the coccal invasion may have been an immediate ante-mortem or post-mortem phenomenon. As far as I know, they have not been seen in stained sections or recovered from lesions during life.

The evidence, therefore, for the local activity of either organism is exiguous. If the lesions are to be ascribed to an *allergic* response to small numbers of organisms reaching the skin through the blood-stream from a distant focus, it is necessary to establish the presence of such foci in a larger proportion of cases than in controls and also to prove that there is, in fact, a specific alteration of reactivity towards the microbes. That a soluble *toxin*, from an infective focus or other source, could be responsible for at any rate the chronic discoid form, with its slowly progressive active margin, seems to me quite impossible.

Foci of Infection. The association of l.e. with *tuberculosis* elsewhere has been carefully studied by many workers, but with extremely contradictory results. In Olessof's analysis of 122 cases there was in 37·5% a preceding tuberculosis. In two-thirds of the cases the cervical lymph-glands were enlarged and tuberculosis noted in the history. Oro made skiagrams of the lungs in a large series. He only counted as positive, which amounted to 83%, the picture of beginning tuberculosis (with hilar adenopathy and ascending peribronchitis with lessening of apical translucency) and pronounced phthisis. Among controls of various other skin-

conditions only 40–50% were positive. Freund found pulmonary tuberculosis in only 46%. Goeckerman found internal tuberculosis in only 35·7%, a proportion only very slightly higher than that among skin-diseases of non-tuberculous nature (32·1%); whilst in tuberculides he found it in 84%. In MacLeod's series the proportion was only 5%. Pillat found chorioiditic foci in 33%.

As to its association with tuberculous skin-lesions, a combination with tuberculides is not rare, especially the papulonecrotic form. In this connection Hutchinson's "chilblain-lupus" is of considerable interest. As Ehrmann pointed out, it has clinical features intermediate between l.e. and papulonecrotic tuberculide, while the histology is, according to Fischl, Lutz and Sachs, quite definitely that of a tuberculide. There is further no question as to the frequent association of chilblain-lupus with true l.e. On the other hand, it is remarkably rare for l.e. and lupus vulgaris to coexist, only about 30 instances having been reported. A very interesting case, watched by Zieler for 20 years, had l.e. on the scalp and lupus vulgaris on the face; frequently repeated subcutaneous tuberculin-injections regularly produced intense focal reactions in the lupus vulgaris, but never any in the l.e.

The coexistence of *streptococcal foci* has not been studied quite so systematically. Starting from an isolated observation in which l.e. was complicated by tonsillitis and regressed after its cure, Barber examined his l.e. patients regularly for infective foci. He always found in the tonsils, teeth, sinuses or fæces septic infections from which could be cultured streptococcus pyogenes longus and occasionally hæmolyticus. He was further attracted to the streptococcal hypothesis by the clinical resemblance of acute l.e. to erythema multiforme, in which disease he also recovered streptococcus from the same localities. Similar findings have been reported by Roberts. But Gray points out the prevalence of streptococci in these situations even without signs of inflammation. Reichenmiller, in 1926, found streptococcus viridans almost constantly in the mouth of 190 healthy subjects, and in many cases hæmolytic strains too.

In a subacute disseminated case Milian recovered streptococci from the spleen.

EXAMINATION OF THE BLOOD. Bloch and Ramel reported a case of acute fatal l.e. whose blood taken 3 weeks before death produced lesions in a guinea-pig in which tubercle-bacilli, staining badly and in the granular form, were found. Bacilli had not been demonstrated directly in the patient's blood even by the antiformin method. At the necropsy no evidence of active tuberculosis was found. This case is sometimes quoted to prove that negative findings at necropsy do not exclude a tuberculous infection; but it must be pointed out in the first place that the tuberculisation of the guinea-pig was not a classical one, and secondly that at necropsy definite evidence of old tuberculosis was present. In many necropsies of fatal l.e., in spite of thorough search, no trace either of fresh or old tuberculosis has been discovered.

Streptococci were cultured from the blood and from suppurating glands in the neck by Gray and Goodhart in a case of l.e. becoming acute; they have also been cultured from the blood by Gibson, Low and others. In Barber's patient there were specific agglutinins against cocci cultivated from the tonsils. In Roxburgh's 5 fatal cases death was attributed to streptococcal septicæmia; but blood-culture was not made in 1, was sterile in 2 and in the 2 remaining cases it only became positive a few days before death. A focus of infection was not ascertained in any case.

REACTIVITY OF THE SKIN. If the skin-manifestations, so characteristic in themselves, are to be attributed to bacteria reaching the skin from a distant focus, one would expect some special reactivity of the skin of l.e. patients towards experimental inoculation of these bacteria or their specific derivatives. The patches themselves and the unaffected skin have been tested by many workers in various ways with *tuberculin*. In Martenstein and Noll's systematic investigation with the intracutaneous inoculation of tuberculin in various dilutions into unaffected areas, referred to in Chapter VIII., the figures for l.e. tally almost exactly with those of controls. In a small series of my own half reacted strongly to tuberculin 1 in 5,000, a much greater proportion than among controls. All of these had either a very

tuberculous family history or had themselves suffered from tuberculous cervical glands. But half the cases, again a higher proportion than in controls, reacted strongly to *staphylococcal vaccine*, though there was no clinical evidence of staphylococcal infection. The tuberculin patch-test of Nathan and Kallós, and the cantharides-blister-test of Sipos, both described in Chapter VIII., are said by their authors to be positive in some cases. If it is true that these tests are positive exclusively in subjects of cutaneous tuberculosis, then a positive result in a patient suffering from l.e., but with no other cutaneous disorder, would be strong evidence in favour of the l.e. being tuberculous.

Ramel and Volk have shown that the injection of tuberculin into either the affected or unaffected skin of an l.e. patient can bring about a reaction with ordinary tubercular histology.

Thus the reactivity of l.e. patients' skin to tuberculin resembles both qualitatively and quantitatively that of controls.

Intracutaneous tests with a *vaccine of streptococcus haemolyticus* were found by Barber and Forman strongly positive in about 50% of l.e., as compared with 20% of controls. In my series only 1 patient reacted to streptococcus, and she was also positive to staphylococcus and tuberculin. This is the patient already quoted, who many years ago had an acute exacerbation with abscesses at the back of the neck. At that time Gray and Goodhart obtained streptococci from the blood and the abscesses. The streptococcal infection subsequently abated, but the l.e. persisted until she was treated with gold, which was very successful. For a long time there has been no activity ; no flare occurred even when she subsequently developed acute tonsillitis followed by tonsillectomy, at which time her skin still reacted strongly to cocci and to tuberculin.

Focal reactions are of some interest in a negative sense. Thus it is significant that not a single focal reaction was ever obtained to tuberculin, injected either intra- or subcutaneously, by either Birnbaum or Schaumann. Positive focal reactions carry little weight, as they have been observed to follow injection of such diverse substances as staphylococcal and streptococcal vaccines, entero-vaccine, sterilised milk, or other foreign proteins, and gold.

THERAPEUTIC ARGUMENTS. Arguments as to ætiology are often based on observations of striking improvement or cure following certain lines of treatment, the deductions generally being quite illogical. Thus reports of improvement after operative removal of tuberculous lymph-glands are paralleled by similar observations following eradication of non-tuberculous infective foci, such as tonsils and teeth infected with streptococci and suppurative appendix (Whitehouse), after cure of chronic gonorrheal prostatitis (Burke), and even after extirpation of uterine myoma (Pusey). Similarly, good results attributed to tuberculin are paralleled by those attributed to streptococcal, intestinal or other vaccines, as well as to milk, turpentine, bismuth or gold. Irradiation of tuberculous lymphatic glands has often been followed by dramatic improvement, but so has irradiation of non-tuberculous or even normal lymph-glands (Goeckerman).

The success of gold-therapy is often acclaimed as a support for the tuberculous ætiology even by the same writers who get equal, or better, results from bismuth and omit to draw the equally justifiable conclusion that l.e. is due to syphilis.

Finally, it is sometimes argued that the differing or capricious responsiveness of l.e. to various treatments is evidence of its multiple ætiology (see below). But staphylococcal furunculosis, for instance, responds sometimes to manganese, sometimes to arsenic, sometimes to autovaccine, sometimes to foreign protein therapy, and sometimes not at all. This does not alter the fact of its staphylococcal ætiology; but individuals may need different forms of assistance in fighting the same enemy. L.e., as compared with other skin-diseases, appears to me to be, on the contrary, relatively uniform in its response to treatment, which seems largely independent of associated infections.

AUTOPSIES. The results of 111 autopsies of acute l.e. are classified by Gawalowski in three groups :—(A) *Tuberculosis was the sole finding* in 45 cases. (In 5 of them it was an old healed infection which could not have caused death.) In the majority the lymph-glands alone were involved. (B) *Tuberculosis together with some other diseases* was found in 15 cases. (But in 3 it only consisted of old healed foci.) (C) *No trace of tuberculosis* was found in 51 cases:

the positive findings were grouped as follows :—(*a*) the majority, 33 cases, had a bacterial infection (pneumo-, strepto- or staphylococcal) ; (*b*) 10 cases had disease of the lymphatic apparatus, viz., hypertrophy of liver and spleen and all lymphatic glands without further changes, or lymphogranulomatosis ; (*c*) 16 cases with incidental disorders, such as carcinoma.

In all groups, whether tuberculosis was present or not, involvement of the lymphatic apparatus predominated over disease of any other organs. Moreover, it is easier to exclude lung-disease than disease of the whole lymphatic system. Of the 57 cases of gland-affection, 38 were macro- and microscopically tuberculous. But the negative cases were not examined by serial inoculation. In Roxburgh's 5 autopsies no evidence of tuberculosis was noted.

Comment on the Tuberculous and Streptococcal Theories. Against tuberculosis being the direct cause of all cases, we have the absence of any sign of such infection in over half the autopsies on fatal cases. (It has to be admitted, of course, that there is great difficulty in excluding infective foci.) Against it, too, is the exact agreement in the proportion of l.e. patients that react to tuberculin with that of " normal " controls. Moreover, in view of the demonstration that both the affected and unaffected skin of l.e. patients reacts to tuberculin, when it reacts at all, by the formation of ordinary tubercular granulation-tissue, it is almost inconceivable, if the l.e. is itself directly due to a tuberculous infection, that it should not, at some stage at least, present a tuberculous histology. If, therefore, we accept the tuberculous theory, we are forced to the very unlikely assumption that the infective agent is present in a quite special form exclusive to l.e. Again, tubercle-bacilli have *never* been demonstrated in the lesions by direct examination. These considerations make it unjustifiable at present to suppose that *any* case of l.e. is caused by tuberculosis.

On the other hand, we are confronted by the instances of positive animal-inoculation from portions of the lesions ; the tuberculin-like action of extracts of lesions (Bloch and Fuchs) and of the blister-fluid raised over them (Sipos) ; and the positive epidermal tuberculin-tests of Nathan-Kallós. It has been pointed

out in Chapter VIII. that, when tuberculosis is present, tubercle-bacilli can occasionally be found in skin-lesions without being the cause of them. This might account for the positive animal-inoculations. The Nathan-Kallós test and the tests with extracts are certainly of importance, but would only prove the tuberculous nature of l.e. if they were found to be positive *only* in cases of tuberculosis of the skin.

The evidence in favour of a streptococcal ætiology is far more tenuous still, and is chiefly confined to the disseminate or acute types. In 1930 Barber expressed the view that the common scaly type is usually, if not always, tuberculous, and he attributed to streptococci the form in which there is no scaling but red raised œdematous patches resembling erythema multiforme. But this involves the conception that the different types of l.e. have different causes. If the common scaly type is always tuberculous and the other always streptococcal, then they are two different diseases; this is not supported by clinical or histological considerations.

Multiple Ætiology Theory. Jeanselme, Burnier, MacLeod and many others look upon l.e. as a symptom-complex or "réaction cutanée" in the sense of Brocq, which can be evoked by different causes. These causes are generally referred to as "toxic." I have already given reasons against at least the chronic fixed type being due to a soluble toxin.

It is inherently difficult to conceive of so very complex and yet characteristic a combination of phenomena being attributable to different causes. That certain relatively simple reactions, such as urticaria or eczema, or even lichenoid eruptions, can be due to different agents has been proved beyond doubt. But in l.e. the claims of the two most commonly suspected causes have been shown to be very doubtful. It must be definitely proved that at least 1 case of l.e. is due to one cause and at least 1 case due to another before one can accept the theory of multiple ætiology.

Many upholders of this theory group l.e. ætiologically with erythema multiforme, pemphigus, dermatitis herpetiformis, urticaria, purpura and several other diseases. It must be admitted that the lesions in the acute disseminate type are frequently

pleomorphic, often resembling one or more of these other diseases. It is just in this type that there are also often signs of a pyococcal infection or other septic or toxic process, of which definite evidence is found in nearly half Gawalowski's autopsies. Thus Schwarz and Parkes Weber report a fatal case in which there was, at least at the end, a staphylococcal pyæmia. Roxburgh ascribes death in all his cases to streptococcal septicæmia, and notes that in 4 of his cases the lymph-glands were found enlarged, but only after the onset of the final illness. It is difficult to escape the conclusion that the urticarial, erythema multiforme-like, pemphigoid and erysipeloid elements represent complications brought about by a superadded infection or intoxication.

The Theory of a Single but unknown Specific Agent. In 1925 Gray concluded that the remarkable uniformity and distinctiveness of the clinical and histological pictures, and especially the behaviour of the chronic lesions, point to the local activity of a single but unknown specific agent. This theory, which is supported by Gawalowski, though lacking all proof, is the easiest to reconcile with the facts. Ramel and Veiel also support the view that there is only one causative agent, but do not reject the possibility of its being the tubercle-bacillus in a form otherwise unknown, peculiar to l.e.

Treatment

Gold. The following are some of the chief preparations of gold, briefly annotated :—

Krysolgan, sodium salt of 4-amino-2-auromercaptobenzol-1-carboxylic acid ; given only intravenously at intervals of 7–14 days or longer ; initial dose 0·0001 gm., the maximum 0·025 gm. ; total for one course may be 0·25 gm.

Gold sodium thiosulphate (Sanocrysin, Crisalbine) is generally given intravenously, but can be used intramuscularly ; the solution must be fresh and colourless ; the initial dose is generally 0·1 gm. and the maximum 0·5 gm. ; higher doses are given but are not necessary.

Triphal, sodium salt of aurothiobenzimidazocarboxylic acid ;

gold-content 44%; much less toxic than the foregoing compounds (for rabbits); can only be given intravenously; initial dose 0·001 gm., or even smaller, and the maximum 0·2 gm.

Lopion, sodium salt of aurothiosinaminebenzoic acid; gold-content 40%; toxicity still further diminished; can be given intravenously or intramuscularly; initial dose 0·01 gm., maximum 0·5 gm.

Solganal, di-sodium salt of 4-sulphomethylamino-2-auromercaptobenzol-1-sulphonic acid: gold-content 36·5%; still less toxic and with high therapeutic index; a dose of 2 gm. is well tolerated, but it is neither wise nor necessary to exceed 1 gm.; usual initial dose 0·001 gm., and the total for a course 0·8–1·5 gm., or even up to 3 gm.; it can only be given intravenously.

Solganal B, aurothioglucose; still more harmless, being ten times less toxic than sanocrysin, though the gold-content is 50%; given intramuscularly or subcutaneously; the initial dose is 0·001 gm. and the maximum 1 gm.

Myocrisin, sodium aurothiomalate; contains 50% gold; given intramuscularly; well tolerated locally and rapidly absorbed; initial dose 0·01 gm. and the maximum 0·3 gm.; after a course of about ten injections it is advisable to allow an interval of 4–6 weeks.

Gold chloride, sodium chloraurate; given once a week intravenously in a 0·1% aqueous solution; the dose ranges from 1 c.c. up to 5 c.c., and even 10 c.c. Twenty injections are given in a series. The solution is strongly bactericidal and does not need boiling.

The doses given for these different preparations do not correspond with each other on any very rational or scientific basis, and the relative toxicity refers to animals. According to Martenstein, the smallest respective curative doses are found to have about the same gold-content. Kolle and Schlossberger showed that small doses have a disproportionately greater effect than large ones (on infected mice). Feldt thinks it acts catalytically on the reticulo-endothelial system and also electively on the mesenchymal cells of the disease-focus ("nosotropism"), leading to autolysis and the pouring-out of defence-substances ("Reiztherapie").

Flarer and Peracchia attempted to discover the mechanism of gold-therapy in l.e. by examination of the blood and metabolism. In improved or healed cases they noted increase of body-weight, of hæmoglobin, red cells, eosinophils and mononuclears, diminution of neutrophils and raising of the refractive index. These findings were reversed in cases that were not improved. They think that gold has a general stimulant action on metabolism and the defence-mechanism.

Excretion. The elimination of gold is slow, being effected to the extent of two-thirds by the kidneys and one-third by the gut. It is essential that the kidneys, in which the greatest concentration occurs, should be sound. In an animal 10 months after a course Christeller found gold in various organs, especially in the Kupffer cells of the liver. Frandsen thinks that only 40% is ever excreted. Jäger and Kohl in a case of triphal dermatitis found gold in the skin after 9 months. It was also demonstrated by Wigley and Patterson in the skin of 3 cases of l.e. that developed dermatitis after treatment with sanocrysin, whereas it was not demonstrable in the clinically normal skin of other l.e. patients, who had received a similar amount of sanocrysin. So gold seems to be retained to a greater degree where an inflammatory reaction is set up; but 2 of Wigley's positive cases, at any rate at the time of the dermatitis, had inefficient kidneys.

Results. Gold has proved superior to any former treatment, and is now, with the close rivalry of bismuth, the method of choice. It was first used for l.e. in 1920 by Kiendl in the form of *krysolgan*, introduced in 1917 by Feldt. The first detailed article was by Martenstein in 1922: its therapeutic efficacy was found to be very much greater than in frankly tuberculous skin-disorders, but he also found that with the same dosage undesirable symptoms were commoner. The original dosage was, however, much too high. Roxburgh and Corsi noted that the proportion of cures or improvement with gold is no greater in cases with an ascertainable tuberculous focus than in those without one, and I have found that the response to gold appears to have no relationship to the cutaneous reactivity to tuberculin. Martenstein has followed up his original cases and finds a good percentage of lasting cures.

Sanocrysin was considered by Rutledge in 1931 to be the most effective preparation but also the most toxic. In more recent cases he finds krysolgan (which is, however, still more toxic) the most satisfactory. Miller obtained clinical cures with sanocrysin in about 60%, using rather big doses. He noted that healing progressed just as rapidly in patients whose infective foci were left alone as in those who had them removed. In 2 cases an acute exacerbation was provoked, which was followed in 1 case by complete disappearance of all lesions, and in the other by improvement. Barber and also MacCormac have observed that their most satisfactory and lasting cures with sanocrysin have followed very severe reactions. This has not been my experience, and it would probably be risky to aim at big reactions. Franklin, using sanocrysin in the usual doses in courses of 8 weekly injections, observed that the patients continued to improve for varying periods up to 6 weeks after the end of a course. He therefore allowed a rest-period of from 1 to 2 months. He obtained clinical cures (maximum period of observation $2\frac{1}{2}$ years) in 64·5% and improvement in 13%. Smith, with slightly higher dosage, obtained cure in 42% and great improvement in 25%, the period of observation being 3 years from cessation of treatment. Throne and co-workers found that the majority of their l.e. patients responded well to *triphal*, which in their hands was quite useless for cutaneous tuberculosis and tuberculides. They gave injections two or three times a week, the first dose being 0·05 gm. and subsequent ones 0·1 gm. (an enormously higher dosage than my own). The reports on *lopion* are very good (Veiel, Schreiner, Wirz, Kerl *et al.*). Those on *solganal* are still uncertain. Its effect seems rather quicker than krysolgan but less lasting. Solganal B is specially recommended by Grüneberg, who uses it in cautious doses even in acute cases. Haxthausen uses *gold chloride* as the standard treatment, obtaining in 25% cure, 50% improvement, and 25% no change. He gets fewer complications than with the organic preparations and equally good results. It is also recommended by Wigley.

My own experiences are as follows. Over a period of 10 years I have used krysolgan, triphal and lopion in a very large number of

cases, and solganal and myocrisin in a few. I cannot give exact figures: the great majority have conspicuously improved; probably about a third have been cured and remained well for several years. On the whole, triphal seemed the most effective preparation. Lopion is satisfactory, but requires a higher dosage to achieve the same therapeutic effect. Good results can be obtained with much smaller doses than are generally given and far below what is usually necessary to produce metallic poisoning. My initial dose even of lopion is generally 0·005 gm.; the rate of increase depends on the clinical effect, the dose being increased by half as much again if there is no obvious change in the lesions, either favourable or unfavourable; as long as there is improvement the same dose is maintained; if, on the other hand, there is aggravation a longer interval is allowed, followed by a smaller dose. As a rule, injections are given at first once a week, and later once a fortnight. I seldom reach as high a dose as 0·25 gm. The majority of cases respond well without any clinical focal reaction; in fact, the prospect of ultimate success seems less good in those cases in which a focal flare, however small, is produced. Very often one finds an optimum-dose than which both higher and lower doses are less beneficial. But the principle of dosage is difficult to arrive at in view of some unpredictably surprising effects. Thus a patient, who had shown uninterrupted rapid improvement under triphal till the lesions were all but completely healed, underwent a very severe exacerbation on having the same dose repeated after an interval of 3 weeks. This is more in favour of the conception of "Reiztherapie" than of a catalytic action. On the other hand, another of my patients who was improving steadily with small doses, on being given a dose five times as big merely continued her improvement at the same rate and without focal reaction. This is more consistent with the idea of a catalytic action. At present we have no guide as to how long, if at all, treatment should continue after the lesions have disappeared.

Ill-Effects. Gold is *contraindicated* in the acute superficial unstable type (though even here the result can be very good), in extensive internal tuberculosis, advanced age, arteriosclerosis, disease of the kidneys and pregnancy.

Moderate malaise, headache and fever are not infrequent for a day or two following injection, but, though calling for special caution, do not indicate discontinuance of the treatment. The following are the more serious complications.

Skin and Mucous Membranes. The commonest ill-effect is dermatitis, often preceded by itching or a tight sensation. It may be morbilliform or scarlatiniform, and there is sometimes swelling of the eyelids and lips. Reuss has reported a case of extreme sensitisation to gold in all forms.

The name "chrysosis" has been given to a pigmentation, resembling argyria, described by Hansborg, Zimmerli and Lutz, which affects the areas exposed to light: it may only appear 2 years after the administration of gold. Histologically there are found in the papillary layer of the corium enormous deposits of deep black granules and clumps, not consisting of melanin. The pigmentation following one of Wigley's cases of gold-dermatitis was, however, due to the over-production of melanin.

The mucous membranes are often attacked before the skin. They may present a diffuse white milky appearance or a lichenoid eruption. There is pain but no increased salivation (Lebeuf and Mollard).

Internal Organs. Hæmorrhagic colitis, nephritis and metrorrhagia have been reported.

There have been a few deaths, but only after very high doses. *The mechanism of the ill-effects* is uncertain. It may be (*a*) heavy metal action; (*b*) capillary poisoning (Heubner); (*c*) autosensitisation from damaged cells in the disease-foci; (*d*) biotropism, *i.e.*, activation of an infection by a drug; (*e*) sensitisation to the drug. Godinho and also Throne conclude that most cases are due to (*a*). A few are more easily explained by (*e*).

Pusey has reported severe complications during a course of *sanocrysin*, which included blisters on the cornea leading to blindness. Ormsby had a fatal case after 2 doses of 0·025 gm., the eruption being scarlatiniform and purpuric. In the two small series of cases treated with sanocrysin in the usual dosage recently reported respectively by Franklin and Smith, there was some complication in about 50%. This is a fearfully high percentage,

and shows quite clearly that sanocrysin should either be given in much smaller doses or discarded in favour of a less toxic preparation. *Triphal* has also caused many cases of hæmorrhagic exanthems and enanthems, but rarely after small doses. In Throne's series, in spite of very high dosage, there were only a few instances of dermatitis, which rapidly cleared up with sodium thiosulphate. There have been many reports of eruption and one death after *solganal*. *Lopion* has, so far, not caused any serious symptoms, but a few mild eruptions. My own experience has been very fortunate. Though my therapeutic results have not, I think, fallen short of those of the majority of therapeutists, and have certainly been better than with bismuth, I have not seen a single case of dermatitis or any other toxic symptoms, beyond a mild temporary malaise or headache. This absence of complications must be attributed chiefly to the small and individually graduated doses.

Bismuth. Nicolas, Lacassagne and Rousset, who published the first detailed paper on this method, observed great benefit in all their patients, the lesions nearly always clearing up by the end of the first course of injections. They gave 12 intramuscular doses of *bismuth hydroxide*, 1·8 gm. in all; there were no ill-effects. Barbaglia noted that in those patients that also had syphilis the skin-lesions which were cured by bismuth had not responded to salvarsan and mercury. MacKenna has reported improvement in all of his series of 24 cases and apparent cure in 67%. Injections are given once weekly or fortnightly. After about 12 injections he recommends an interval of 6 weeks. The average adult can tolerate a dose of 0·3–0·4 gm. of *metallic bismuth* or bismuth *oxychloride*. The oxychloride is the less likely of the two to cause local induration and proved therapeutically more effective than *thiobismol*. Hallam (1930) is also impressed by this method. Bismuth is inoperative when given by mouth.

Smith, giving *quinby* in a course of 12 weekly injections of 0·3 gm., sometimes repeated after a few months' rest, obtained cure in 33% and great improvement in 42%. In no case was there any apparent ill-effect. He found its therapeutic value about equal to that of sanocrysin, but preferable in being less

toxic, much cheaper and less likely to light up a visceral tuberculosis or cause a severe focal reaction. I have, however, already commented on the unnecessarily high percentage of ill-effects in his series treated with gold. I have seen a few cases improve on bismuth in which gold had been ineffective, but far more in which gold proved useful when bismuth had failed.

MacKenna claims equal, if not even greater, success by the use of bismuth locally in the form of a 10% *colloidal bismuth oxychloride ointment.* I have seen great improvement from the use of the following paste :—bismuth carbonate dr. 2, soft paraffin dr. 4, liquid paraffin dr. 2; but not in inveterate cases. Owing to its harmlessness and convenience, it is the most suitable method to try first.

Arsenical Compounds. NEOARSPHENAMINE. This has been successfully employed by many authorities. Ravaut and Bocage found that subjects of l.c. are particularly sensitive to it, but that their intolerance is diminished if the drug is dissolved in a glucose sodium thiosulphate mixture. About 12 weekly doses of 0·45 gm. were found necessary, and the course generally had to be repeated after 2 or 3 months. Cure was obtained in about one-third of the cases and improvement in a further third. Ristic claims cure in 60%. Oro, after testing many methods, concludes that the best prospect for permanent cure lies in an alternation of gold and neoarsphenamine.

ACETARSOL (Stovarsol, Spirocid). This has the advantage that it can be given by mouth, and it has many supporters. Volk considers it superior to bismuth but inferior to gold. MacCormac reports marked improvement in 2 out of 3 cases, though both developed a dermatitis. He started with a daily dose of gr. 8, but had to reduce it to gr. 4 every alternate day.

Plasmoquine. This has been advocated by Martenstein for acute l.c. He has seen it improve even severe febrile cases with nephritis, till they were eventually able to tolerate small doses of gold.

Moogrol. One of my most inveterate cases has responded better to intramuscular injections of iodised moogrol than to gold or bismuth.

Local Treatment. Apart from bismuth ointment, this is seldom efficacious by itself, but it is often useful in obstinate chronic cases that are responding incompletely to internal measures. The most useful procedures are short exposures of CO_2 *snow* or the *Kromayer lamp* with blue glass filter (Volk) or painting with a mixture of *iodine and carbolic acid* (Martenstein). I prefer superficial *electrocoagulation*, as it is followed by less inflammatory reaction.

Bibliography

BARBER, H. W. (*a*) "A Case of Lupus Erythematosus associated with Streptococcal Infection of the Tonsils," *Brit. Journ. Derm. and Syph.*, 1919, **31**, 186. (*b*) "Taylor's Practice of Medicine," 1930, 976.

BARBER, H. W., and FORMAN, L. "The Results of Intradermal Tests in Certain Dermatoses and the Therapeutic Effect of Intradermal Vaccines," *Brit. Journ. Derm. and Syph.*, 1933, **45**, 4.

BLOCH, B., and FUCHS, H. "Ueber die Beziehungen des chronischen Lupus Erythematodes zur Tuberkulose," *Arch. f. Derm. u. Syph.*, 1913, **116**, 742.

CANNON, A. B., and ORNSTEIN, G. G. "The Tubercle Bacillus as an Ætiologic Factor in Lupus Erythematosus," *Archives of Derm. and Syph.*, 1925, **12**, 691.

CUMMINS, LYLE and others. "Discussion on Gold Treatment," *Proc. Roy. Soc. Med.*, 1930, **23**, 1383.

FELLNER, M. "Die Goldtherapie in der Dermato-Venereologie," *Zbl. f. Hautkr.*, 1932-33, **43**, 489 and 585.

FLARER, F., and PERACCHIA, L. "Osservazioni e richerche sulla cura del lupus eritematoso e del lupus volgare con preparati d' oro," *Giorn. Ital. Dermat.*, 1929, **70**, 11.

FRANKLIN, J. L. "The Treatment of Lupus Erythematosus with Sanocrysin," *Brit. Journ. Derm. and Syph.*, 1934, **46**, 66.

GAWALOWSKI, K. "Lupus erythematodes acutus," *Acta dermato-vener.* (Stockholm), 1929, **10**, 1.

GILMAN, R. L. "The Senear-Usher Syndrome," *Archives of Derm. and Syph.*, 1931, **1**, 84.

GODINHO, P. A. "Drei Fälle von Sanocrysin Exanthem bei Lupus Erythematodes," *Schweiz. med. Woch.*, 1927, **57**, 2, 37 (*cit.* Fellner).

GOECKERMAN, W. H., and MONTGOMERY, H. "Lupus Erythematosus," *Archives of Derm. and Syph.*, 1932, **25**, 304.

GOUGEROT, H., BURNIER, and ELIASCHEFF, O. "Lupus Erythematodes Tumidus," *Ikonographia dermatologica*, 1932, **1**, 15.

GRAY, A. M. H. "The Ætiology of Lupus Erythematosus," *Brit. Journ. Derm. and Syph.*, 1925, **37**, 406.

LEBEUF, F., and MOLLARD, H. "Morphologie des aurides; essai de classification," *Ann. de Dermat.*, 1931, **2**, 214 (*cit.* Fellner).

MACCORMAC, H. "Two Cases of Lupus Erythematosus treated with Stovarsol," *Proc. Roy. Soc. Med.*, 1934, **28**, 107.

MACKENNA, R. M. B. (*a*) "Treatment of Lupus Erythematosus with Bismuth," *Lancet*, 1930, **218**, 178. (*b*) "The Possibilities of Bismuth Therapy in the Treatment of Cutaneous Diseases," *Brit. Journ. Derm. and Syph.*, 1931, **43**, 565.

MACLEOD, J. M. H. "Lupus Erythematosus," *Archives of Derm. and Syph.*, 1924, **9**, 1.

MILLER, H. E. "Gold and Sodium-thiosulphate in the Treatment of Lupus Erythematosus," *California Med. Journ.*, 1928, **29**, 243.

NICOLAS, J., LACASSAGNE, J., and ROUSSET, J. "Le traitement du lupus érythémateux par les injections de sels de bismuth," *Paris Méd.*, 1929, **1**, 62.

NOEL, P. "Le lupus érythémateux dans les races noires," *Ann. de derm. et de syph.*, 1928, **9**, 372.

PILLAT, A. "Ueber das Vorkommen von Chorioiditis bei Lupus erythematodes," *Graefes Arch.*, 1935, **133**, 566 (*Abs. Zbl. Hautkrank*, 1935, **52**, 103).

RAVAUT, P., and BOCAGE. "Le traitement du lupus érythémateux par le novarsenobenzol," *Ann. de derm. et de syph.*, 1926, **7**, 657.

ROXBURGH, A. C. "Acute Disseminated Lupus Erythematosus: Five Fatal Cases," *Brit. Journ. Derm. and Syph.*, 1933, **45**, 95.

RUTLEDGE, W. U. "Lupus Erythematosus; Treatment with Gold Preparations," *Archives of Derm. and Syph.*, 1931, **23**, 874 (*cit.* Fellner).

SCHWARZ, E., and PARKES WEBER, F. "Acute Disseminated Lupus Erythematosus with Staphylococcal Pyæmia in a Child," *Brit. Journ. Derm. and Syph.*, 1932, **44**, 486.

SENEAR, F. E., and USHER, B. "An Unusual Type of Pemphigus combining Features of Lupus Erythematosus," *Archives of Derm. and Syph.*, 1926, **13**, 761.

SMITH, A. G. "Gold and Bismuth in the Treatment of Lupus Erythematosus," *Brit. Journ. Derm. and Syph.*, 1934, **46**, 399.

THRONE, B., CLARK, A. S., VAN DYKE, L. S., and MYERS, C. N. "Treatment of Lupus Erythematosus with Gold Compounds," *New York State Journ. of Med.*, 1927, **27**, 1064.

THRONE, B., KINGSBURY, J., and MYERS, C. N. "Unusual Clinical Manifestations following Intravenous Administrations of Gold Compounds," *Archives of Derm. and Syph.*, 1932, **25**, 494.

VEIEL, F. "Lupus Erythematodes," *Jadassohn's Handbuch*, 1931, **X/1**, 687.

WIGLEY, J. E. M. "Some Observations on the Deposition of Gold in the Skin," *Brit. Journ. Derm. and Syph.*, 1932, **44**, 69.

WISE, F. "Lupus Erythematosus Bullosus or Pemphigoides." Report of Two Cases with a Discussion of the "Senear-Usher Syndrome," *Med. Journ. and Record*, 1931, **134**, 227.

ZIMMERLI, E., and LUTZ, W. "Eine eigenartige Form von Pigmentierung nach Goldbehandlung," *Arch. f. Derm. u. Syph.*, 1929, **157**, 523 (*cit.* Fellner).

"Recent Advances in the Treatment of Lupus Erythematosus: Replies to a Questionnaire," *Derm. Woch.*, 1934, **1**, 24 (*Abs. Brit. Journ. Derm. and Syph.*, 1934, **46**, 196).

CHAPTER X

FUNGOUS INFECTIONS

Classification

THE last two chapters have shown the great difficulties in relating even the single well-defined bacillus of tuberculosis to disorders of the skin. In the case of fungi this problem is, in certain respects, even more difficult; for we are dealing with almost innumerable species or varieties of organism. Moreover, it is uncertain how many of those described really are different species, since they undergo such big modifications, both morphologically and biochemically, according to their age and environment. Thus Lecoulant has drawn attention to the great macro- and microscopic variations undergone by cultures of the same fungus on the same medium by repeated subcultures. Especially striking was a transition from trichophyton faviforme by way of pleomorphic cultures to characteristic epidermophyton inguinale. He looks upon T. faviforme as a dysgonic form, from which the characteristic culture develops only after adaptation to a favourable milieu.

Ringworm-Fungi (**Gymnosaceæ**). Attempts to improve on Sabouraud's classification are numerous. There is great confusion owing to the various names having been derived, some from the appearance of fungi during their parasitic life, some from the macroscopic appearance of cultures and some from microscopical details. Thus Grigorakis (1929) lays down that the group achorion is characterised by arthrospores, the group microsporon by spindles and the group trichophyton by aleurons. To this Langeron rightly objects that the terms microsporon and trichophyton are retained, but are emptied of their essential meaning. By the term trichophyton Sabouraud himself would now only express that the particular fungus, as opposed to epidermophyton,

attacks the hair; he divides these hair-follicle fungi into the following groups:—(1) Achorion, (2) Microsporon, (3) Endothrix, (4) Microides, (5) Megaspores. Langeron and Milochevitch, on the basis of an extensive study of the morphology of the ringworm-fungi on natural and polysaccharide-containing media, divide them into the following genera:—(1) *Ctenomyces*: this includes microides, which comprises trichophyton asteroides, Tr. granulosum, Tr. lacticolor, Tr. interdigitale and Tr. radiolatum, hitherto considered distinct. (2) *Sabouraudites*: this incorporates the old microsporon and also achorion gypseum, Ac. gallinæ and Ac. quinckeanum, hitherto considered distinct. (3) *Epidermophyton*, consisting only of the one species Ep. floceulosum, which is the old Ep. cruris or inguinale. (4) *Trichophyton*, which includes all the other ringworm-fungi.

For the purpose of differentiation Bruhns and Alexander attach importance to the results of animal-inoculation. Another method is by observing the occurrence or non-occurrence of *hyphal fusions* in hanging-drop preparations. Davidson, Dowding and Buller, working with microsporon Audouini, Mi. lanosum and Tr. gypseum, find that hyphal fusions (1) are formed between hyphæ of one and the same mycelium isolated from a single patient; (2) are formed between any two mycelia of the same species isolated from two different patients; (3) are not formed between a mycelium of one species and a mycelium of another species.

Monilia. Castellani classifies the yeast-like fungi broadly as follows. Those with:—

(1) No mycelium and no asci . .	Cryptococcus
(2) No mycelium but with asci . .	Saccharomyces
(3) Mycelium but no asci . . .	Monilia
(4) Mycelium and asci . . .	Endomyces

Langeron and Thalice attempt a botanic classification founded on the spore-bearing apparatus. They exclude the term "monilia," for which they substitute "mycotorula." Castellani claims to have differentiated over 20 varieties of monilia, but at St. John's Hospital, MacLeod and Muende have only been able

with certainty to distinguish two types, Mo. Pinoyi and Mo. albicans, which have the following characters :—

(A) Direct examination of scrapings of lesions :—

Monilia Pinoyi	Monilia albicans
Budding oval Gram-positive spores, varying in size, with an average of 2·25μ × 4μ, generally arranged in short chains. Mycelium scanty, short, and usually non-septate and non-branching.	Budding oval Gram-positive spores, varying greatly in size, long diameter 1–6μ, usually arranged in clusters. Large number of branching mycelial elements with conidial spores in the region of the septa.

(B) Cultures on Sabouraud's maltose-agar at 25° C. :—

Monilia Pinoyi	Monilia albicans
Small pin-head colonies make their appearance within 18–36 hours, and later coalesce to form larger irregular ones, smooth, shiny and of a pale fawn colour. They are composed of oval budding cells with very few mycelial elements. With age the colonies lose some of their lustre and the microscopical examination then reveals the presence of more mycelium.	Thin " crinkled paper " brownish-yellow colonies appear within 18–48 hours. They are composed of masses of branching septate mycelium, with clusters of oval spores at the septal nodes. With age the colonies become darker in colour and the surface matt ; microscopical examination shows still greater tendency to mycelial development.

The most definite differences in biochemical reactions are that Mo. albicans produces acid from galactose and liquefies gelatine, whereas Mo. Pinoyi does neither.

Staehelin, Jui-Wu-Mu and van Schouwen examined 14 strains of various origin, some from normal skin, some from moniliasis (thrush, interdigital erosion, diabetic intertrigo, levuride), together with pityrosporon Malassez and saccharomyces cerevisiæ. They were grown on various media under similar conditions and compared microscopically. Only those organisms were studied that comprised budding spores with mycelium (occasional or constant). They found that, apart from the beer-yeast, the differences between the strains were neither so constant nor so profound as to justify the setting up of different types and they propose grouping all the agents of these dermatoses under the term " oidium " or " monilia."

The best medium according to Milochevitch is liver-agar or liver-broth. Bloch obtained the largest percentage of positive cultures on carrots and the next largest on glucose-agar. Haler states that monilia will not grow freely on media entirely devoid of sugar and that their sugar-reactions are stable. According to Plaut and Grütz the addition of glycerine or alcohol to a fluid medium encourages budding cells, whilst saccharose and dextrin promote mycelium. Further, budding cells are favoured by acid reaction and oxygen; mycelium by the opposite conditions as well as by the presence of toxins.

THE PITYROSPORON OF MALASSEZ. MacLeod and Dowling (1928) describe this fungus as grown by the method used by Garner since 1908. On Sabouraud's maltose-agar at 25° C. it begins to grow in about 24 hours and forms a white glistening smooth culture, later becoming yellow. In peptone-broth with 1% oleic acid and 1% glucose at 25° C. it appears as a flocculent growth in which there is an abundant fine mycelium. It is the presence of this mycelium in fluid media which chiefly differentiates the pityrosporon from monilia.

But Ota and Huang (1933) hold that previous workers, including MacLeod and Dowling, have failed to make any clear distinction of pityrosporon from other monilia. They state that the true pityrosporon grows best at 37° C., forming minute colonies on Sabouraud's glucose-agar, resembling those of the gonococcus. On Petragnani's medium the growth is more vigorous, but cultures are only obtained in either case infrequently. It has, however, a widespread distribution on all parts of the normal skin, buccal mucosa and external auditory meatus. They describe it in culture as a relatively small ellipse, 3–4μ by 2–3μ, never forming mycelium or ascospores. No gas is produced from any sugar and it is non-hæmolytic and non-pathogenic to animals.

Geographical Distribution

The boundaries are becoming less distinct, but statistics show enormous variations from time to time, pointing to epidemics of certain species. The commonest fungus in Italy has been reported

as Tr. violaceum, accounting in Naples for 87% of the cases. From Paris Rivalier (1930) reports that the inflamed lesions of children's scalps, often leading to kerion, and tinea barbæ were caused by Tr. asteroides, Mi. felineum or Mi. lanosum. Sabouraud says that, thanks to the systematic treatment of tinea capitis in Paris, the incidence among school-children has dropped from 5% to 0·15%.

Habitat and Biology

Pollacci and Nannizzi and others have shown that fungi can survive for a long time on plants, grains of corn, chaff, dung and horn. Catanei proved that hairs from a guinea-pig inoculated with Tr. gypseum radiolatum were still actively infective after being kept for 52 days in paper. Urbain observed that Tr. gypseum-cultures remained alive for 2 years on chaff, and that from cage-straw, in which infected guinea-pigs had sat, Tr. gypseum in a pathogenic state could be recovered after 9 months. Kadisch has further shown that trichophytons and achorions can survive for many months on silk, linen, wool, leather, sweepings, feathers, horse-hair, refuse, earth and peat. J. W. Williams has cultured Tr. interdigitale and Ep. inguinale from floor-scrapings, mats and gymnastic apparatus at a school.

Bonar and Dreyer failed to grow fungus on sound new wood, but grew it easily on floor-material covered by a coating of slime or algæ. Their mode of existence on these various materials is probably a purely vegetative one and not truly saprophytic.

A still more important question is to what extent they exist on the human skin in a vegetative, or non-pathogenic, state. One can, strictly speaking, only refer to a "saprophytic" existence there, if active growth takes place in virtually dead scales. Ballagi (1929) made cultures from scabs, crusts and pus in 190 different skin-diseases, and from subungual material in 19 persons. He found in 75% of the skin-diseases a hyphomycete or oidium. In 29% it was penicillium; the rest included various moulds and oidia, but none of the recognised pathogenic ringworm-fungi. Bruhns considers it certain that *ringworm-fungi do not vegetate*

"*saprophytically*" (by which he probably means harmlessly) *on the healthy human skin.* But this is not so in animals. Brumpt examined stained hairs from a horse affected with sarcoptic mange, without the slightest suspicion of ringworm, and found many loaded with chains of spores indistinguishable from Sabouraudites. Further, Livesey quotes the blue Persian cat which infected at least 16 persons with tinea circinata; microsporon was found inside the shaft of some of the hairs, but the cat showed no clinical lesion.

There is, however, little doubt that *monilia can vegetate harmlessly on the human skin.* Jessner and Kleiner have isolated it from the nail-groove of about 60% of normal persons. This is confirmed by Bruhns and Alexander. Staehelin, Jui-Wu-Mu and van Schouwen in Bloch's Clinic at Zürich obtained positive cultures by a single implantation of healthy horny layer in 81% of cases, which included normal persons and subjects of eczema and various other skin-disorders. The highest percentage was actually in normal persons. They were obtained in order of frequency from the toes, breast, groin, nails, leg and scalp; a very similar fungus being isolated in all cases. They think that their high percentage, as compared with the results of some other workers, may be attributable to geographical differences. Benham and Hopkins are, however, a little more confident of their powers of differentiation. They examined 100 apparently normal young adults for the presence of yeast-like fungi on the skin and in the intestines. Those recovered fell chiefly into 3 groups, namely, monilia, cryptococcus and "mycoderma"; by the latter they mean forms producing dry corrugated or flat downy growths and a septate mycelium of oblong cells which break up into spores. From the skin or nails they obtained cryptococci and mycodermata in 72%, but in no case Mo. albicans. From the tongue and fæces they grew yeast-like organisms in 80%, but Mo. albicans only in 18%. If, therefore, Mo. albicans were found regularly in certain types of skin-lesion, there would be justification for considering it pathogenic and the source of infection might well be the alimentary tract.

Pathology

The problem of fungous infection is, however, in one respect simpler than that of tuberculosis, in that the organisms (at least those usually encountered in England) do not invade the human internal organs. The mucous membranes of the respiratory and alimentary tracts may, however, be invaded by monilia.

This *dermatotropism* is susceptible of several explanations. The optimum-temperature for most fungi, according to Kadisch, is round about 27° C., and they need plenty of oxygen. W. Jadassohn and Stachelin put guinea-pigs in an incubator at 36°–39° C. till the rectal temperature became about 40° C. and inoculated the skin with Ac. quinckeanum. The infection took; but the incubation-period was prolonged, the ensuing inflammation much milder than in controls, and histological examination showed a slighter growth of fungi. But the fact that the inoculation took at all shows that skin-temperature and oxygen are not the only factors in their dermatotropism. They do, however, grow on *dead* internal organs. Perhaps in the living body they thrive on the horny layer because it is virtually dead tissue. Sulzberger, after endocardiac injection of Ac. quinckeanum in guinea-pigs, was able to cultivate it from the blood, heart, liver, kidneys, spleen and lungs 2 hours to 12 days later, but there was no active growth in these internal organs.

Skin-lesions can follow inoculation of the blood. Thus Fried and Segal found that 38% of rabbits injected intravenously with spores of Tr. gypseum developed infective lesions on the skin, but only (as Kogoj had already shown) where it had been subjected to trauma. Truffi studied the lesions developing at sites which had been traumatised or irritated by a short application of chloroform, by mixing Indian ink with the spores injected intracordially. The earliest deposits were seen in the hair-follicles and later ones in the surface horny layer. In regression, too, the fungus disappeared last from the hairs.

If the skin itself of a guinea-pig, whether allergic or not, is inoculated with Ac. quinckeanum, W. Jadassohn showed that 1–2½ hours later the fungus can be found circulating in the blood

and hæmatogenous skin-metastasis takes place at sites previously traumatised and occluded to prevent exogenous infection. After such cutaneous inoculation Sulzberger could grow the fungus from the blood 1–48 hours and 10–13 days later, but not between these periods. The second period coincided with the climax of the primary reaction and a state of maximal allergy of the skin.

The pathogenicity of *monilia* is probably more facultative than that of ringworm-fungi. Redaelli in 1924 proved the pathogenicity of several varieties, including Mo. Pinoyi, for rabbits, rats and guinea-pigs, when introduced intravenously, intra-arterially or into serous membranes; certain other varieties, on the contrary, have been found quite harmless. Strains cultured directly from active lesions are usually the most virulent. Animal-experiments carried out by Knott with strains of monilia obtained by Dowling from human moniliasis were practically negative. But Haler reports that 3 rabbits injected intravenously with Mo. Pinoyi derived from human perionychia became extremely ill and, when killed 48 hours afterwards, revealed multiple miliary abscesses in the kidneys and a few elsewhere. These lesions were proved to be due to a pure infection with Mo. Pinoyi. A rabbit injected with four times the dose of *killed* monilia suffered no ill-effects. Intracutaneous injection of living cultures on the back produced a scaly erythematous rash. Haler finds the pathogenicity of strains is higher the lower their thermal death-point; and that the only modifications produced by passing them through animals are increase of virulence and lowering of heat-tolerance. Jessner and Kleiner demonstrated that the apparently harmless monilia, cultivated by them from normal nail-folds, can, when inoculated on normal skin, produce lesions resembling spontaneous moniliasis, provided that maceration and scarification are maintained.

The pathogenicity of MacLeod's cultures of *pityrosporon* have been tested by Dowling on the human skin. He found that cultures placed in simple contact are harmless, but that a strong emulsion injected intracutaneously always produces a scaly patch, even in normal persons. The most striking lesions, however, follow implantation on light scarifications. Seborrhœic subjects

react more vigorously. The reaction consists of a group of papules which become scaly in the course of some days and usually disappear within 2 or 3 weeks. The relationship to seborrhœic dermatitis is discussed later.

Clinical Aspects

Moniliasis. The cutaneous lesions are almost as multiform as those of ringworm and vary in appearance according to the particular soil. Monilia flourishes best on a moist, seborrhœic type of skin and in situations where there is naturally both warmth and moisture. The sites of election are the perianal region in infants, and in adults the interdigital spaces, groins and internatal cleft, submammary folds, axillæ and nail-folds. The lesions start as small red papulosquamous patches which become vesicular. The vesicle ruptures to expose a bright red, smooth, moist area surrounded by a fringe of sodden, opaque, white epithelium (see Fig. 20). The patches enlarge peripherally with a tendency to heal in the centre. Beyond the spreading edge are usually some isolated vesicular outrunners. In severe cases there are inflamed crusted patches, resembling eczema secondarily infected with pyococci. The following are the chief clinical forms :—

Thrush. Though a large number of different fungi have been found in thrush by Castellani the commonest is Mo. Pinoyi.

Interdigital Lesions of Feet and Hands. These begin as a papulovesicular eruption and may spread on to the back of the hands or feet in the form of red patches dotted with vesicopustules. When situated on the webs it often produces a denuded area, tapering towards the finger-tips, with the usual epithelial fringe in which yeast-like bodies are easily demonstrated. Sometimes, especially between the toes, the whole lesion appears white, sodden and leathery, with a tendency to crack along the bottom of the fold, as in ringworm (" erosio interdigitalis blastomycetica " of Fabry).

The pathogenic effect on the human skin of monilia derived from these lesions was first proved by von Graffenried in 1918.



FIG. 20.—Moniliasis. The situation is unusual but the lesions themselves characteristic. The scales were packed with spores and mycelium. (Author's case.)

Hopkins and Benham succeeded in reproducing similar lesions by experimental inoculation of monilia so derived. Dowling has also produced mild artificial lesions between the digits with monilia

albicans. Generally they were of short duration and did not amount to an erosion, but the ideal natural conditions could not be copied. In vesicular and scaly eczemas of the palms and fingers he has found monilia in the scales and cultivated it. When replanted on the skin it produced an inflammatory scaly patch, resembling the natural lesion.

PERIONYCHIA. Those chiefly attacked by monilial perionychia



FIG. 21.—Perionychia with bolster-like swelling of nail-wall. Monilia Pinoyi cultivated. (J. M. H. MacLeod, *Brit. Journ. Derm. and Syph.*, 1930, p. 555, part only.)

are women who have their hands frequently in water or exposed to sugar, whether dry or in solution. Manicuring probably also contributes, partly through trauma and partly, perhaps, through the use of certain alkaline preparations. MacLeod describes the clinical appearance as a bolster-like swelling of the nail-fold: on being squeezed it emits a bead of pus, which comes from minute abcesses on the under surface of the nail-wall, just inside the

margin (see Fig. 21). As a rule, only a few of the fingers, but occasionally all the digits of hands and feet, are involved. In a series of cases of perionychia examined bacteriologically by Corsi the majority yielded B. coli, occasionally with staphylococcus pyogenes aureus; monilia being found only in a minority. He did not consider the clinical appearance characteristic for any particular infective agent. But Haler found monilia in all the typical cases as above described, and, though various other organisms, such as pyococci and B. coli, were also occasionally present, they did not occur in any fixed ratio or with any constancy. As controls he made similar cultures from the nail-folds of 10 normal persons. Only in one of them was any yeast-like organism isolated, and that was of the higher true-yeast type. Of 2 cases of acute perionychia with copious suppuration and lymphangitis one gave a pure growth of B. coli and the other of staphylococcus aureus, and neither of them any monilia. The nail-plates, if attacked, assume the same appearance as is produced by ringworm-fungi. The condition is not infrequently associated with moniliasis of the cheeks (thrush) or anus. Kingery, Thienes, and also Shelmire have produced acute inflammation of human nail-folds by implanting Mo. albicans isolated from cases of perionychia. The inflammation reached its climax in about 10 days and then subsided. Similarly Haler, using Mo. Pinoyi obtained from human perionychia, produced swelling and suppuration by injecting it perionychially in rabbits. The same organism was recovered from the lesions. He therefore claims that for the monilial causation of the bolster-nail type of perionychia Koch's postulates have been fulfilled.

Perlèche. The clinical picture was first described in 1885 by Lemaistre, who adopted one of the names prevalent in the local Limousin dialect: a variant of "pourlécher," to lick. The epithelium of the labial commissures is white, macerated, adherent and wrinkled. The colour is nearly that of mother-of-pearl. In advanced cases the wrinkles are deep, and there may be transverse fissures with red bases. They rarely bleed. It is chiefly a disease of childhood and is highly contagious, often affecting a whole family or spreading widely in a school.

Lemaistre and subsequent writers have considered it a streptococcal infection. But Finnerud in 1929, studying an epidemic in an orphanage, grew monilia from 77% of the cases. He was able by inoculation of these cultures to produce a clinically identical disorder in 9 out of 10 cases. Robinson and Moss (1932) report a



FIG. 22.—Perlèche. Monilia Pinoyi cultivated. (J. M. H. MacLeod, "Diseases of the Skin," 1933, p. 1310.)

series of cases, some of which were complicated by superficial glossitis, interdigital erosion, perionychia or dermatitis of the toes. Mo. albicans was cultured from the majority of the perlèche lesions as well as from the other sites. It was also found in the mouths of half of a group of patients with perlèche but no oral lesions. In a severe case MacLeod grew Mo. Pinoyi (see Fig. 22).

Perlèche in Adults. Freund (1931) draws attention to a form

in women, generally over the age of 40 years, which he considers clinically and ætiologically different from that described by Lemaistre. The patient's resistance is generally lowered by some general illness, including menopausal or senile symptoms. Its monilial ætiology is based on (1) the microscopical demonstration of fungus in the fresh preparation ; (2) culture, which is generally both copious and pure, contrasting with those from mouth-corners that are either normal or affected in other ways ; (3) association with dermatoses in which the causative *rôle* of monilia is recognised, such as the interdigital and submammary forms ; (4) positive



FIG. 23.—Interlabial mycosis in a sixty-two-year-old woman. (H. Freund, *Arch. f. Derm. u. Syph.*, 1931, p. 616.)

inoculation-tests with the pure culture (Skolnik, Freund and Finnerud) ; (5) the favourable therapeutic activity of tincture of iodine. Freund stresses the originally harmless nature of the monilia and the importance of the abnormal soil. As predisposing factors, in addition to the general lowering of resistance, he mentions salivation, often induced by dentures. In Freund's interlabial mycosis the inflammation is usually more intense and less superficial than in the perlèche of Lemaistre. Commonly the border is greyish-white and sometimes crusted ; the centre is vivid red, moist and eroded or fissured (see Fig. 23). In contrast with perlèche in children, Freund has seen no instance of transmission to others. It is true that Finnerud's investigations point to the existence in children of a contagious perlèche of

monilial origin, though he does not mention whether streptococci were present in addition. In Freund's cases they were only rarely met with: moreover, the condition was generally aggravated by white precipitate ointment.

Frank cultivated monilia from 4 cases of perlèche in adults, and with cultures so obtained produced a similar lesion by inoculation into his own interlabial commissure. Cultures taken as controls from apparently normal commissures of 100 persons yielded yeast-like organisms in 19.

Diabetic Moniliasis. It especially attacks the genito-anal and submammary regions, and, as in the case of other forms of moniliasis, chiefly females. In Stachelin's cases monilia was found copiously in the horny layer as budding forms and large quantities of mycelium. In all cases an almost identical monilia was cultivated. The eruptions were healed with comparative ease, at any rate temporarily, by local measures, in spite of persistence of the glycæmia.

Experimentally it has been proved that diabetic skin is more easily infected with monilia than the normal: the reason is, however, obscure; for the course of an infection does not run parallel with the degree of hyperglycæmia. The dermatophytosis may be the first indication of a metabolic disturbance.

Pustular Moniliases. They arise most frequently after prolonged application of wet compresses or immersion in baths. There are numerous superficial pustules, together with diffuse inflammation and maceration. Monilia derived from the lesions can cause inflammation when inoculated on the skin of normal persons (Stachelin).

Vulva and Anus. In these regions the mucous membrane may also be involved, and the infection can lead to pruritus. Sometimes the urethra and glans penis are attacked.

Stachelin concludes from his work that monilia normally vegetates harmlessly on the skin. Constant moisture and maceration favour its multiplication and this results in an increase of toxic and irritating substances. Pathogenicity is also favoured by general causes, such as cachexia, disorders of metabolism and

intoxications such as salvarsan dermatitis. Under these circumstances it may acquire increased virulence. Ramel, as also Ballagi, thinks that monilia plays an important part in complicating and prolonging eczemas due to other causes.

Foot-Ringworm: Tinea Interdigitalis. It was in 1908 that Whitfield first showed that some vesicular and scaly eruptions.

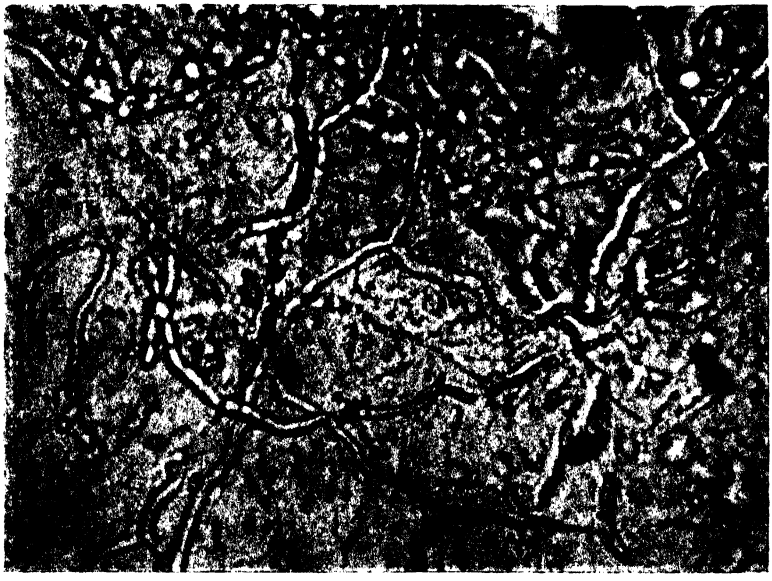


FIG. 24. Photomicrograph showing mycelium of Trichophyton Interdigitale embedded in skin-scale. (L. Bonar and A. D. Dreyer, *Amer. Journ. of Public Health* 1932, p. 910.)

between and under the toes and, more rarely, between the fingers and on the palms, were due to ringworm. This affection has become so common in England and even more so in America, that it constitutes a serious problem. Brunsting states that at the New York Skin and Cancer Hospital between 1913 and 1927 it ranked as the seventh or eighth most frequent disease, whereas in 1928–29 it had risen to second place. There seems little doubt that infection is spread by the common use of bathrooms and changing-

rooms. In the University of California in 1928, Legge, Bonar and Templeton found that 51·5% of the new men-students and 15·3% of the new women-students had clinical evidence of foot-ringworm. Among those who attended gymnasium for one term the percentage



FIG. 25.—Epidermophytosis. The lesions started as large vesicles. The other foot was symmetrically affected and there was peeling between the toes. (A. D. McLachlan and W. H. Brown's case.)

increased among the men from 51·5% to 78·6%, whilst among the women the increase was only 2%. One important reason probably was that the women were never allowed to put their bare feet on the floor. At other American universities the figures are similar. But Weidman also found the proportion less among the women, though their gymnasium-conditions were worse than those of the

men. Templeton thinks the greater incidence in men may be due to their wearing heavy shoes and woollen socks, on which Tr. interdigitale grows more easily than on silk or cotton.

In making the diagnosis by culture Legge and his co-workers emphasise the necessity of making a large number of plants of the diseased tissue. They found that, when the number of plants from each case was increased by about half, the percentage of positive cases was more than doubled. The organisms held responsible are obtained in America in the following proportions :— epidermophyton interdigitale of Kaufmann-Wolf (= Tr. interdigitale of Priestley) three-quarters (see Fig. 24); Ep. cruris (Castellani), Ep. inguinale (Sabouraud) and Ep. rubrum, together, one-quarter. Monilia was also often found in large quantities (Williams and Barthel).

Clinically Gray divides the disease into three types :—(1) Intertriginous; (2) Vesicular (see Fig. 25); (3) Hyperkeratotic. Of these there may be various combinations, which Brunsting thinks are determined largely by the nature of the soil. If the skin is dry hyperkeratosis predominates, but in the presence of hyperhidrosis the picture is intertriginous with scattered vesicles tending to coalesce. The nails are frequently involved, which is probably one important cause of the tendency to relapses: they sometimes contain fungus without showing any clinical alteration. Similarly, Strickler and McKeever have shown the presence of fungus in the skin from 1 to 2 inches beyond the apparent disease.

The infection is favoured by increased sweating, which, according to Kornbleet, is induced by flat feet and the wearing of ill-fitting shoes. Marchionini, confirmed by Levin and Silvers, has shown that the soil upon which intertriginous dermatophytosis, particularly that of the feet, develops is especially favourable, owing to a considerable lowering of surface-acidity as compared to the rest of the skin. This results chiefly from an alkaline decomposition of sweat prevented from evaporating. Infection of the hands is particularly favoured by the alkalising and macerating effect of soap. According to Keller the optimum *p*H for the Kaufmann-Wolf fungus is between 6·8 and 7, but recent work on the optimum *p*H of media is very conflicting.

Dermatophytides

Just as in tuberculosis, so in fungous infections certain exanthematic or distant eruptions are met with, which one supposes to be due to hæmatogenous dissemination of fungus from a primary focus, together with an allergic supersensitiveness of the skin. Jadassohn demonstrated the first case of *lichenoid* trichophytide over 20 years ago. Dermatophytides of this kind are commonest in infections, often from an animal, with a virulent fungus, especially Tr. ectothrix gypseum, causing a hypertrophic granulomatous lesion. Most cases have been observed in boys between the ages of 3 and 14 years, perhaps because kerion of the scalp is commonest in boys. But a dermatophytide can also result from superficial human ringworm, especially after some irritating local treatment.

The development of an allergic state in guinea-pigs has been demonstrated by Saeves and Kogoj. They showed that, after an intravenous inoculation which had produced fungus-containing skin-lesions, a second inoculation led to fewer and less pronounced lesions which appeared earlier and disappeared more rapidly. In a case of kerion due to Tr. granulosum, with an acute scarlatiniform dermatophytide becoming later lichenoid, Sutter recovered fungus from a lymph-gland and from the skin-eruption. On the first day the skin-material afforded rich cultures, on the second day only isolated colonies, and later no growth, suggesting that the allergic skin rapidly killed the fungus. Blood-cultures have been found positive in dermatophytides, but generally only in the first few days. Arzt and Fuhs tell of a young boy with non-inflammatory tinea tonsurans due to Mi. Audouini and a negative trichophytin-reaction. With the beginning of the defluvium after X-ray treatment the scalp-lesions became inflamed. A fortnight later the inflammation increased and blood-cultures yielded Mi. Audouini. Three days later a lichenoid eruption broke out and the intracutaneous trichophytin-reaction was now strongly positive. A probable mechanism is that, at an early stage in the development of the primary lesion, fungal elements enter the blood-stream and sensitise other parts of the skin. At some later

period, perhaps when the primary reaction reaches its climax, there is a further shower of fungus into the blood-stream. On reaching the sensitised skin it sets up a sharp reaction, the dermatophytide, which soon kills it. This conception is strongly supported by Sulzberger's experiments in guinea-pigs described on p. 339. Dermatophytides may be provoked in infected cases by the injection of trichophytin.

The commonest exanthematic dermatophytide is the *lichenoid*, a symmetrical eruption of groups of minute pink conical follicular papules; they may also resemble those of lichen planus or spinulosus. In an early stage it may be scarlatiniform and be followed by desquamation of the palms (Peck). Other forms include *maculopapules*, *urticaria*, *erythema nodosum* and *erythema multiforme*. An almost conclusive example of the last-named, following a laboratory-infection with trichophyton Priestley, has been fully described by me. The individual varieties are not strictly related to any particular group of fungi.

TRICHOPHYTIN. Trichophytin is the name given to preparations made in different ways from various ringworm-fungi, mainly for diagnostic purposes. Difficult as it is to interpret the results of tuberculin-injections, reports on the responses to trichophytin must be judged with far greater caution still, for there is no standard trichophytin. Those most frequently employed are :— (1) *Bloch's*. This is obtained by crushing a culture of Ac. quinckeanum. The mush is filtered and the filtrate dried, dissolved in water and precipitated with methyl-alcohol. The final product is a dry, water-soluble powder which keeps well. It contains no protein. The biologically active principle is in close relationship with a polysaccharide. This preparation is essentially of the endotoxins. Bloch finds a close relationship between the intensity of the clinical lesions, especially if allergic, from which a strain is derived and the activity of the endotoxin which it elaborates on artificial media. (2) *Trichophytin of Metz* (*Bayer*). This is a polyvalent extract of various species of trichophyton prepared by Scholz's method, which is similar to that used in the preparation of old tuberculin. It therefore contains the soluble metabolic products and a considerable amount of the

chemical constituents of the bodies of the fungi, that is to say, both exo- and endotoxins, as well as the components of the medium. (3) *Jausion and Sohier's filtrate-toxin.* A large number of common dermatophytes are grown in a fluid medium for 2 months. The fungus is filtered off and the filtrate, after the addition of phenosalyl, 1 drop to 2 c.c., is used. This is, therefore, a preparation of exotoxins, together with many other substances including proteins.

In addition to these, various mono- and polyvalent extracts have been used. Their activity is influenced by the variety of fungus, the age of the cultures, the loss of virulence by subculture and the technique of extraction. It is found that trichophytin, epidermophytin, microsporin and favin give group-reactions with each other. However, in Kerl's case of extensive superficial dermatophytosis only epidermophytin was positive.

The local reaction to intracutaneous injection of Jausion's filtrate-toxin appears in 24 hours, reaches its height on the 3rd day, and may be isomorphic. But trichophytin can occasionally produce an immediate urticarial reaction, as in my case of erythema multiforme, generally associated with circulating antibodies. On several occasions I have seen intracutaneous injection of Bloch's trichophytin bring about an *eczematous* patch. Of all the allergens that I have tested in this way, this is the only one that has done so. It indicates an affinity of the *toxin* to the epidermis as well as the known epidermotropism of the living fungus.

The test is of some service in the diagnosis of allergic manifestations of doubtful ætiology, where the presence of fungus cannot be demonstrated.

Passive transmission of sensitiveness to trichophytin has been demonstrated by the P.-K. method by Sulzberger, using the serum of a patient who gave an immediate urticarial response to a direct intracutaneous injection. It was interesting that some of the test-subjects proved refractory, and it subsequently transpired that all of these in a previous experiment had received a cutaneous inoculation of cultures of Ac. quinckeanum and afterwards several intracutaneous injections of trichophytin. Now, though they were refractory as regards an immediate urticarial response, they

all developed an extremely severe, indurated, painful reaction 48 hours later, resembling tuberculin-reactions, a type apparently only met with after actual infection.

Eczema. Evidence has recently been adduced that dermatophytides may take the form of eczema, and, in fact, that many eczemas, especially interdigital, are to be so interpreted. In particular "dyshidrotic eczema" of the hands (pompholyx) is thought to be, in at least a large proportion of cases, an epidermophytide from the feet (Bloch). In many cases foot-ringworm, in which fungus can be found in the lesions, is followed by an interdigital eczema of the hands of pompholyx type. Very often fungus cannot be demonstrated in the hands, but the skin gives a positive trichophytin-reaction and the eczema of the hands disappears if the feet are adequately treated.

Peck has furnished some interesting experimental evidence. He produced an epidermophyton-infection of the feet in a person who presented no evidence of any previous fungous disease and whose trichophytin-test was completely negative. Thirteen days later the trichophytin-test became positive, and 24 hours after that a slight "dyshidrotic" eruption appeared on both hands, from which no fungus could be recovered. Subsequent reinfection of the feet of the same patient with fungus grown from the first infection was followed after 14 days by a severe and more typical cheiropompholyx.

Peck and Salomon report a child with vesico-pustular epidermophytosis of foot and hand with, in addition, eczematous patches on hands, feet, body and face. The trichophytin-test was positive. Fungus was demonstrated in the vesico-pustular lesions, but not in the eczematous ones. Whitfield's ointment was applied to the former only; all lesions disappeared in 5 weeks.

Strickler, Ozellers and Zaletel describe 3 cases of foot-ringworm associated with an eruption on the hands. Fungus was demonstrated microscopically and by culture in the feet, but not in the hands. The responsible fungus was also cultured from the blood.

Much therefore points to some cases of eczema, especially pompholyx, being due to fungus or some derivative conveyed by

the blood-stream in a sensitised individual from a focus in the feet.

But Matras opposes this view of Bloch. He will only admit as epidermophytides extensive exanthems and only if there is an allergic reaction to specific or related fungous extract. Of 100 cases of foot-ringworm (in which Ep. interdigitale was found) with eczema of the hands, he found that the trichophytin-reaction was negative in 33. [But he admits that it was also negative in 2 cases of eruptions which he considered otherwise indubitable epidermophytides and offers as explanation that an excess of fungus had absorbed all antibody.] Moreover, in cheiropompholyx he sometimes found fungus in the hands themselves. Griff and Itkin, too, found fungus in the lesions themselves of 80% of cases of cheiropompholyx and support Matras in the view that the hand-affection is by no means always a dermatophytide but often a direct epidermophytosis. To this Bloch replies that the fungus may, nevertheless, have arrived by the blood-stream and not yet been killed. I would add that unless fungi were *sometimes* found in the lesions of pompholyx one would not be able to uphold the theory that it is ever a dermatophytide : it would be more reasonable to interpret its connection with the primary focus as a non-specific autosensitisation.

What proportion of cases of pompholyx are dermatophytic, whether primary or secondary, is a matter of great difference of opinion. In 1919 Darier said that, if exogenous dermatitis were excluded, pompholyx was probably always due to a direct fungous infection. In 1930 Williams stated that most cases of pompholyx are produced by ringworm-infections. Dowling in 1931 expressed the same view. Wise and Sulzberger in the same year considered that it is generally a dermatophytide secondary to foot-ringworm. Of 100 cases, Rageb (1934) found trichophyton in 53 and monilia in 15. But only in 5 cases were they found in lesions of the hands. He classifies pompholyx in four ætiological groups :—(1) " True dyshidrosis," by which he appears to mean eczema due to various causes ; (2) direct mycotic infection ; (3) dermatophytides ; (4) toxinides.

But McLachlan and Brown comment that all Rageb's illustra-

tions look like typical primary ringworm rather than pompholyx. From their own experience they conclude that cases of pompholyx due to fungus are uncommon in comparison to those due to other causes, such as foci of bacterial infection in teeth, tonsils or elsewhere, and autosensitisation from trauma. They also stress the hereditary factor, finding that a considerable

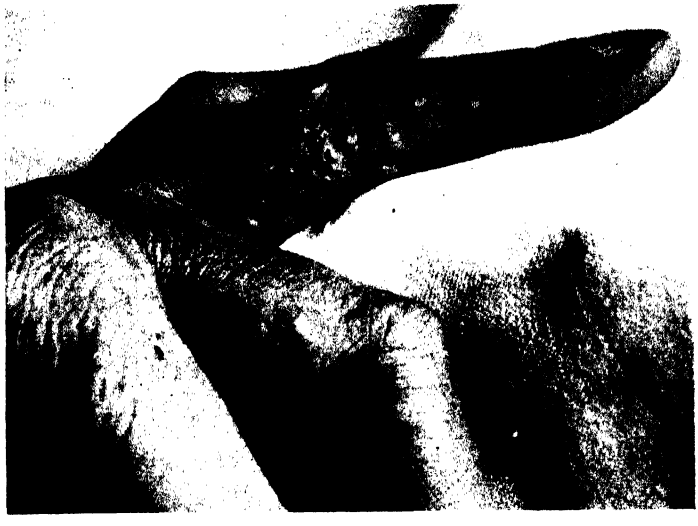


FIG. 26.—Cheiropompholyx following an operation. This attack occurred within 10 days of a major operation on the kidney. She had had a slight attack 6 months previously, also after an operation. For 4 years she was subject to very frequent attacks of what she called hay-fever. There was no hyperidrosis, and no possibility of ringworm infection. (A. D. McLachlan and W. H. Brown, *Brit. Journ. Derm. and Syph.*, 1934, p. 474.)

proportion have a family-history of eczema and hay-fever. (See Fig. 26.)

Much depends on whether it is possible to distinguish clinically between primary vesico-pustular epidermophytosis and pompholyx (see Fig. 27). Muende considers that true pompholyx is never due to direct fungous infection: for it is unlikely that the organism could grow so rapidly as to give rise within a few hours to a bilateral vesicular eruption or that it would produce the peculiar

linear distribution along the sides of the fingers; nor would an attack be likely to clear up spontaneously within a fortnight to relapse again after a few weeks. In cases of bilateral cheiro-



FIG. 27. Cheiropompholyx, exfoliating stage. This eruption started as pin-head, sago-grained vesicles in the centre of the palm and gradually spread centrifugally. Tilbury Fox described this exfoliating phase and pointed out that it sometimes simulated a serpiginous tertiary syphilide. This phase is also a little suggestive of epidermophytosis. No evidence of ringworm infection could be found. (A. D. McLachlan and W. H. Brown's case.)

pompholyx Muende has never been able to recover fungus from different vesicles on both hands. When fungus was isolated it was always confined to a circumscribed patch and the history revealed that this area was affected first and that the symmetrical non-fungus-containing rash appeared a week or so later. Sicoli

also found that in true cases of cheiropompholyx the vesicles were always sterile and that fungous infection was capable of giving rise to peripheral vesicles, which were not, themselves, parasitic. In Muende's experience more than 50% of cases of clinical cheiropompholyx are associated with fungous infection elsewhere. In 90% of these the primary lesions are in the feet. All of them react positively to Bloch's trichophytin 1 in 500. [In 150 cases he has never seen it give a true positive result except in those affected either at the time of the examination or in the recent past with ringworm.]

Marchionini thinks that " dyshidrotic " eruptions of hands and feet can be distinguished according to the *p*H of the fluid in the vesicles, finding that in " true dyshidrosis " it is 5, the same as sweat, in direct fungous and staphylococcal eruptions it is 7, whilst in epidermophytides it is 7·2–8·2. For practical differentiation he recommends the use of blue litmus-paper, which is only reddened by the blister-fluid of true dyshidrosis. This needs confirmation, and it is not clear what is meant by " true dyshidrosis."

If then epidermophytides take the form of eczema, it should be possible to show an eczematous type of supersensitiveness by means of patch-tests with trichophytin. This has been done by Sulzberger and Wise. Passive transmission experiments, with the serum of a patient suffering from eczema of the hands who gave an immediate urticarial reaction to intracutaneous trichophytin, showed that the serum contained antibodies to trichiphyton and achorion but not to monilia.

Alopecia Parvimaculata Epidemica. Werther described an epidemic in Dresden in 1931 involving 400 children between the ages of 3 and 14 years. The symptoms were an association of microsporon-ringworm of the scalp and alopecia parvimaculata, which began and disappeared contemporaneously. The baldness was neither a true alopecia areata nor pseudopélade nor folliculitis decalvans, but corresponded to the picture of epidemic small-flecked alopecia already observed elsewhere in children and given the above name by Dreuw. It was referred to in connection with microsporosis by Crocker, and has since been reported several times

in cases of favus and trichophytosis too. Werther interprets the alopecia as a dermatophytide, brought about probably in an analogous way to the moth-eaten type of alopecia in syphilis.

Levurides. Till recently *monilia* had only been held responsible for the typical localised clinical pictures already described. They depend, or should depend, for their recognition as moniliases on the microscopical demonstration of large quantities of the organism *in situ*.

But recently dermatoses of quite other kinds have been ascribed to it, especially by Ravaut. He pointed out in 1929 that, accompanying intertriginous moniliasis, there occur elsewhere outbreaks of *eczema*, and especially the frequent eczematoid erythematosquamous eruptions most commonly referred to as *seborrhœic dermatitis*. In these eruptions, which disappear and reappear with the primary lesion, monilia can either not be found or only be demonstrated by culture. Injection of levurin (oidiomycin, monilia-extract) often lights up the eczema. Therapeutically it suffices to treat the primary foci. He concluded that monilia is capable of causing sensitisation of the skin from the fact that the latter gives a positive reaction to levurin. But the intracutaneous test is, according to Biberstein and Epstein, of little value in diagnosis. They were unable to find a concentration of monilial extract which with any regularity gave a positive result in infected patients, without also doing so in a considerable number of normal persons. [On the other hand, they found complement-fixation was positive in about half the cases of moniliasis and only in about 3% of controls.] Stachelin and his co-workers also found that oidiomycin caused a reaction just as often in normal as in infected skins. All gave an immediate urticarial response and, after about 24 hours, a reddened papule. In some it was slightly eczematoid. Ravaut, however, lays stress, as characteristic for his levurides, on a late reaction resembling the levuride itself, whether eczematous or parakeratotic.

Ramel has isolated monilia in intertriginous, " dyshidrotic " and psoriasiform eczemas and very frequently in varicose ulcers. In a high proportion of the cases he obtained a positive intracutaneous and patch-test with levurin.

Taking it as a whole, the evidence for the existence of levurides is slenderer than for dermatophytides due to ringworm-fungi: for (1) cultures from the lesions, if positive, have small significance in dealing with an organism so frequently found on the normal skin; (2) positive blood-cultures have not been reported; (3) the intracutaneous tests with levurin, even if specific, do not practically differentiate infected from non-infected skin.

SEBORRHŒIC DERMATITIS. MacLeod states that from all the types of lesions comprised under the term seborrhœic dermatitis the pityrosporon has been cultivated, and Dowling has reproduced similar lesions by experimental inoculation of the cultures. But he has also produced such lesions with cultures of monilia. In some patients suffering from seborrhoeic dermatitis the largest reaction was produced by Mo. albicans, in others by Mo. Pinoyi, and in others again by the pityrosporon. This does not prove that the lesions were dependent on the activity of the living organisms, for it is just this type of response that Ravaut obtained with levurin and which he claims to be characteristic for levurides. It is significant that Dowling found that the site of inoculation made no difference. He does not mention what controls were used.

The organism which Ota and Huang believe to be the true pityrosporon (see p. 335) they found on experimental inoculation to be quite harmless and incapable of provoking seborrhœic dermatitis.

Diagnosis with Wood's Light

If the rays from a mercury-vapour-lamp are passed through a filter of cobalt nickel glass, the luminous rays are cut off and only the long-wave U.V. come through. This is known as Wood's light. In 1927 Vignes observed that hairs infected with microsporon fluoresce a brilliant green when viewed by it in a dark room. A single infected stump can in this way be picked out from the rest of the hairs with great ease. The method is of particular value after epilation, in making sure that cure is complete, and also for routine inspection in schools.

According to Davidson and Gregory both the genera microsporon and achorion produce this green fluorescence in the substance of hairs infected by them. But they have demonstrated that the spores and hyphæ of the fungus itself, whether within or without the hair, are relatively non-fluorescent. The substance responsible for the green fluorescence can be extracted from the hair with hot water. They reckon that in Winnipeg two-thirds of the separate outbreaks of microsporon-ringworm are due to Mi. felineum, and in about half of these the infection is caught from a cat or dog. The hairs of cats infected with this fungus exhibit the same green fluorescence as infected human hairs. In England 90% of cases of tinea capitis are due to Mi. Audouini.

Occasionally the microsporon fails to produce fluorescence. Hairs infected with other trichophyta appear a pale bluish-white, whilst normal pigmented hairs look dark.

Tinea versicolor glows a dull golden yellow; this distinguishes it from superpigmentation which is merely dark.

Treatment

Biological Methods. In view of the impossibility of avoiding exposure to these common organisms, the difficulty of eradicating some foci of infection and the frequency of dermatophytides, it would be of the greatest value if we could desensitise or immunise the skin against them. Attempts to do so with trichophytin or with Jausion and Sohier's filtrate-toxin have not been very successful. Sulzberger and Wise have found that, though repeated intracutaneous injections of trichophytin bring about desensitisation to itself in the majority of cases, by no means all of these are clinically benefited. Moreover, trichophytin often causes local, focal or general reactions; sometimes of alarming degree.

Claso-vaccines. Very encouraging results, on the other hand, are claimed by Jausion and Sohier with their polymycosic claso-vaccines, justifying, they think, their widespread use, especially in countries where dermatophytoses are common. To prepare claso-vaccines, they grow the commoner dermatophytes in the dark at room-temperature for 2 months in a liquid medium

containing honey. The masses of fungus are separated from the remains of the medium by filtration, mashed up and disintegrated with nitric acid. The liquid is neutralised with normal soda and refiltered.

Subcutaneous and intramuscular injections are not painful and arouse very slight local reaction. The initial dose is ½ c.c. and the maximum 3 c.c. Generally only 6 injections are found necessary, at an average interval of 5 days. It is usually after the third that the lesions begin to regress. They report 36 cures out of 45 cases of direct dermatophytoses and 14 out of 17 cases of eczematous dermatophytides. The successes include trichophytosis capitis, favus capitis, sporotrichosis, trichophytic kerion, sycosis, erythemato-vesicular trichophytosis, marginate eczema due to epidermophyton inguinale, erythrasma and tinea interdigitalis.

They consider that, not only vesicular eczema, but also parakeratotic psoriasiform and seborrhœic types can be sterile and secondarily due to sensitisation to fungus, and that this group of dermatophytides is curable by claso-vaccines.

The trichophytin-reaction remains positive in spite of clinical cure. This is the exact opposite of the consequences of repeated injections of trichophytin, from which the claso-vaccine also differs in that, in a proved case of dermatophytosis, it may cause no local reaction.

Attempts at reinoculation of the fungus that caused the illness, as well as of other fungi, were unsuccessful in those vaccinated; but this immunity is not permanent.

Fungicides. On cultures of the fungi causing foot-ringworm, Li Hsueh Yi has proved the active killing power of *thymol*, *Castellani's basic fuchsin paint* (see Martindale's "Extra Pharmacopœia," 20th Edition, p. 320) and *benzoic* and *salicylic acids*. Sodium thiosulphate is valueless. Gould and Carter find that *hexyl-resorcinol* has about the same inhibitory power as salicylic acid. Mercurochrome is much less active. According to Legge, Bonar and Templeton, metaphen is also relatively inactive and kerosene in full strength has no destructive action. This has a bearing on the dry cleaning of infected clothing. They agree as

to the effectiveness of hexyl-resorcinol and the inactivity of sodium thiosulphate. But *sodium hypochlorite* (1% solution of chlorinated soda) kills all spores within 5 minutes. *Iodine* in potassium iodide solution is fungicidal even in a dilution of 1 in 100,000. Ultra-violet rays at about 2,500 A.u. (cold quartz-light) have inhibitory power but do not completely sterilise cultures.

These authors made some further experiments by testing the fungicidal efficiency of chemicals on infected scales of human skin, and found that the following killed all fungi in an hour or less :— thymol, 3% in spirit ; salicylic acid, 6% in spirit ; benzoic acid, 5% in spirit ; chlorinated soda, 1% ; iodine in potassium iodide solution, 1 in 10,000.

Lane finds that while a *mercury-iodide-containing soap* is fungicidal, ordinary soaps are not.

Haler has found *monsol* a very efficient germicide for monilial cultures.

Ayres, Anderson and Youngblood have proved that infected material from active lesions, as well as cultures, are killed by exposure for 4 hours to the fumes of a *formaldehyde* candle in a closed room.

Dermatophytosis of Feet and Hands. For the acute bullous and vesicular type Gray recommends baths and moist dressings of *potassium permanganate* 1 in 4,000. Free evaporation should be allowed and the feet rested. After the acute phase, the permanganate baths are continued in the morning and evening, but *liniment of calamine with ichthammol* 2% is used as a dressing on lint, each toe being tied up separately. When the dry scaly stage is reached he employs *Whitfield's compound benzoic acid ointment* till all scaling has ceased. Though some writers express a contrary opinion, Gray thinks that this ointment is an adequately efficient fungicide in foot-ringworm, if persevered with. For the localised intertriginous type it is necessary to continue it for some months after every trace of the disease has disappeared. To counteract the sodden condition maintained by the ointment, he alternates it every fortnight with a powder composed of *boric acid* 1 part, *talc* 7 parts. If the disease is still active this powder might, I think, with advantage be replaced by Castellani's *fuchsin*

paint. Gray finds the paint especially useful in cases characterised by small crops of vesicles, which are pricked before its application. Sabouraud emphasises the necessity of destroying whatever hinders penetration of the fungicide. He considers the most effective means of thinning the epidermis is a *barium sulphide* depilatory. He recommends it to be removed and reapplied every quarter of an hour; as a rule about three applications are necessary. It may have to be repeated about once in 2 days. In the meantime he applies *iodine* 1% in alcohol. For the hyperkeratotic form, in addition to the above treatment, Gray gives *X-rays*, $\frac{1}{4}$–$\frac{1}{3}$ B weekly, three or four times. Thick and horny masses can be removed by daily painting with *salicylic acid* dr. 1 to ℥ 1 of spirit, followed by friction with lint.

Ayres and Anderson report some failures with Whitfield's ointment (which they used in double strength) owing to intolerance. The patients' skin gave strongly positive patch-tests to the ointment, though not to the ingredients tested separately.

Lomholt has recently recommended a rather similar ointment, which he claims to be better tolerated as well as more effective. He has found it superior to anthrarobin, crystal-violet, brilliant green, iodine, sulphur, mercury, formalin and benzyl benzoate. It is composed of lead oxide ointment (Danish Pharmacopœia) 60, liquid paraffin, "mycocten," salicylic acid, of each 3 parts. *Mycocten* is the name given to paraoxybenzoic acid-ethyl-ester, which is used for the preservation of food against yeasts and moulds. Its efficacy is increased by the addition of 5% of mercury amidochloride, which is, however, not always well tolerated. He recommends that the feet be washed every evening with soap and, after drying, bathed with mycocten 5% in spirit; when this has dried, a thin layer of the ointment is applied; a further inunction is made in the morning. He finds this treatment has a surprisingly rapid and soothing effect on practically all cases, even quite acute ones; only when there are large weeping surfaces he starts with *Burow's solution* 1% for a few days. The lead helps to macerate the skin and thereby aids the penetration of the fungicides. It is clean in use, except that it may cause a greyish-brown staining of the nails.

Brunsting testifies to the efficiency of *iodine* in solution in benzol or acetone. Sometimes *cignolin* 2% in benzol has succeeded when other remedies, including fuchsin paint, chrysarobin 8% ointment and Whitfield's ointment, have failed.

Marchionini urges that antiparasitic measures must be supported by treatment of the soil in the form of *acid*. In fact, he claims to have cured 23 out of 26 cases of foot-ringworm with acid alone, the good effect being more rapid than with tincture of iodine. He uses concentrated hydrochloric acid 0·4 c.c. in 70% alcohol 100 c.c., painted on several times a day. When the lesions are nearly healed, boric acid powder is strewn into the interdigital spaces. Boric acid, even in the most concentrated form, only reaches a *p*H of 4·2, but when constantly present can keep the interdigital space at a reaction approximate to that of the free skin-surface. He also obtained cure by acid alone in 6 out of 13 cases of monilial interdigital erosion of the hands.

For erosio interdigitalis blastomycetica, if obstinate, MacLeod first *curettes* and then applies 5–10% solution of *silver nitrate*. Castellani's fuchsin paint is also very effective.

It is important not to neglect the nails, as they are a frequent source of reinfection, even though showing no clinical changes. If the whole nail is involved the only cure, according to Sabouraud, is *avulsion*, followed by painting the bed with *iodine* 1% in alcohol. In less severe involvement they should be filed down thin and tied up with one of the above fungicides.

Prophylaxis. This problem concerns measures, on the one hand to minimise the spread of infection in institutions, and on the other to protect a cured patient from recurrence. The latter can be due either to reinfection or to renewed activity of fungi still present. In view of the observations of Strickler and McKeever, it is essential during treatment to apply the remedies not only to the lesions but also over a *surrounding zone* up to a distance of 2 inches. The skin must be kept as *dry* as possible and relatively *acid* in reaction by means of boric acid powder, talc powder containing 1–2% salicylic acid (Levin and Silvers), or talc containing 5% mycocten and 5% salicylic acid (Lomholt).

The socks should be made of boilable material. Failing this

they must be chemically *disinfected*, for which purpose Kadisch recommends immersion in 1% thymol spirit: 1 hour is long enough for ringworm-fungi, but 4–10 hours are required for monilia. To disinfect the shoes Henderson recommends leaving them for about 48 hours in a closed tin box containing a small dish holding about 50 c.c. of formalin.

Brunsting suggests a period of mild treatment before the onset of warm weather.

As regards *public measures*, Gray advocates separate bath-mats, and Legge, Bonar and Templeton the compulsory wearing of rubber shoes in swimming-baths. In public changing-rooms it is wise to swab the feet with sodium hypochlorite 1% (Osborne) immediately before dressing. It must be freshly made every 2 days. For the disinfection of wooden floors, if covered with any slime or algal material, Bonar and Dreyer find that 1% sodium hypochlorite must remain in contact for more than 24 hours. As they failed to grow fungus on clean wood, it is clear that ordinary scrubbing is more important than disinfection.

Perionychia. After being bathed in warm saline for a quarter to half an hour and carefully dried, *silver nitrate* 5%, *iodine* 1% in spirit or liquefied *phenol* is introduced beneath the nail-fold. Haler also recommends compresses of collosol *ichthyol* 4% with *copper nitrate* ½%, or *monsol* 1 in 5. Corsi has found saturated solution of *chrysarobin* in chloroform useful, as suggested by Morrow and Lee.

Perlèche. For streptococcal cases the most effective treatment is an ointment containing 2–10% *ammoniated mercury* to which *resorcin* 2–5% may be added. Monilial cases, in Freund's experience, yield better to *iodine* 1% or 2% painted on twice a day, and even after healing continued once a day for a while. MacLeod recommends *gentian violet* 2–5% in 15% spirit.

Tinea Capitis. X-RAYS. Shanks (1931), in a review of a series of 2,400 cases epilated by him, discusses the technique and describes a method of restraint for young children, by which they can be kept absolutely still during the exposures without harm or discomfort (see also page 444).

THALLIUM. Epilation by means of the oral administration

of thallium acetate has been used on a considerable scale with much success but some fatalities, since it was recommended by Buschke in 1914 and by Cicero in Mexico in 1917. Owing to its danger when given in excessive doses, it should not be used when X-rays and an expert operator are available; but it is a valuable alternative method when they are not, or when they have been used unsuccessfully, or when the scalp is inflamed.

Though there is no disputing the great dangerousness of grossly excessive or repeated doses, the risk of the treatment when accurately and properly administered has been exaggerated. A review of the literature leads Ingram to the belief that it is those with the greatest experience with the drug whose opinion of it is the most favourable, partly perhaps owing to their having gradually evolved a satisfactory technique. He finds that after a correct dose any toxic symptoms always clear up completely within a short time and are only severe in older children, to whom correspondingly large doses are given, and in cases where the treatment, having failed once, has been repeated. Nevertheless, Divella (1925) reported that all of 58 children who received 8 mgm. per kgm. of body-weight remained weak for several months after regrowth of the hair, and Varadi had a patient aged 6 years who, in spite of only receiving 8 mgm. per kilo., died 6 days later with characteristic symptoms. Possibly in different geographical regions the tolerance towards thallium may vary.

Toxic Symptoms. The commonest, according to Karrenberg, are loss of appetite, general malaise, pains in the legs and feet, loss of weight, and occasionally drowsiness and muscular weakness. After the muscles and joints and the alimentary canal, the nervous system is most often involved, usually in the form of sensory and motor neuritis of the lower limbs. But central disturbance has also been described by Cortelli in 1930: he mentions tremor of the head of Parkinsonian type, ataxic gait, intention-tremor and other disorders; I have seen one such case with complete recovery. The best prophylactic, as well as cure, is rest in bed. Percival (1931) and Ingram have both followed up their cases and find no support for the idea that the treatment may do permanent damage to any organ.

The following is a summary of Ingram's *routine*, which he finds successful in over 90% of cases. After clinical examination and test of the urine, which must be free from albumen, the child is weighed naked. The weight in pounds multiplied by 4 gives the required dose in milligrammes. This is equivalent to a dose of 8·8 mgm. per kgm. of body-weight. More than 250 mgm. are never administered. The average age requiring 250 mgm. is 9 years, up to which, therefore, there is little danger. Errors in dispensing may arise from using solutions of the drug. Tablets of varying strength can be made in different colours and swallowed by the child with a drink of water. Epilation generally begins about the 11th to the 14th day. It is necessary to remove all the stumps quickly, as the new hair begins to grow at the end of 3 weeks. To achieve this, Ingram recommends clipping the hair quite short and painting the scalp three times every day from the onset of the treatment with 2% tincture of iodine. This leads to a coarse desquamation which reaches its height towards the end of the 3rd week. Washing should be avoided for the first 2 weeks; but the scalp is washed about the 17th day to loosen the desquamation, and again on the 21st when most of the scaling comes away. After that it may be washed about once a week. The painting with iodine is continued till examination with Wood's light shows that all infected stumps have disappeared. This usually happens about 9 weeks from the beginning of treatment. If the iodine is carefully kept away from the forehead, nape of the neck and the retroauricular folds, it causes no serious discomfort and never, in Ingram's experience, provokes eczema. It is wise, however, to omit it for 24 hours after washing. He has found this routine perfectly safe and highly efficacious. But if it fails it is unwise to repeat it.

The *mode of action* of thallium is not clear. Buschke and his co-workers think it is primarily on the endocrine apparatus, whereas Truffi and others suppose a direct action on the skin itself. Vásárhelyi, in experiments on animals, finds that the thallium is excreted by the skin-glands, where inflammation occurs with multiple minute sterile abscesses: pus-cells were found in the hair-follicles. It is interesting that Louste and Rabut noted

" septic folliculitis " during the 2nd month in 20% of their cases. Cortelli has noted in rats degenerative changes in the axis-cylinders of the perifollicular nerve-fibres. It has a particular affinity for all nerve-tissues, but the relationship of this to changes in the hair-matrix is doubtful.

Peli has compared thallium acetate experimentally with thallium *salicylate*, by administering the morally and hypodermically to guinea-pigs to determine their minimum lethal and minimum depilatory doses. The acetate was found much more toxic than the salicylate, whilst the epilating power was the same. Larger doses of the salicylate can, therefore, be given with safety.

Bibliography

BENHAM, R. W., and HOPKINS, A. McH. " Yeast-like Fungi found on the Skin and in the Intestines of Normal Subjects," *Archives of Derm. and Syph.*, 1933, **28**, 532 (*Abs. Brit. Journ. Derm. and Syph.*, 1934, **46**, 389).

BIBERSTEIN, H., and EPSTEIN, S. " Immunreaktionen bei der menschlichen und tierexperimentellen Oidiomykose der Haut," *Arch. f. Derm. u. Syph.*, 1932, **165**, 716.

BLOCH, B. " Some Remarks on Infections of the Skin by Monilia and other Yeast-like Organisms," *Brit. Journ. Derm. and Syph.*, 1930, **42**, 569.

BONAR, L., and DREYER, A. D. " Studies on Ringworm Funguses with Reference to Public Health Problems," *Amer. Journ. of Public Health*, 1932, **22**, 910.

BRUHNS, C. " Uebersicht ueber die neueren Ergebnisse und Fortschritte auf dem Gebiete der Mykologie," *Zbl. Hautkrank.*, 1932, **41**, 1.

DAVIDSON, A. M., DOWDING, E. S., and BULLER, A. H. R. " Hyphal Fusions in Dermatophytes," *Can. Journ. Research*, 1932, **6**, 1.

DAVIDSON, A. M., and GREGORY, P. H. (*a*) " Note on an Investigation into the Fluorescence of Hairs infected by certain Fungi," *Can. Journ. Research*, 1932, **7**, 378. (*b*) " Kitten Carriers of Microsporon and their Detection by the Fluorescence Test," *Can. Med. Assoc. Journ.*, 1933, **29**, 242.

DOWLING, G. B. " The Pathogenicity of Monilia and other Yeast-like Fungi," *Brit. Journ. Derm. and Syph.*, 1930, **42**, 562.

FRANK, L. J. " Perlèche in Adults," *Archives of Derm. and Syph.*, 1932, **26**, 451 (*Abs. Brit. Journ. Derm. and Syph.*, 1933, **45**, 374).

FREUND, H. " Ueber eine klinisch und aetiologisch charakterisierte Form von Perlèche bei Erwachsenen ; ' Interlabialmykose ' und ihre symptomatische Bedeutung," *Arch. f. Derm. u. Syph.*, 1931, **164**, 614.

GOLDSMITH, W. N. " A case of Erythema Multiforme apparently of Trichophytic Origin," *Brit. Journ. Derm. and Syph.*, 1931, **43**, 121.

GOULD, A. G., and CARTER, E. K. " Fungistasis in Ringworm of the Toes and of the Feet," *Archives of Derm. and Syph.*, 1932, **25**, 348.

GRAY, A. M. H. " Fungous Infection of the Feet," *Brit. Med. Journ.*, 1934, **2**, 541.

HALER, D. H. (*a*) "Notes on the Incidence of Yeast-like Organisms in Chronic Perionychia," *Brit. Journ. Derm. and Syph.*, 1931, **43**, 343. (*b*) "Monilia Pinoyi: Some Further Studies in Connection with its Cultures and Chemical Reactions," *ibid.*, 1932, **44**, 435.

INGRAM, J. T. "Thallium Acetate in the Treatment of Ringworm of the Scalp," *Brit. Med. Journ.*, 1932, **1**, 8.

JAUSION, H., and SOHIER, R. "Les Claso-Vaccins," *Presse Méd.*, 1930, **37**, 621.

KADISCH, E. "Disinfection attempts with Ringworm Fungi and Yeasts," *Derm. Woch.*, 1931, **37**, 1433.

KARRENBERG, C. L. "Nebenerscheinungen nach therapeutischer Verabfolgung von Thallium," *Zbl. Hautkrank.*, 1932, **42**, 1.

LANGERON, M., and MILOCHEVITCH, S. "Morphology of the Dermatophytes on Natural Media and Media with basis of Polysaccharides," *Ann. de Parasit.*, 1930, **8**, 465.

LANGERON, M., and TALICE, R. V. "Nouvelles méthodes d'étude et essai de classification des champignons levuriformes," *Ann. de Parasit.*, 1932, **10**, 1.

LECOULANT, P. "Etude de quelques mycoses observées à la clinique dermatologique de Bordeaux," *Ann. de Derm. et de Syph.*, 1934, **5**, 745 (*Abs. Zbl. Hautkrank.*, 1934, **49**, 616).

LEGGE, R. T., BONAR, L., and TEMPLETON, H. J. "Epidermomycosis at the University of California," *Archives of Derm. and Syph.*, 1933, **27**, 12.

LI HSUEH YI. "The Growth-Inhibitory and Killing Actions of various Chemical Substances on Epidermophyton Rubrum, E. Interdigitale, and Trichophyton Pedis A and B," *Derm. Woch.*, 1933, **43**, 1526 (*Abs. Brit. Journ. Derm. and Syph.*, 1934, **46**, 108).

MCLACHLAN, A. D., and BROWN, W. H. "Cheiropompholyx," *Brit. Journ. Derm. and Syph.*, 1934, **46**, 457.

MACLEOD, J. M. H. "Skin-Diseases due to Monilia and other Yeast-like Fungi," *Brit. Journ. Derm. and Syph.*, 1930, **42**, 549.

MACLEOD, J. M. H., and DOWLING, G. B. "Experimental Study of the Pityrosporon of Malassez," *Brit. Journ. Derm. and Syph.*, 1928, **40**, 139.

MARCHIONINI, A. (*a*) "Säurebehandlung intertriginöser Epidermophytien," *Derm. Zeit.*, 1929, **56**, 248. (*b*) "Zur Pathogenese und Differentialdiagnose dyshidrotischer und dyshidrosiformer Bläschenerkrankungen der Hände und Füsse," *ibid.*, 1930, **58**, 222.

MATRAS, A. "Ueber atypische Epidermophytien," *Arch. f. Derm. u. Syph.*, 1931, **164**, 291 (*cit.* Bruhns).

MUENDE, I. (*a*) "Observations on Monilia," *Brit. Journ. Derm. and Syph.*, 1931, **43**, 3. (*b*) "Cheiropompholyx," *ibid.*, 1934, **46**, 479.

OTA, M., and HUANG, P. T. "Sur les Champignons du genre Pityrosporum (Sabouraud)," *Ann. de Parasit.*, 1933, **11**, 49 (*Abs. Brit. Journ. Derm. and Syph.*, 1933, **45**, 375).

PECK, S. M. "Epidermophytosis of Feet and Epidermophytids of Hands: Clinical, Histologic, Cultural and Experimental Studies," *Archives of Derm. and Syph.*, 1930, **22**, 40 (*cit.* Muende).

PECK, S. M., and SALOMON, G. "Eczema due to Fungi," *Archives of Derm. and Syph.*, 1931, **24**, 554.

PELI, G. "Experimental Contribution to our Knowledge of the Acetate and Salicylate of Thallium as Depilatories," *Giorn. Ital. di Derm. e Sif.*, 1933, 1613 (*Abs. Brit. Journ. Derm. and Syph.*, 1934, **46**, 507).

RAGAB, A. F. "Les Eruptions Dyshidrosiformes," Paris, 1934 (*Abs. Brit. Journ. Derm. and Syph.*, 1934, **46**, 196).

RAVAUT, P. "Les eczématides secondaires d'origine allergique survenant

au cours des intertrigos à levures (Levurides)," *Bull. Acad. Méd.*, Paris, 1929, 101, 680.

ROBINSON, L. B., and MOSS, M. C. "Superficial Glossitis and Perlèche due to Monilia Albicans," *Archives of Derm. and Syph.*, 1932, **25**, 644.

SABOURAUD, R. "The Treatment of Epidermophytosis of the Cutaneous Folds of the Nails," *Med. Press and Circ.*, 1933, **187**, 206.

SHANKS, S. C. "X-ray Treatment of Ringworm of the Scalp," *Brit. Journ. Derm. and Syph.*, 1931, **43**, 477.

STAEHELIN, A., JUI-WU-MU, and VAN SCHOUWEN, M. "Contribution to the Clinical Character and Pathogenesis of the Oidiomycoses," *Arch. f. Derm. u. Syph.*, 1932, **165**, 294.

STRICKLER, A., OZELLERS, E. A., and ZALETEL, R. P. "Modern Interpretation of Mycotic Infection of the Feet and Hands," *Archives of Derm. and Syph.*, 1932, **25**, 1028.

SULZBERGER, M. B., and WISE, F. "Ringworm and Trichophytin," *Journ. Amer. Med. Assoc.*, 1932, **99**, 1759.

WERTHER. "Ueber die Dresdner Epidemie von Mikrosporie und Alopecia Parvimaculata und Deutung der letzteren als Mikrosporid," *Arch. f. Derm. u. Syph.*, 1931, **163**, 402.

WILLIAMS, C. M. "Dermatophytide complicating Tinea Cruris," *Archives of Derm. and Syph.*, 1930, **22**, 637 (*cit.* Muende).

WILLIAMS, J. W. "The Habitat of Trichophyton Interdigitale outside the Body," *Proc. Soc. Exper. Biol. and Med.*, 1934, **31**, 984 (*Abs. Zbl. Hautkrank.*, 1934, **49**, 550).

CHAPTER XI

FILTER-PASSING VIRUSES

General Characters

Viruses are invisible under ordinary conditions of microscopical examination, but it has been proved by various physical and chemical tests, including filtration, that most of them are particulate bodies, varying considerably in size. By special methods the minute particles can be seen. Some have a diameter as large as 0·25μ: those of herpes have been estimated by different observers to lie between 0·1μ and 0·22μ. [For comparison it may be mentioned that the smallest bacteriophages have a diameter of 0·008–0·02μ. The staphylococcus is 1μ.] The smallest discrete particles are called elementary corpuscles. Larger forms, even bigger than some bacteria, also sometimes occur in the cycle of development, and masses of aggregated particles or of undivided virus can produce plasmodial forms. It is chiefly upon the minuteness of the particles that the ability of a virus to pass through bacterial filters depends, and, while the larger forms of virus cannot pass, the smallest bacteria, such as some of the leptospira and Bact. prodigiosum, can.

Viruses, with the possible exception of that of bovine pleuropneumonia, are unable to develop and multiply except on a medium of living cells, a fact which makes difficult the conclusive proof that they are themselves alive. They can apparently multiply without limit in the tissue of affected plants and animals and show a capacity to adapt themselves, often irreversibly, to a changed environment, which is highly characteristic of living things. Thus human small-pox, passed through a sufficient number of calves, becomes vaccinia; but it does not, even after repeated passage through man, return to its original condition. Similar

phenomena are observed in the adaptation of herpes-virus to brain-tissue. Boycott in 1929 considered it impossible as yet to decide between two possibilities :—(1) that a virus behaves like a bacterium ; (2) that it behaves like a growth-promoting enzyme. Gye and Ledingham consider that the histopathology of a virus-lesion is inconsistent with the second view. When the virus of vaccinia, for example, is introduced into the dermis, certain cells of the reticulo-endothelial system are observed to break up, and polynuclear cells that enter the lesion in great numbers are also destroyed. Further, evidence of multiplication of virus *in vitro* in contact with living tissue has been obtained, even when the tissue has shown no signs of growth. If, as Boycott thinks, there is no sharp dividing line between living and dead, it is probable that the larger viruses approach nearer to the characters of bacteria and the smaller ones to enzymes.

They have an elective affinity to epithelial tissue and tissue in active regeneration. Viruses can sometimes be found in healthy carriers, and may remain latent in the tissues after causing an initial infection.

Perhaps the most important feature differentiating the majority of virus-diseases from the majority of those caused by visible microbes is the presence in the former of certain peculiar histological appearances about to be described.

Inclusion-bodies. These bodies are found in the cytoplasm or the nucleus, or sometimes both, of the cells of the lesion ; they vary according to the disease and also according to the host. Nuclear inclusions occur in herpes, varicella and zoster ; variola gives rise to inclusions in the cytoplasm as well. Their shape may be rounded, oval, pyriform or irregular ; they can either be homogeneous or contain one or more, often numerous, elementary corpuscles. The bodies are usually acidophilic, but in some cases basophilic, and the elementary corpuscles sometimes stain differently from the ground-substance. In several diseases affecting the skin, *e.g.*, variola and the common wart, inclusion-bodies are formed only in the epidermis ; but in others, as zoster, varicella and genital herpes, they are found in the corium as well. Whilst the morphology of some inclusions is quite specific, *e.g.*, the

Guarnieri body in vaccinia, the intranuclear acidophile body is common to a number of virus-diseases.

Inclusion-bodies can be experimentally produced only by the inoculation of living, never by dead, viruses. After inoculation, the bodies make their appearance at varying intervals according to the different infections. In common warts they are demonstrable only in the earliest stages ; in genital herpes they are best seen on the 3rd day. There seems to be some relationship between their presence and the infectivity of the tissue. In herpetic keratitis of rabbits, for example, it is said that with the disappearance of the nuclear inclusion-bodies, the disease ceases to be inoculable.

Chronologically the following have been the three main ideas as to their nature. (1) They represent a stage in the life-cycle of the virus (originally thought to be protozoon). The recent work of Bedson and Bland (1932) on psittacosis revives this possibility. (2) They are simply reaction-products, formed by the cell in answer to the attack of the virus. There is no question that a cell is profoundly modified by the activity of a virus. (3) They are colonies of virus (elementary bodies) which, as a result of the cellular reaction excited by their presence, become enveloped in some plastic material produced by the cell (von Prowazek, Lipschütz and da Rocha Lima). It was this conception that gave rise to the name " chlamydozoa," literally " cloak-animals."

Goodpasture thinks the hyaline matrix may be produced by the virus itself.

Recent work points clearly to the identity of the elementary corpuscles with the virus. Woodruff (1929) and Goodpasture (1930) demonstrated the infectivity of isolated washed Bollinger bodies (the inclusions of fowl-pox), which consist of masses of elementary corpuscles. Ledingham (1931) showed that these elementary corpuscles, and those of vaccinia too, can be flocculated by specific antiserum. Similarly, Bedson (1932) has demonstrated the infectivity, specific agglutination and specific complement-fixation of the washed elementary corpuscles of psittacosis. It is unlikely that they are merely tissue-particles on to which the virus is adsorbed, since they do not react specifically with an appropriate antitissue-serum (Bedson).

Allergy. Smith has shown that the early or immediate reaction of the human skin on revaccination, already known to be specific for vaccinia-virus and obtainable even when it has been killed by heat, can also be elicited by a boiled extract of tissues infected by it. Now Craigie and Wishart have evoked this specific allergic reaction by means of the washed and killed elementary corpuscles (Paschen bodies) obtained from the skin-lesions of recently vaccinated rabbits. The experiments were fully controlled : positive reactions were obtained in all vaccinated persons tested, and in none of the unvaccinated. These observations provide further evidence in favour of the identity of the elementary corpuscles with the virus.

IMMUNITY. In most virus-diseases a second attack is uncommon. Humoral antibodies have been demonstrated with a virucidal or at least a neutralising effect. On the other hand, it is not always possible to find circulating antibodies in immune animals. Moreover, in one and the same disease, immunity may develop at different times in different tissues.

Tissue-responses. Ledingham (1924, 1926) finds that in the skin-lesions produced by vaccinia-virus the reticulo-endothelial cells bear the brunt of the attack and play the chief part in the process of repair. If these cells are first blockaded with Indian ink, the characteristic vaccinial lesions fail to develop.

Goodpasture (1929) points out the wide range of responses between, at one end, the rapid necrosis of ectodermal cells in a herpetic infection of the rabbit's cornea and, at the other end, the slow epidermal proliferation caused by the virus of the common wart. As a rule each virus has a predilection for one kind of cell.

Herpes

Symptoms. The clinical appearances of simple herpes need no description here, but some points may be noted about *genital herpes.* In men this attacks the balano-preputial groove, the glans and the prepuce. On covered parts it rapidly gives rise to erosions, which are very superficial, isolated or confluent, round or polycyclic, red or diphtheroid, and slightly painful. Unless they

are unsuitably treated, there is no induration of the base and they heal in about 10 days. But, if they are cauterised or treated with strong antiseptics, there may ensue induration, inflammatory phimosis, swollen and painful glands and some ulceration, which make the diagnosis very difficult. In women herpes attacks any part of the vulva and occasionally the vagina and cervix. Sometimes a profuse vulvar herpes is accompanied by fever and œdema and forms large plaques with agglomerated or confluent blisters, extending from the vulva over the pubis, inner aspect of the thighs and intergluteal fold. Very soon the blisters become macerated, burst, and are transformed into erosions or are covered with a diphtheroid membrane secreting a muco-purulent fœtid liquid. The glands are swollen and painful. The condition lasts about 3 weeks. When they heal, the lesions may occasionally become elevated and simulate the papular mucous plaques of syphilis. Though genital herpes is not in itself a serious complaint, it can serve as the portal of entry for more serious infections or may coincide with and mask the appearance of a chancre.

The buccal mucosa, pharynx or conjunctiva may sometimes be involved.

Histology. Minute acidophil intranuclear bodies (the alpha-bodies of Lipschütz) can be seen in the epithelial cells. They increase in size, coalesce, and finally occupy the greater part of the nucleus. Some of the affected cells become swollen and present a reticular degeneration; others are transformed by amitotic nuclear division into large multinuclear cells. There is a serous exudate in the epidermis, leading to the vesicle-formation, and a leucocytosis in the underlying corium. The alpha-bodies are not specific for the epidermis nor even for herpes, as they are found also in other organs and other virus-diseases, *e.g.*, zoster and varicella. They are, therefore, probably the result of a peculiar form of degeneration.

Infectivity. It is not clinically contagious. Auto- and hetero-inoculation of the vesicular fluid intracutaneously have, however, been successful, the lesion produced resembling in all respects spontaneous herpes. Several animals can be infected by means of human vesicular fluid. If it is inoculated on to the scarified

cornea of a rabbit, there follows a severe keratitis, which can be propagated indefinitely by passage. The corneal lesions, if examined during the first 24 hours, are found to contain numerous nuclear inclusion-bodies. A certain proportion of rabbits so inoculated develop after a few days a fatal encephalitis, the virus travelling chiefly along the nerves (Goodpasture and Teague). Direct intracerebral or subdural inoculation of vesicular fluid gives rise to a fatal meningo-encephalitis, which is transmissible in series by inoculation of brain-suspension. The virus has also been found in the salivary glands and in the suprarenals of infected rabbits.

The virus responsible for these phenomena is filtrable and has been grown in tissue-cultures by Parker and Nye (1925). According to Gruntfest it can be grown on yeast.

The vesicular fluid from *herpes genitalis* is much less virulent, both on corneal and subdural inoculation, than that of herpes simplex. Lipschütz succeeded in transferring genital herpes in human beings. Both in the human lesions and in the rabbit's cornea he found nuclear inclusions of the so-called " beta type " in large numbers. He was unable to produce immunity to the virus of H. genitalis by inoculation of the rabbit's cornea with that of H. simplex. He, therefore, regarded the two viruses as biologically distinct.

Susceptibility and Immunity. Herpes is one of the few known virus-diseases that do not lead to lasting immunity, at least in man. Relapses are generally frequent and are sometimes determined by a general disturbance, such as fever, menstruation or mental excitement. The influence of the emotions has been discussed on page 117. In other cases relapses occur with some degree of periodicity, without any apparent determining cause, often in the same area each time. In some patients the recurrences, though at different points, are always in the territory of the same nerve. In one of my cases it attacked a different part of the trunk, limbs or face each time, but always on the left side.

In the vast majority of attacks a fresh infection from outside can be dismissed, and especially in those instances where the eruption recurs at the same site. One must here suppose that the individuals are already carriers of the virus, waiting to produce

its specific effects under the influence of some determining factor; or else assume that the virus can arise *de novo* as the result of some change in the cells. But the latter assumption is difficult to reconcile with its specificity and the fact that it has been shown to be present in the saliva and conjunctival sac in the absence of clinical lesions. Such latency has also been proved in animals. Gastinel and Reilly (1928) have found herpes-virus in the brain of guinea-pigs that have recovered from experimental keratitis. Though there were no cerebral symptoms, inoculation of the brain on to the cornea of a normal guinea-pig caused keratitis.

A period of immunity is brought about by the acute exanthemata during their eruptive phase.

After a series of "passages" have been made in the same individual by inoculation of his own vesicular fluid, he usually becomes insusceptible to his own strain of virus though remaining susceptible to foreign ones.

Rabbits that have undergone an experimental keratitis present a considerable amount of immunity to subsequent corneal, or even cerebral, inoculations. There is evidence to suggest that this immunity is largely dependent on humoral antibodies (Bedson and Crawford, 1927), and that the virus can unite with its specific antibody *in vitro*.

Infection appears to be extremely common. Andrews and Carmichael found neutralising antibodies to herpes-virus in the serum of 75% of unselected persons and in every subject of recurrent herpes, but in very few children under the age of 7 years. Brain, using the somewhat less sensitive complement-fixation method, obtained positive fixation in 45% of unselected cases; but on going carefully into their history he found there was a definite relationship between complement-fixation and past attacks of herpes. In view of the fact that herpetic attacks do not lead to lasting immunity, it is thought likely that the persistence of antibodies is maintained by the continued presence of virus: in other words, that the patients have become carriers.

Active immunisation by means of dead virus is impossible.

Treatment. After Plesch had announced that he had freed himself from oft-recurring herpes by *autoinoculation*, Hruszek

tried the method in about 100 cases ; in only 1 did a further attack develop, and in that case only as a result of fever-treatment. He advocates repeated inoculations with fluid from successive lesions at 2-day intervals until it no longer takes. Recovery sometimes follows such non-specific methods as *autohæmotherapy*. When the recurrences are always at the same site they can often be stopped by a few fractional doses of *X-rays*.

Zoster

Symptoms. Only a few points need be noted. As a rule the groups of blisters are arranged along the territory of a sensory nerve on one side of the body only. Commonly zoster involves



FIG. 28.– Survey-preparation. Multi-locular vesicles, the base made up of " balloon " epithelial cells, several of which may be seen also in the serofibrinous exudation. The side-walls consist of swollen rete-cells. (E. Bruusgaard, *Brit. Journ. Derm. and Syph.*, 1932, p. 44.)

2 or even 3 spinal roots, and exceptionally it is bilateral or even generalised. The corresponding lymphatic glands always become swollen, sometimes even before the eruption appears. The eruption may be preceded by general phenomena, such as malaise, aching of the limbs, coated tongue, loss of appetite and moderate fever. These symptoms, together with the cyclical course of the disease, its occasional occurrence in epidemics (generally in the autumn) and the immunity that follows an attack, bear a similarity to the eruptive fevers.

Recurrences are uncommon, but Grundmann quotes instances



FIG. 29. Smear-preparation showing swollen mononuclear cells and one large multinuclear (balloon) cell. (E. Bruusgaard, *Brit. Journ. Derm. and Syph.*, 1932, p. 44.)

to show that they are not so rare as is generally supposed.

Histology. Bruusgaard's more recent observations tally with those of Lipschütz. The structure of the vesicle is identical with that of varicella (see Fig. 28). It arises in the rete from intercellular œdema. The cells present the appearance known as "ballooning," which consists in hypertrophy and vacuolation with multiplication of the nuclei. These cells are easily demonstrated in ordinary smear-preparations, fixed in methyl alcohol and stained with diluted Giemsa for 24 hours (see Fig. 29). In some of the nuclei there is an accumulation of round particles (inclusion-bodies). This is followed by disintegration. There is more or less necrosis of the base of the vesicle and invasion of

leucocytes. The fully developed vesicles present an extremely polymorphic picture of cellular degeneration.

Oxyphile inclusion-bodies in the epithelium are generally a prominent feature, but are not always demonstrable. They have sometimes been seen not only in the nuclei but in the cytoplasm, or even between the epidermal cells, and occasionally in the connective tissue and the swollen intima of vessels. Lipschütz regarded them as a product of nuclear reaction towards the specific virus and specifically characteristic, but Luger and Landa say they are due to degeneration of nuclear oxychromatic material and not specific.

Ætiology. Zoster has for some time been looked upon as a nervous symptom-complex, due to a variety of infectious or toxic agents. Those cases in which there is thought to be an obvious cause have been called " symptomatic " and the rest " idiopathic." It is relatively prone to occur when the first sensory neurone is otherwise damaged, as in syphilitic radiculitis or compression by carcinoma of the vertebræ. But if the eruption were directly due to such nerve-injury it would occur in every case, which is far from the fact. Similarly, trigeminal zoster may follow any intracranial lesion of the 5th nerve, even alcoholic injection of the Gasserian ganglion; but the fact that it so seldom does so shows that zoster is not the result of the mere trauma. It can be distinguished from neuroparalytic keratitis, a much commoner complication of this therapeutic measure.

There is considerable evidence of its *contagiousness* and of its *relationship to varicella*. The same individual may have both zoster and a scattered eruption resembling varicella. This has been described by some authors as " zoster generalisatus." But others, struck by its resemblance to varicella, refer to " zoster and varicella in the same patient." Usually the generalised rash appears within 3 or 4 days of the zoster and is most often met with in persons of poor resistance between the ages of 50 and 70 years. Numerous instances have been reported in which zoster seems to have given rise in contacts to varicella and *vice versâ*. Svenson reports that in January, 1932, the great majority of the population of Malmö were vaccinated on account of a severe

epidemic of small-pox: there ensued in the following half-year a quite unwonted number of cases of varicella and of zoster.

The experimental evidence as to their ætiological relationship was summarised in 1925 by Lipschütz and Kundratitz as follows:—(1) in infants inoculated with zoster-fluid there develop not only local vesicles but sometimes a general varicella-like eruption; (2) children brought into contact with infants inoculated with zoster may develop varicella; (3) children who have recovered from varicella prove immune to inoculations of zoster-fluid; (4) children who have recovered from natural or experimental zoster are immune to varicella-fluid: (5) the serum of patients convalescing from zoster protects against varicella; (6) varicella and experimental zoster have the same incubation-period.

Kundratitz's experiments have been repeated and confirmed by Bruusgaard (1932). He noted that the general exanthem following inoculation of zoster-fluid was morphologically and histologically indistinguishable from varicella. Only children under the age of 5 years proved susceptible. A striking feature was the frequency with which healthy children in the same ward as those inoculated with zoster developed varicella a fortnight afterwards.

Further evidence is furnished by Netter and Urbain (1924, 1926), who demonstrated by the complement-fixation test that the sera of subjects of zoster and of varicella contain identical antibodies. Moreover they showed that antibodies to varicella are equally present in the serum of "symptomatic zoster" (following treatment with arsenic, bismuth or mercury). Brain (1932), using different antigens and a different technique, has confirmed Netter and Urbain's results.

Pascher (1933) has found regularly in the blister-fluid elementary corpuscles similar to those of varicella and vaccinia. Suspensions of them are specifically agglutinated by the sera of zoster-convalescents. Crossed agglutination experiments show no clear relationship with varicella (Amies). Transmission to animals is uncertain and filtration-experiments have not yet succeeded. Glaubersohn and Barg, who were unable to cultivate any ordinary bacteria from the contents of fresh zoster-blisters, showed that the virus can be kept for at least 4–6 days in 4% glycerine on ice.

They were also able to set going tissue-cultures in which the virus remained virulent for several days, as tested by inoculation into children.

There remains, therefore, little doubt that zoster is caused by a virus and that it has a close relationship to varicella. Moreover, all the experimental evidence applies equally to the so-called symptomatic and idiopathic cases. What then is the relationship between the eruption and the nerve-lesion ? It seems most direct when gross injury of the posterior root is followed by zoster. Probably in such cases the primary lesion has lowered the resistance of the nerve-tissues to the zoster-virus, and it is likely that exogenous and endogenous toxins operate in the same way. When the virus has invaded the first sensory neurone, it proceeds centrally towards the neuraxis and peripherally to the skin, where it gives rise to the blisters. These are therefore a *direct effect of the virus* and not neurogenic.

If symptomatic and idiopathic zoster are both caused by virus, it is, *a priori*, most likely that all cases of zoster are caused by the same virus. Yet there are certain difficulties in accepting the view that it is in all cases identical with the agent of varicella. Thus varicella leaves a very pronounced immunity to itself, while it is not very rare for varicella patients subsequently to contract zoster, even though zoster is a relatively uncommon disease. This objection alone would not be very cogent, as zoster might be considered an expression of partial immunity ; but it is also true, according to Bruusgaard, that though zoster generally protects against zoster, as object of it not very rarely develops varicella subsequently, and this in spite of the average age-period of zoster being so much later than that of varicella. The objection is also raised that it is ten times commoner for zoster to give rise to varicella than *vice versâ*. But this is really not surprising, since varicella is a disease of susceptible children and zoster predominantly of relatively immune adults, chiefly between the ages of 50 and 60 years. Accordingly we find a striking difference in the average age of patients developing zoster from varicella and those getting varicella from zoster ; the first group including very few children and the second comprising almost exclusively children

(Netter). On the monistic theory one might perhaps explain these facts by supposing that adults are relatively immune to the virus (as we know them to be experimentally), but that this immunity wanes again in later life, and that in this phase a person who becomes susceptible develops zoster rather than varicella. But in my view there must have developed not only a changed general susceptibility but also an increased vulnerability of the nervous system. Perhaps the strongest objection is that Cantor, during 20 years' work in some small Pacific islands, often saw zoster but never varicella, and Storen had a similar experience in an isolated district in Norway. If, then, the viruses are not identical, they must with great frequency be associated with each other symbiotically.

Treatment. A few new remedies have been described in recent years.

Pituitrin. Its efficacy was first reported by Vaudel. Niles in 1932 tested its value against controls treated by other methods. He found it shortened the course of the disease and relieved the pain. He gave an average dose of 1 c.c. intramuscularly on alternate days, and 3 injections were nearly always enough. The greatest successes were achieved in early cases. The only contra-indication he considered to be pregnancy. It did not upset senile patients or those suffering from hypertension, cardiac disease or diabetes. Gillett, though he finds it an uncertain method, agrees that it sometimes relieves the most intense pain with extraordinary rapidity.

Sulphur. Sézary, Miget and Facquet, in a small series of cases, observed shortening of duration and relief of symptoms from intramuscular injection of a 1% suspension of sulphur in oil (sulfosin). The injections can be repeated when the reactions, local pain and fever, have subsided.

Thiosinamine Ethyl Iodide. This has been specially recommended for the post-herpetic neuralgia, 1 c.c. (3 gr.) being injected daily; it is rarely necessary to give more than 6 injections.

Atophanyl. From his experience with 234 cases of zoster Luttenberger considers atophanyl (sodium salt of atophan and sodium salicylate) the method of choice. One ampoule is given

intramuscularly every day. No harmful effects were observed, but caution is necessary in the presence of hepatic disorder and old age.

X-RAYS. For post-herpetic pains Darier recommended deep X-ray exposures over the corresponding nerve-roots, but subsequent experience has not substantiated their value. Wettenhall has found X-rays, 4/5 B. to the eruption itself, most efficacious during the acute stage when the blisters are tense, but of little use later.

Warts

The common warts need no description here. But a few words on some of the less common varieties are necessary in order to make it clear what are included under the term.

PLANTAR WARTS. These were described by Dubreuilh in 1895. Their infective nature is very often not recognised and they are confused with pressure-callosities. Like them, they attack by preference the points of pressure on the sole of the foot. But they are not limited to those areas : moreover, warts on the palms have a similar character. Close examination reveals that they are composed of tiny dark-coloured horny papillæ closely packed and encircled by a distinct, raised, slightly undermined epithelial collar. They may occur singly or, more often, in small groups. Pressure has the effect of forcing the interpapillary pegs downwards so as to invaginate the corium, which becomes condensed. The opening of the pocket containing the wart is, as a rule, narrower than the bottom. They are very tender.

DIGITATE WARTS. These occur as soft finger-like processes with a horny cap, especially on the scalp, neck and face.

FILIFORM WARTS. These are similar to the digitate, though more circumscribed. One or more delicate thread-like elevations are seen, especially on the eyelid or face.

CONDYLOMA ACUMINATUM = " moist " or " fig wart." For a long time these were known as venereal or gonorrhœal warts. In men they develop on the glans penis, around the frenulum and on the prepuce ; in women about the clitoris and labia, perineum and anus. Occasionally they are seen in the axillæ,

around the navel, between the toes or in the mouth. They vary greatly in size, occasionally becoming as large as an egg. They present a luxuriant cauliflower-like pink or brownish growth, and may be sessile or pedunculated. In pregnant women they sometimes develop rapidly and disappear suddenly after parturition.

JUVENILE OR PLANE WARTS. These are very tiny raised flattened papillomata. The colour is generally that of the normal skin, but is occasionally violet or even vivid red. The surface is shiny. They are generally found in large numbers on the face, and less often on the hands and legs. It is remarkable how often they are mistaken for a vesicular eruption.

Senile flat warts (*seborrhœic warts*) have probably no ætiological relationship to the other warts and are perhaps to be looked upon as late nævi (Darier).

Ætiology. Jadassohn (1896) showed that common warts could be produced in human beings by experimental inoculation. Cuiffo (1907) showed that the infective agent could be filtered. More recently Wile and Kingery (1919) succeeded with a Berkefeld filtrate of a suspension of ground-up wart-material. In one case the warts were carried over successfully for two generations. The incubation-period varied from 4 weeks to 6 months. Findlay also finds that the incubation-period following inoculation with filtrate varies greatly, apparently depending on individual susceptibility. That condyloma acuminatum is caused by the same virus as common and digitate warts appears from such experiments as those of Waelsch (1918), who inoculated healthy skin and mucosa with condyloma acuminatum and obtained flat warts on the skin and digitate papillomata on the mucosa. Sera (1924) found that Chamberland-filtrate of condyloma acuminatum gave rise to common warts on the hand. As regards plantar warts, Whitfield doubts whether all are infective and thinks that some may be due to a subjacent telangiectasis caused by bruising. Moreover, in the infective type it is doubtful whether the virus is identical with that of the other warts: I have recently observed an extensive epidemic of plantar warts in a girls' school; in no case was there a single wart on any other part of the body.

THE RELATIONSHIP OF HUMAN AND ANIMAL WARTS. It is

impossible to infect laboratory animals with human warts, and dog-warts fail to infect man.

Immunuty. It is by no means uncommon for warts to disappear spontaneously. In some persons inoculation with human wart-material produces no lesions. Findlay found that after



FIG. 30.—Lesion of molluscum contagiosum. The dark areas in the epithelial cells are masses of the elementary bodies. In the desquamating portion the molluscum bodies are not stained. (E. W. Goodpasture and H. King, *Amer. Journ. Path.*, 1927 p. 385.)

inoculating himself with three crops he became immune to further inoculation. The serum can acquire antiviral properties after active immunisation. Dogs are also capable of developing an antiviral serum, but a serum which neutralises human wart-virus has no action on that of dog-warts and *vice-versâ*.

Inclusion-bodies. Occasionally cytoplasmic, but more often nuclear, acidophilic inclusions have been observed. Kyrle regarded

these as an oxychromatic change of the nucleoli. Similar nucleolar changes are present in early psoriasis (Lipschütz 1926) as well as in rabbit-warts caused by spirochæta cuniculi.

Treatment. Since warts can, and often do, disappear spontaneously, it is difficult justly to evaluate the efficacy of any treatment that is not directly destructive.

Biological Treatment. Biberstein has had considerable success by the intracutaneous injection of human wart-extract. He has also succeeded in a small series of ordinary warts and condyloma acuminatum with the subcutaneous injection of a vaccine prepared from bovine warts. The percentage of cures following injection of extract from normal skin as a control was, in all types, strikingly lower, and cases which resisted the latter yielded to the wart-extract.

Psychotherapy. This has been dealt with on page 124.

Internal Medication. Lurie has been very successful with *bismuth salicylate*. Thirty-four patients, chiefly children, were followed up and all were completely cured. The dose for children from 6 to 10 years is gr. 1, and for adults gr. 2. A single injection is given intramuscularly. Regression usually begins immediately and no further treatment is given until the condition becomes stationary. Subsequent injections are then administered at intervals of 2 or 3 weeks. Plantar warts respond particularly well; often only 1–3 injections are required. My own results with bismuth have been completely negative.

Local Measures.

Plantar Warts. The method of choice is *X-rays*. The dose should be $1\frac{1}{2}$ B., and a second similar dose can be given, if necessary, about 5 weeks later. For the small proportion of cases that resist X-rays it is best to apply CO_2 *snow* for 3–5 minutes; a large bleb develops, allowing the wart to be painlessly excised about 3 days later.

Flat Warts. If scattered they are best destroyed with a ball-pointed *galvano-cautery*. When large numbers are massed together in a circumscribed area an exposure of *X-rays*, $\frac{3}{4}$ B., repeated if necessary in a month, often brings about their disappearance. Another good method is to make the skin *peel* by

means of a paste containing 6% or more of sulphur and of resorcin.

Common Warts. The larger ones are best removed with CO_2 *snow* and smaller ones with the *galvano-cautery.* Brain recommends *ionisation with magnesium sulphate*, after moistening the warts with solution of caustic potash. When a large number are widely scattered over the body, it is worth while giving a general anæsthetic and removing them all at one sitting by a combination of *curetting* and the *galvano-cautery;* recurrences after this are unusual.

Condyloma Acuminatum. I have found the large *Paquelin cautery* the most effective weapon. It is quicker than electrocoagulation and less likely to cause excessive destruction.

Molluscum Contagiosum

Histology. The main features are well known (see Fig. 30). The development of the peculiar molluscum-bodies has recently been reinvestigated by Goodpasture and King (1927). In the germinal layer of the involved epidermis the only abnormality is an active mitosis and swelling of the cells. The first conspicuous change occurs just peripheral to the germinal layer. Both cells and nuclei enlarge. The nucleoli become more prominent and nucleolar material is extruded into the surrounding cytoplasm, where it eventually vanishes. In the cytoplasm there appear numerous small vacuoles, to the periphery of which are attached little granules. The cell gradually enlarges as the result of the increase in number and size of the vacuoles, while the nucleus is pushed to one side of the cell and becomes flattened and crescentic. The basophilic cytoplasm condenses in the form of an irregular network between the vacuoles. At the same time the vacuoles are filled with minute fairly discrete bodies and increase in size, until they fill the greatly enlarged cell except for the narrow cytoplasmic network between them (see Fig. 31). In this fully developed form the entire mass of granules and basophilic cytoplasm appears to separate from a peripheral cellular membrane and fuse to form an oval hyaline body within a framework composed of its own membrane and the remnant of surrounding

keratinised cells. The main factor in the hyalinisation appears to be desiccation.

The minute granular bodies in the vacuoles were believed by Lipschütz (1911) to be the actual parasites of molluscum

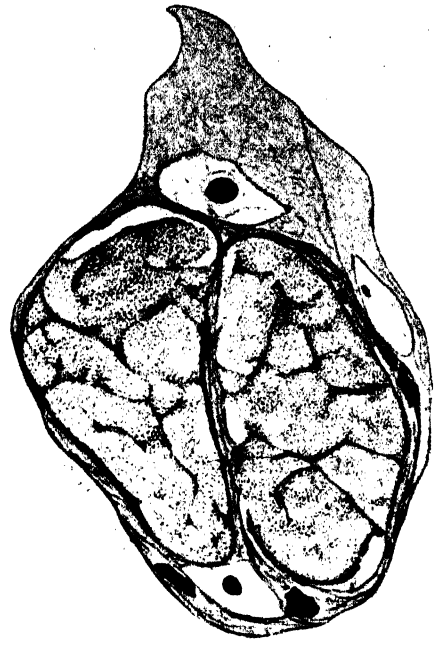


FIG. 31. Two cells showing elementary bodies in cytoplasmic compartments. Three compressed cells about them unaffected by the virus, containing keratohyaline particles (black). This is the stage before desiccation of the affected cells to form molluscum-bodies. (E. W. Goodpasture and H. King *Amer. Journ. Path.*, 1927, p. 385.)

contagiosum and were named by him "Strongyloplasma hominis." Goodpasture and King found that in smear-preparations from the nodules the minute particles, not demonstrable by ordinary bacteriological stains, can by their special method be shown as round or slightly elliptical bodies, often paired as if dividing.

Attempts to cultivate them on artificial media have failed. The evidence at present is insufficient to determine whether or not they actually constitute the ætiological agent.

Infectivity. If not treated, molluscа persist indefinitely and multiply by autoinoculation. Their infectious nature was first demonstrated by Patterson in 1841. Epidemics have often been traced to contact in schools and particularly Turkish baths.

The virus was first shown to be filtrable by Juliusberg in 1905. This was the first demonstration of a filtrable virus in connection with any human dermatosis. Findlay finds that it can pass through Berkefeld 5 and Chamberland L1 filters, is only pathogenic to man and attacks only the epidermis, the incubation-period after inoculation with the filtrate being 5 weeks. The virus remains active for at least a month in 50% glycerine. Leber implanted anaerobically in human serum material obtained aseptically from the depth of a molluscum. After 48 hours there was already an increase of formed elements. Subcultures, even with filtrates, succeeded to the tenth generation. There developed not only typical strongyloplasms but also larger coccus-like forms embedded in a sort of zoogloea. Inoculations with cultures were negative; but it is only rarely that positive results are obtained even by inoculation of material taken direct from lesions.

There is no evidence that it is related to avian molluscum (fowl-pox), though the inclusion-bodies of the two conditions are almost identical.

Brain, by means of the complement-fixation reaction and using suspensions of elementary corpuscles from curetted molluscа, has demonstrated the presence of antibodies in the serum of a patient with multiple lesions.

Treatment. When they are very numerous, *sparking* with a monopolar high frequency current is more convenient than the usual curetting and chemical caustics. The molluscа disappear within a few days without scarring (Goodman).

Pityriasis Rosea

Thomson and Cumings (1931) prepared a filtrate as follows :— scales from a herald-patch were added to saline and kept in the

ice-chest for 8 days; the mixture was then passed through a Jenkins filter. The filtrate was sterile for ordinary bacteria and contained no spirochætes. Intracutaneous tests with this filtrate gave positive reactions in nearly all healthy persons or patients with other skin-diseases, while the reactions were negative in nearly all of a series of persons who had had pityriasis rosea. Among the latter the only positives were in a patient during an attack, and in 2 cases 5 and 8 years respectively after the eruption. If the extract of scales was filtered earlier than the 8th day, it produced proportionately weaker reactions. Filtrates from the generalised patches gave similar results. The authors consider these phenomena analogous to the Schick and Dick tests. They do not mention what seem to me to be essential controls, namely, comparison with similar extracts from scales from psoriasis or dandruff or normal skin.

None of the 15 persons who gave positive reactions developed a characteristic or progressive lesion, even at the site of injection; but many other attempts have shown the great difficulty of experimental transmission of the disease, even with material direct from the lesions. The observations, though interesting and suggestive, do not prove that the reactions were specific or that the filtrate contained a living virus.

Bibliography

AMIES, C. R. "The Elementary Bodies of Zoster and their Serological Relationship to those of Varicella," *Brit. Journ. Exper. Pathol.*, 1934, **15**, 314 (*Abst. Zbl. Hautkrank.*, 1935, **51**, 507).

ANDREWS, C. H., and CARMICHAEL, E. A. "A Note on the Presence of Antibodies to Herpes Virus in Post-Encephalitic and other Human Sera," *Lancet*, 1930, **218**, 857.

BEDSON, S. P. "Herpes, Zoster, Varicella." A system of Bacteriology. *Med. Research Counc.*, 1930, **7**, 157.

BEDSON, S. P., and BLAND, J. O. W. "Complement-fixation with Filtrable Viruses and their Antisera," *Brit. Journ. Exper. Path.*, 1929, **10**, 393.

BIBERSTEIN, H. "Die Immuntherapie der Warzen und Kondylome," *Klin. Woch.*, 1932, 1021.

BOYCOTT, A. E. "Ultra Microscopic Viruses infecting Animals and Plants," *Proc. Roy. Soc. London*, 1929, B., **104**, 537.

BRAIN, R. T. (*a*) "The Demonstration of Herpetic Antibody in Human Sera by Complement Fixation, and the Correlation between its Presence and Infection with Herpes Virus," *Brit. Journ. Exper. Path.*, 1932, **13**, 166. (*b*) "The Relationship between the Viruses of Zoster and Varicella as demonstrated by the Complement-fixation Reaction," *ibid.*, 1933, **14**, 67.

BRAIN, W. R. "Zoster, Varicella and Encephalitis," *Brit. Med. Journ.*, 1931, **1**, 81.

BRUUSGAARD, E. "The Mutual Relation between Zoster and Varicella," *Brit. Journ. Derm. and Syph.*, 1932, **44**, 1.

CRAIGIE, J., and WISHART, F. O. "Skin Sensitivity to Elementary Bodies of Vaccinia," *Canad. Pub. Health Journ.*, 1933, **36**, 185 (*Abs. Brit. Med. Journ.*, 1933, **1**, 925).

FINDLAY, G. M. "Molluscum Contagiosum" and "Warts" A system of Bacteriology. *Med. Research Counc.*, 1930, **7**, 248 and 252.

GILLETT, F. H. "The Pain of Herpes Zoster treated with Pituitrin," *Lancet*, 1934, **227**, 307.

GLAUBERSOHN, S. A., and BARG, S. G. "Beitrag zur Erforschung des Zoster Virus," *Acta. Med. Scand.*, Stockholm, 1934, **82**, 579 (*Abst. Zbl. Hautkrank.*, 1934, **49**, 546).

GOODPASTURE, E. W. "Cellular Inclusions and Ætiology of Virus Diseases," *Archives of Path.*, 1929, **7**, 114.

GOODPASTURE, E. W., and KING, H. "Cytologic Study of Molluscum Contagiosum," *Amer. Journ. Path.*, 1927, **3**, 385.

GRUNDMANN, H. "Zur Kenntnis des rezidivierenden Zoster," *Münch. med. Woch.*, 1933, **80**, 1437.

GRUNTFEST, M. "Die Zuechtung des Herpes Virus auf Hefe in Vitro," *Z. Mikrobiol.*, 1934, 12, German Summary, p. 70 (*Abst. Zbl. Hautkrank.*, 1935, **49**, 666).

GYE, W. E., and LEDINGHAM, J. C. G. "Viruses and Virus Diseases." A system of Bacteriology. *Med. Research Counc.*, 1930, **7**, 13.

HRUSZEK, H. "The Treatment of Recurrent Herpes," *Derm. Zeit.*, 1933, **68**, 27 (*Abs. Brit. Journ. Derm. and Syph.*, 1934, **46**, 296).

LEBER, A. "Untersuchungen ueber das Virus des Molluscum Contagiosum," *Zbl. Bakter*, 1913, 1. Orig., **67**, 58.

LEDINGHAM, J. C. G. "Aetiological Importance of Elementary Bodies in Vaccinia and Fowl-pox," *Lancet*, 1931, **220**, 525.

LUTTENBERGER, A. "Klinisch-therapeutische Erfahrungen mit Atophanyl-Injektionen bei Herpes Zoster, febrilis und progenitalis," *Wien. med. Woch.*, 1934, **2**, 1393 (*Abst. Zbl. Hautkrank.*, 1935, **51**, 508).

NETTER, M. "Varicelle et Zona," *Bull. et Mém. Soc. Méd. des Hôp. de Paris*, 1928, **52**, 1014.

NETTER, A., and URBAIN, A. "Les rélations du Zona et de la Varicelle," *Compt. rend. Soc. de Biol.*, 1926, **94**, 98.

SÉZARY, A., MIGET, A., and FACQUET, J. "Treatment of Herpes Zoster with Injections of Sulphur in Oil," *Bull. de la Soc. franç. de Derm. et de Syph.*, 1934, **41**, 322 (*Abs. Brit. Journ. Derm. and Syph.*, 1934, **46**, 509).

SMITH, WILSON. "Heat-stable precipitating Substance extracted from Vaccinia Virus," *Brit. Journ. Exper. Path.*, 1932, **13**, 434 (*Abs. Brit. Med. Journ.*, 1933, **1**, 925).

THOMSON, M. S., and CUMINGS, J. N. "Investigations into the Causation of Pityriasis Rosea," *Brit. Journ. Derm. and Syph.*, 1931, **43**, 617.

CHAPTER XII

CANCER

Histological Types

It is not yet widely enough recognised how common cutaneous cancer is and how various are its clinical and histological forms. In contrast with cancers of other organs, it is often a widespread process, the growth arising not from one point but from many.

The disease is generally divided into two main groups: (1) prickle-celled (squamous epithelioma), and (2) basal-celled (rodent ulcer, etc.). The first is said to arise from the prickle-cells, and the second from the basal-cells, either of the surface-epithelium or of the appendages. The first keratinises and metastasises, and the second does neither. This simple differentiation is fraught with two difficulties: the prickle-cells are of basal origin and the basal-cells are prickle-cells. It is therefore not surprising that we meet with "metatypical" examples which form connecting links. These are grouped as follows:—

Metatypical Carcinoma. Though the mixed and intermediate forms were mentioned by Krompecher when he first separated off basal-celled from the rest of the squamous epitheliomas, their importance was first emphasised by Darier and Ferrand in 1922. Only those tumours should be included in which the greater part is metatypical, for even in the ordinary basal and prickled growths one can often find some metatypical portions.

Epithéliome Métatypique Mixte. The general structure approximates to the basalioma, but in certain parts of the tumour there are cells of more or less pronounced prickle-cell form (see Fig. 32). Tumours in which typical basalioma and typical prickle-celled carcinoma occur side by side are very rare.

Epithéliome Métatypique Intermédiaire. In this variety

are cells which can neither be called basal nor prickled. They are larger, paler and rounder than the basal, but lack prickles and do not keratinise. It is true that they form concentric lamellar nests, but the process is one of parakeratosis.

In a fairly large series of cases of carcinoma of the skin of the

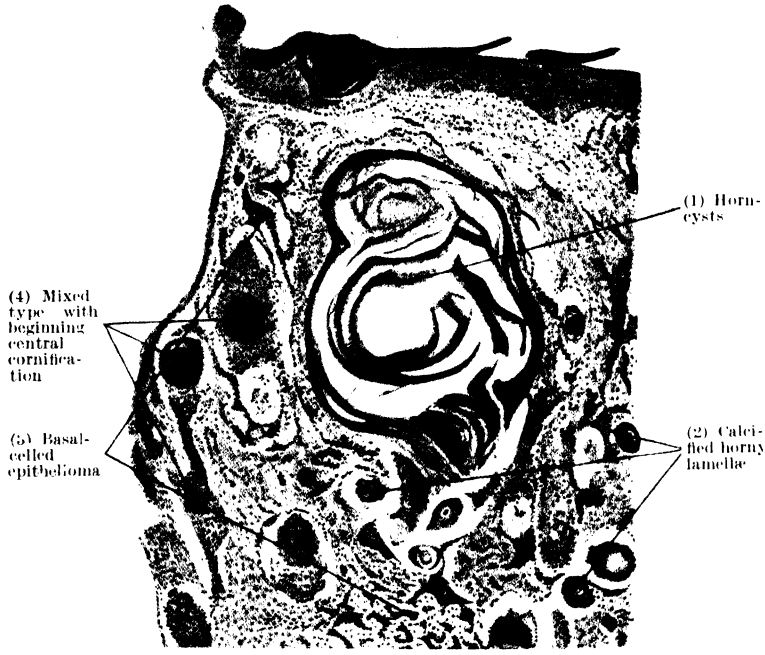


FIG. 32. Mixed Form: (1) horn-cysts; (2) calcified horny lamellæ; (3) basal-celled epithelioma; (4) mixed type with beginning central cornification. (J. Jadassohn, *Bruns' Beiträge z. klin. Chir.*, 1926, p. 348.)

nose, examined histologically, Epstein reports that by far the greatest proportion were basal; but the metatypical were four times as numerous as the prickle-celled.

There is only a rough correspondence between clinical and histological pictures. Metatypical carcinoma may clinically, too, be metatypical (see Fig. 33) or appear identical with basalioma,

especially the proliferating or burrowing varieties. But even a histologically pure basalioma may clinically resemble such widely different conditions as soft mole, sebaceous cyst, sebaceous or sweat-gland adenoma, molluscum contagiosum (a central

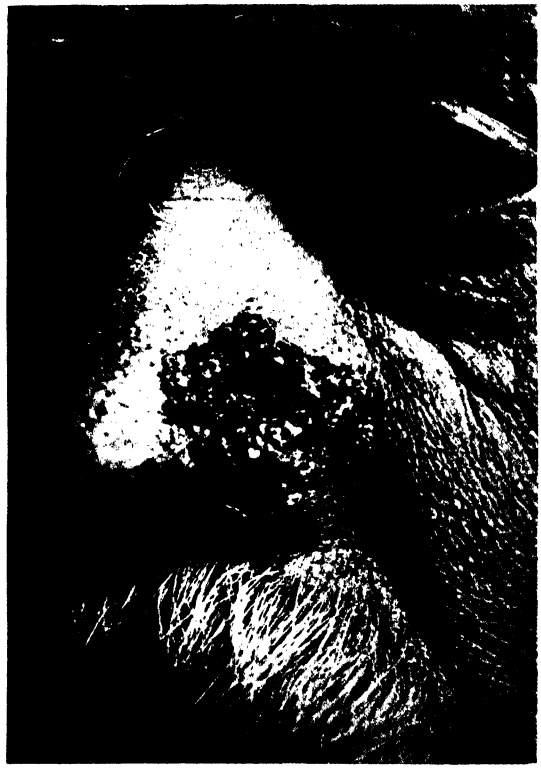


FIG. 33.—Epithéliome métatypique mixte. (S. Epstein, *Zeit. f. Hals-Nasen u. Ohrenheilk.*, 1932, p. 319.)

dimple being common), morphœa, senile keratoma, senile wart, molluscum fibrosum and, if ulcerated, tertiary syphilis or other chronic infection.

The progress of metatypical cancer is more rapid than that of a basalioma and is subject to sudden spurts, making it rapidly

mutilating. It may, though rarely, spread to the lymphatic glands and metastasise.

Some authors, including MacCormac, think there is no essential difference even between basal and prickle-celled cancers, and that the differences in histological structure are merely an expression of the rates of growth. Support is found for this view in the observation that some basaliomas suddenly begin to grow more rapidly and then assume the histological structure of a mixed or prickle-celled type. But there are certain difficulties in this view. Not every basal-celled cancer grows slowly or every prickle-celled quickly. Even typical prickle-celled epitheliomas may remain small and localised for many years and without invading the lymphatic glands. Moreover, when metastases occur they tend to reproduce the special character of the primary growth. Thus Juon describes a case in which there were several cutaneous cancers of intermediate type, the histology resembling that of Bowen's disease (see below). Eventually metastases occurred in lymph-glands and many internal organs which retained the cellular characteristics of the skin-lesions.

Intra-epidermal Cancer. Sometimes the proliferating neoplastic epithelial cells, instead of growing down into the dermis, spread upwards and sideways and remain, at any rate for a long time, within the epidermis. This was first clearly demonstrated by Jadassohn in 1926. The simplest form is seen in Fig. 34, which represents basal cells proliferating into the rete. According to Savatard *all* cutaneous epitheliomas, whether basal, prickle-celled or mixed, are initially intra-epidermal. The neoplastic process may either remain within the epidermis indefinitely, or atrophy may supervene, or the growth eventually invades the corium or the deeper tissues, when it gives rise to the ordinary picture of rodent ulcer or squamous epithelioma. It is often impossible to say at what point a carcinoma has ceased to be intra-epidermal, though the transition can be very abrupt. The superficial carcinomas now under discussion only differ, therefore, from the more usual cutaneous carcinomas of epidermal origin in that their intra-epidermal stage is prolonged.

HISTOLOGY. There is a variable degree of hyperplasia of the

epidermis, especially of the rete, with increase in length of the interpapillary pegs and often too of their breadth, resulting sometimes in the complete obliteration of the papillæ. The basal layer is, however, usually well-defined and entire.

The epidermal changes present several types. In the *first type* ("Bowen's disease," see below) the cells show a striking variety, both as regards size, shape and stainability (see Fig. 35). Their protoplasm is normal or finely granular. A large proportion

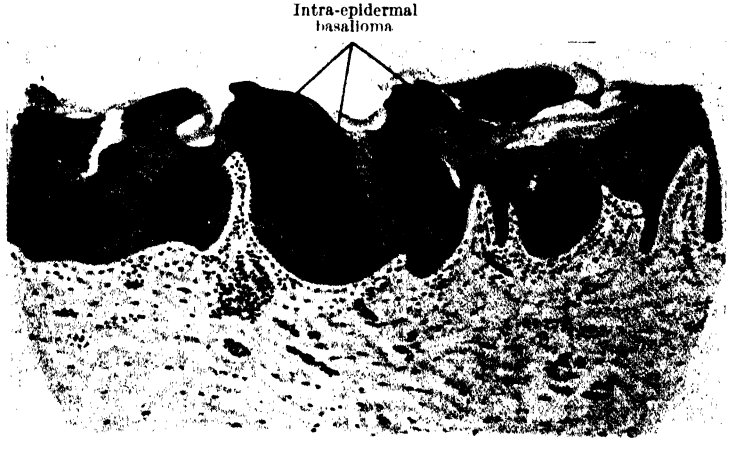


FIG. 34.—Intra-epidermal development of a basalioma. (J. Jadassohn, *Bruns' Beiträge z. klin. Chir.*, 1926, p. 351.)

are œdematous or vacuolated. The nuclei are often misshapen, fragmented, multiple or *clumped*, and contain abnormal mitoses. Some dyskeratotic cells, or "round bodies," are seen in the horny layer. In the crusted lesions there are hyper- and parakeratosis with much intercellular œdema. In the *second type*, though some giant and multinucleated cells may be seen, there are few, if any, vacuolated ones. There is confusion of the rete layers, and here and there are clusters of cells with large, deeply staining nuclei, arising from the basal layer and surrounding and almost obliterating the normal epidermal cells, remnants of which have the appearance of pseudo-cell-nests. Mitotic figures are very numerous. In the *third type* the rete cells are largely, or

entirely, replaced by a spindle-celled proliferation (see Fig. 36). In the *fourth type* the cylindrical cells of the basal layer are almost replaced by vacuolated cells (the Paget cells of Darier), in which, on account of their distension, it is difficult to discern the prickles; though when the process is less advanced they can still be seen. Mitoses are not numerous.

In all types the cancerous metaplasia generally appears to start at some point in the basal layer. The process extends not



FIG. 35.—Intra-epidermal carcinoma of Bowen type. (Microphotograph of Author's case.)

only by proliferation of the cells from the original focus but by a spread of the metaplasia to neighbouring basal cells. The neoplastic cells are often of the non-cornifying, prickled, intermediate type.

Evolution is generally very slow and glandular metastases are rare. The usual clinical picture of a pure intra-epidermal growth of many years' duration is a psoriasiform plaque (see Fig. 37). The colour varies from brownish pink to crimson. The surface may be covered by only slight branny scales or by a thick horny

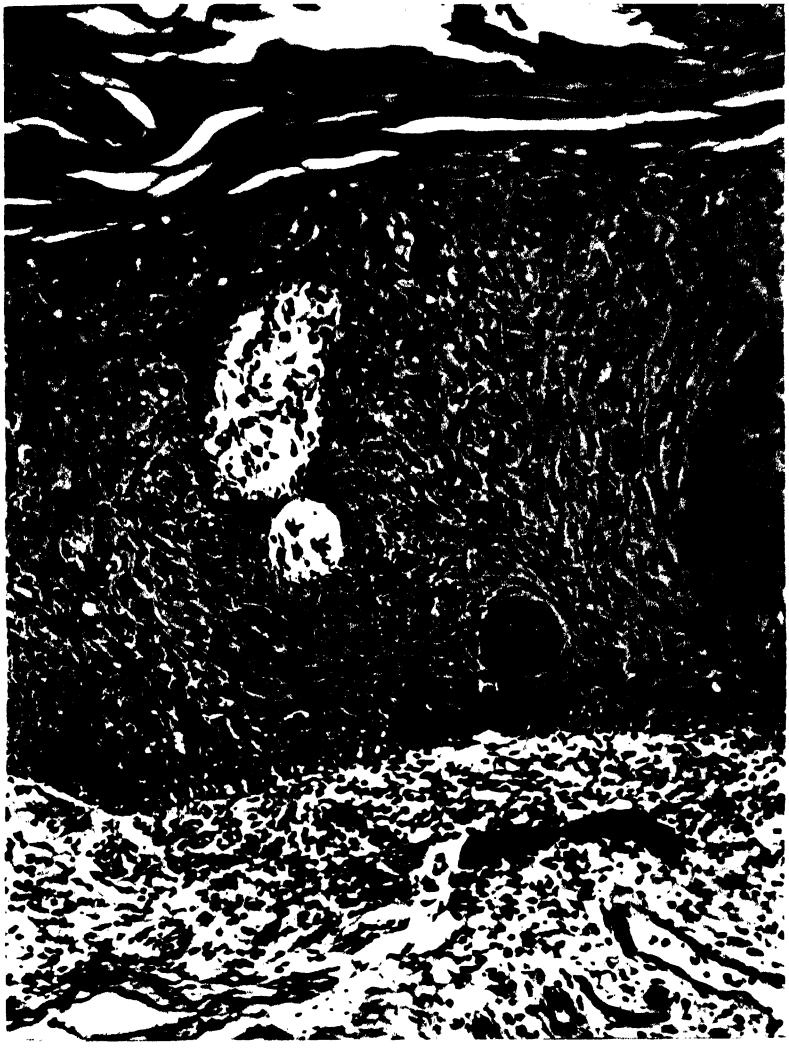


FIG. 36. — The epidermis is almost entirely replaced by spindle-cell proliferation. The papillæ are obliterated. (From L. Savatard micro-photograph, *Brit. Journ. Derm. & Syph.*, 1935, p. 51.)

layer, sometimes mixed with serous exudate to form a crust, the removal of which lays bare a red oozing granular surface (rupial type). The lesions are sharply demarcated and are annular or

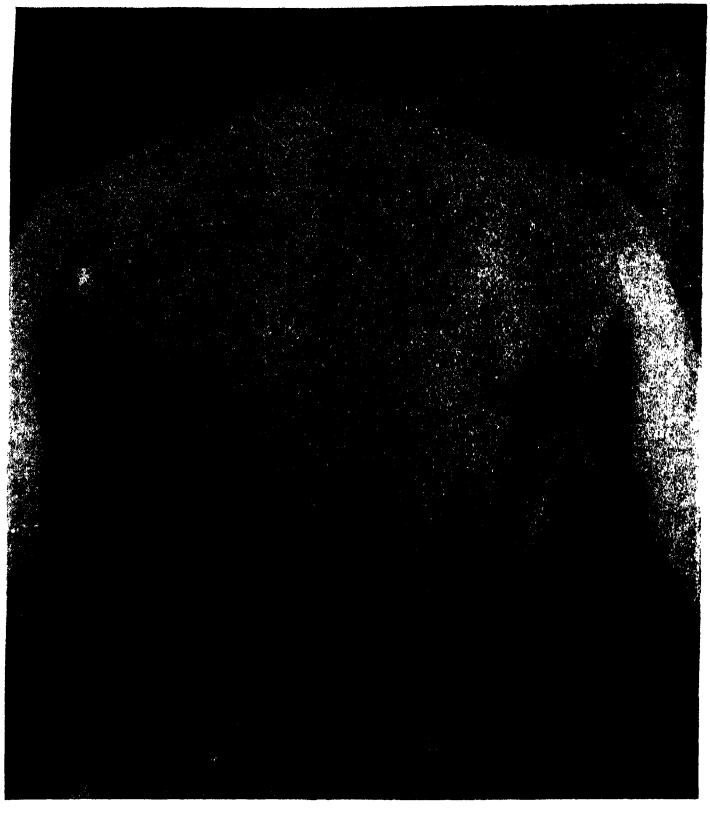


FIG. 37.—Multiple psoriasiform carcinoma: histologically intra-epidermal. (Author's case.)

serpiginous in outline. Occasionally there are little islets beyond the main lesion, increasing its resemblance to a tertiary syphilide (see Fig. 38). Ulcerated areas sometimes epithelíate over spontaneously, but as a rule only temporarily. In certain regions, for example on the scrotum, penis and vulva, the plaque may be

more erythematous and its surface velvety or shiny : this is the condition that Quéyrat called " érythroplasie." Its histology is as varied as that of the psoriasiform plaques.



FIG. 38.—Psoriasiform carcinoma, twelve years' duration. Note the central atrophy. Resemblance to tertiary syphilis. (L. Savatard, *Brit. Journ. Derm. & Syph.*, 1935, p. 51.)

More than one variety of cellular proliferation can be found in one lesion or even in one section. Lesions presenting the same clinical picture may vary histologically and dissimilar clinical lesions may present almost identical microscopical appearances.

"BOWEN'S DISEASE." This is now only a histological conception, corresponding with the first type of intra-epidermal carcinoma, and no longer looked upon as a clinical entity. It can

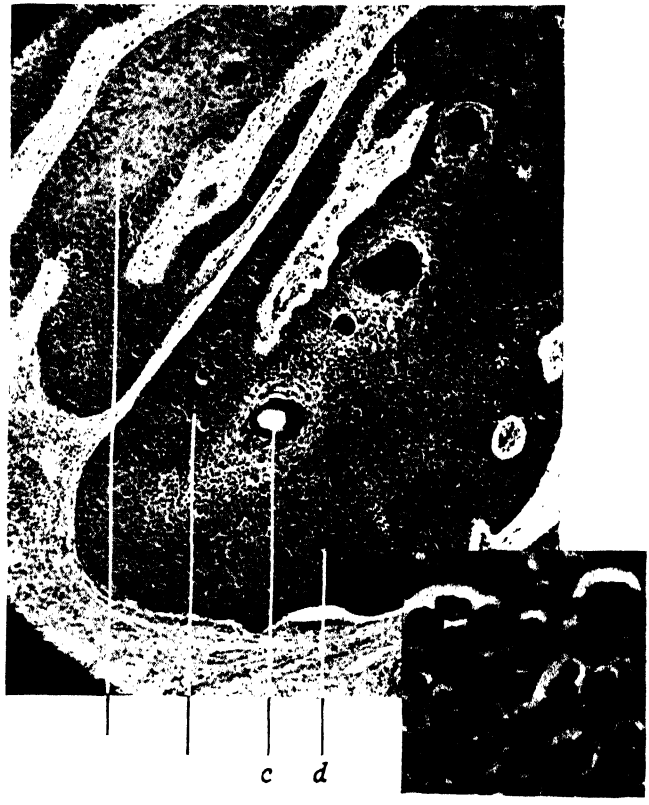


FIG. 39.—Metatypical epithelioma with numerous clumped cells. (*a*) intermediate epithelioma; (*b*) clumped cells (shown by higher power in inset); (*c*) horny pearl; (*d*) basalioma. (Microphotograph from material of W. Freudenthal.

occur on any part of the skin and even on the mucous membranes; indeed, in 22% of the cases, according to Nicolas, Massia and Rousset, there is involvement of the mucous membrane of the vulva. Bowen in 1912 described the clinical appearance as made

up of slightly scaly lenticular papules or nummular discs of dull rose colour, covered with crusts but not much infiltrated. By extension and coalescence these elements gradually form sheets with polycyclic or irregular outlines persisting indefinitely.

But just the same microscopic structure can be found in other lesions, such as in patches resembling seborrhœic eczema or psoriasis, in senile keratosis (Hookey), in the dermatosis and epithelioma caused by X-rays and radium and by tar and arsenic



FIG. 40. Paget's disease of the nipple : psoriasiform type. (L. Savatard, *Brit. Journ. Derm. & Syph.*, 1935, p. 51.)

(Bloch), in the growing edge of an early prickle-celled epithelioma (Savatard), or in metatypical epithelioma (see Fig 39).

After a long time a certain proportion of the lesions invade the dermis and spread more rapidly. The histology now shows the features of prickle-celled epithelioma, but generally retains to some degree the dyskeratotic features of the original intra-epidermal process. Bowen's disease may be looked upon as a chronic prickle-celled carcinoma.

PAGET'S DISEASE. In its typical forms this attacks almost

exclusively women over the age of 40 years. Paget himself described two clinical types: (1) the psoriasiform (see Fig. 40); and (2) the red, raw-looking, eczematous plaque which is more



FIG. 41.— Paget's disease of the nipple: early stage. Note numerous "vacuolated" cells. (A) shows their nuclei pressed to one side by intracellular œdema. (Microphotograph from material of H. M. Carleton.)

commonly associated with his name. The rawness is, however, often more apparent than real.

It is characteristic that the margins never recede and the centre is never transformed into scar. The most prominent micro-

scopical changes are intracellular *œdema* and the presence of " Paget cells " in the rete (see Fig. 41). These large round clear cells are isolated or in groups, and when fully developed have lost their prickles and appear to have become *segregated.* They are often vacuolated by a retraction of their cytoplasm and the nuclei may be double or treble. Eventually a frank cancer develops which may still contain Paget cells or be identical with the ordinary prickle-celled epithelioma.

There is little difference of opinion that the Paget cells are cancerous, but their origin is still in dispute. Masson, Pautrier, Fraser, Muir and Crosti think they have immigrated into the epidermis from a previously existing cancer of the milk-ducts or glands. Pautrier is convinced that in every case in which there has been an exhaustive histological examination of the whole breast a deep-lying carcinoma, either canalicular or mammary, has been found. Now in recent times Paget's disease has been reported elsewhere than in the neighbourhood of the nipple, especially on the female genitals, perineum, scrotum, buttocks, back and armpits. Even in these situations a deep-seated carcinoma has frequently been reported; for example, Civatte observed carcinoma of the sweat-glands in association with Paget's disease of the axilla, and Arzt and Kren reported carcinoma of the rectum in a perineal Paget.

But against this view Darier and Civatte assert that Paget's is not always accompanied by deep carcinoma, that for years it can remain as a superficial change, that typical Paget cells can be found which still show the characteristic prickles of epidermal cells, and that direct transitions can be traced between normal prickle-cells and Paget cells. Moreover, when the neoplasm has invaded the corium it can often be shown to originate from the changes in the surface-epithelium. In 1929 Drake published a case of extensive Paget's disease of the vulva, the histology of which was thoroughly investigated by Whitfield. Typical histological changes were found, not only in the surface epithelium but also in that of the appendages, such as tubules of the sweat-glands; but perfectly normal sweat-ducts separated the superficial and deep foci. Nowhere in the sweat-ducts, sweat-glands or hair-

follicles was there any evidence of a burst-through of the diseased epithelial cells, so that they could reach another part of the skin by a devious route. Whitfield came to the conclusion that the characteristic changes of Paget's disease originate in more than one place; this is also the view of Darier, Gans, Bloch and Savatard, namely, that it may arise in the surface-epithelium alone and that it may also arise independently, either at the same time or at intervals, in the milk-ducts or other epidermal appendages. The disease starts in the basal layer, individual cells becoming affected, not closely enough grouped to prevent completely the generation of the rete. In the sweat-ducts and glands the Paget cells maintain their original position, and Cheatle has emphasised the intraepithelial spread of the process to neighbouring cells in the intraduct carcinoma of the breast. The latter, therefore, behaves similarly to the intra-epidermal carcinoma of the skin. But in the constantly proliferating surface-epidermis the Paget cells are detached and carried up between the normal prickle-cells, eventually reaching the horny layer.

Kreibich and Whitfield both see a resemblance between the Paget cells and those of an actively growing mole or nævo-carcinoma, where segregation is also a characteristic manifestation. It is interesting that Kreibich finds that the Paget cells have the same peculiar staining reactions as Langerhans cells, those anaplastic epithelial cells which line the lymph-spaces of the epidermis, and which we have seen in Chapter III. may be closely related to melanoblasts.

Savatard considers that the significant feature in the histology is not the presence of the distended Paget cells but the proliferation in the rete of crowded hyperchromatic prickle-cells, some of which have become vacuolated. He finds that in clinical Paget's disease, even in cases where the ducts and acini are also involved, vacuolated and distended cells may be practically absent and that there is no essential difference from the histology of psoriasiform carcinoma on other parts of the skin. If this is so, it is rather curious that lesions with the classical Paget histology are nearly always solitary, whereas those with a typical Bowen histology are frequently multiple.

Multiple Superficial Epitheliomatosis. Even in persons apparently presenting only a solitary lesion on the face, careful search will often reveal other superficial carcinomas elsewhere. But it has come to be recognised that not very uncommonly epitheliomas occur as a veritable rash on the trunk and limbs as well as on the face. The histology may be extremely varied, being either that of basal-celled, prickle-celled, metatypical or intra-epidermal cancer.

Graham-Little in 1923 described a special form under the name "benign erythematoid epithelioma," owing to its resemblance to lupus erythematosus. It appears as a sharply demarcated pink area with rounded outline. Little scales and crusts lie on an atrophic base. The margin is marked by a fine thread-like rim or string of minute pearls. Individual patches may persist for 30 years or longer with very little alteration. There is absence of ulceration or local destruction and some lesions heal spontaneously leaving only slight atrophy. It chiefly attacks the trunk. The histology of this type is generally that of an ordinary, but unusually shallow, basalioma.

Broadly speaking, one can generally distinguish this variety of basal-celled cancer from an intra-epidermal cancer by the presence of the thread-like border, which can be made more obvious by stretching the skin; but occasionally the histology may prove to be intra-epidermal in spite of the thread-like border, whilst conversely such a border may be absent in a superficial basalioma.

In one of my cases of the Graham-Little type, in which the majority of lesions were histologically basalioma, one section showed an early prickle-celled and early basal-celled cancer starting independently side by side. Crusted eczematoid patches and fungating tumours developing in the centre of erythematoid plaques are usually, but not always, prickle-celled.

Not all multiple superficial epitheliomas are benign. Internal metastases have been recorded from growths of Bowen, prickle-celled and even basal-celled structure.

The clinical appearances can vary to an extraordinary degree in the same individual, even if the histology is essentially uniform. In a patient recently described by Tauber and Goldman many of

the lesions were of the Little type : some of the patches were studded with pin-point to pin-head sized firm vesicles. In addition there were a papillomatous growth elevated 2 cm. above the surface, brownish papules, brown crinkled patches like senile warts, soft spongy red tumours covered with fine capillaries, small reddish brown macules and a large serpiginous lesion with central atrophy and raised black firm edge. All these clinical varieties were found to have the microscopic structure of a basal-celled carcinoma. The bladder contained multiple papillomata.

Ferguson Smith has reported two very remarkable cases of multiple primary prickle-celled carcinomata which healed spontaneously ; one of the patients was a lad aged only 16 years. The lesions first appeared as reddish macules, then became papular, resembling acne, enlarged, ulcerated and after some months healed, leaving pitted scars with here and there undermined bridges. Apart from the actual lesions the skin was in every respect healthy. The histological structure of the early lesions was that of prickle-celled carcinoma with unequivocally malignant characters. In the older parts one could trace how the malignant characters diminished and the down-growths ceased and were replaced by fibrous tissue. It is particularly remarkable that these tumours actually grew more rapidly than the usual prickle-celled cancers and yet did not involve regional lymph-glands and underwent complete spontaneous regression.

Ætiology

Precanceroses. Precancerosis is a phase, without sharp dividing lines, between the normal and carcinoma. Deelman looks upon precarcinoma as irreversible ; but experience with experimental carcinoma has shown that it is reversible, and we have seen that even fully developed active prickle-celled epitheliomas can regress. A combination of several microscopical changes are required for the diagnosis, such as hypertrophy of the epidermis, irregularity and disorder in its structure, increased number and abnormality of mitoses, polymorphism of the cells, especially of the nuclei (micro-nuclei or giant, multiple or clumped), and dyskeratosis.

It must not be forgotten that most cases of multiple epitheliomata arise from apparently normal skin. But Puhr states that in the neighbourhood of cutaneous carcinomas there are always peculiar changes in the *elastic apparatus of the dermis.* The elastic fibres swell, stain deeply with orcein and form circumscribed coils immediately under the epidermis. They may show lipoid degeneration. These changes, which he considers precancerous, resemble atherosclerosis.

KERATOSIS SENILIS. This is the commonest precancerosis and

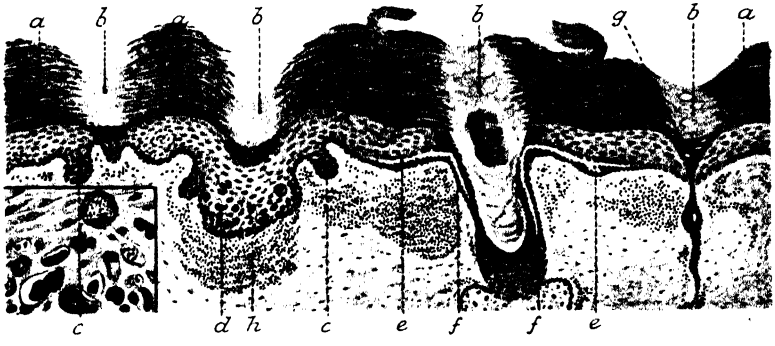


FIG. 42. Keratosis senilis: (*a*) parakeratotic pillars; (*b*) hyperkeratotic intervals; (*c*) whorls and buds; (*d*) clumping and giant cells (in left corner by higher power); (*e*) gap; (*f*) epidermal sheet around hair-follicle; (*g*) darker stained funnel on sweat-duct; (*h*) lymphocytic infiltration. (Semi-diagrammatic from material of W. Freudenthal.)

is considered such by all those who accept the idea of precancerosis at all. It occurs on skin affected by senile atrophy. The age at which "senile" atrophy develops is largely dependent on the amount of exposure, especially to sunlight. The keratoses are generally multiple, sharply circumscribed, dirty-looking patches, the surface of which is covered by fine clinging horny scales.

The histology, which has recently been thoroughly studied by Freudenthal, has the following main features (see Fig. 42). The horny layer is thickened and areas of parakeratosis alternate with hyperkeratosis, the latter being at the orifices of the follicles and

the sweat-ducts. The rete-cells stain more darkly than those in the neighbourhood and there are some clumped and giant cells. Sometimes buds from the basal layer project into the papillary body. There is often a space just above the basal layer or the proliferating parts of the epidermis.

Hookey estimates that about 25% of such keratoses give rise to frank epithelioma, which may be of any of the histological types. It is curious that on the face it is usually basal-celled and on the hands prickle-celled. This development is indicated clinically by induration at the base, a persistent pink halo, or subjective sensations.

Leucoplakia. According to Darier only the following features are precancerous: (1) papillomatous forms, (2) hard raised plaques which superficially are easily eroded, (3) fissures which feel hardened and heal with difficulty.

Leucoplakia of the vulva is encouraged by leucorrhœa and pruritus. According to Taussig (1929) carcinoma develops in 50% of cases. The penis, too, may be the seat of leucoplakia, Paget or Bowen-like affections.

Sunlight. Paul, from his experience in Australia, emphasises the great importance of chronic solar dermatitis, which resembles mild X-ray dermatitis. It is mostly produced by natural sunlight, but Colquhoun, of Melbourne, has observed the development of multiple keratoses on the chest of a man who had been treated with quartz-light for about 18 months. Deficiency of pigment is a predisposing factor: Hewer has described several cases of multiple epithelioma of varied histology and dry wrinkling of the skin in albinos of dark races much exposed to the sun.

Chemical Agents. The chief chemical causes are arsenic, hydrocarbons of high boiling-point from coal (soot, tar, pitch), derivatives of raw petroleum and Scottish shale-oil; these account for most occupational and therapeutic carcinomas. The phase that immediately precedes frank cancer is characterised by papillary or verrucous changes resembling senile keratoses. The final cancer is most often prickle-celled, though in the same individual the same agent may produce many varieties of growth. Guggenheim (1933) described a patient who, after taking

arsenic for many years, had an outcrop of carcinomas with the characters of basalioma, metatypical epithelioma, Bowen and Paget.

ARSENIC. Under natural conditions this brings about cancer through internal intoxication, but Leitch and Kennaway have induced keratoses and cancer in rats by applying a compress of 0·12% solution of arsenious acid for several months. The sites of election are the palms and soles, but any part of the body, especially exposed areas, may be involved. The keratoses are sometimes associated with superficial irregular ulcers with clean-cut edges and red granulating base: many years may elapse between the taking of the arsenic and their appearance. Many authors have noted its association with multiple superficial epitheliomatosis.

HYDROCARBONS. Those especially attacked are chimney-sweeps and workers with tar, pitch, petroleum and coal-briquettes. As with arsenic, the type of carcinoma is generally prickle-celled. In man it particularly attacks the genital region and the extremities.

There is ample experimental proof that the external action of tar is carcinogenic. Bloch and Widmer have succeeded in animals with distillates of tar containing neither nitrogen, sulphur nor arsenic, and Kennaway with synthetic tar (isoprene).

Kennaway observed that there was a resemblance between the fluorescence-spectrum given by cancer-producing products, obtained by heating coal and certain other materials, and the spectrum given by benzanthracene. Benzanthracene itself, however, proved to have only feeble carcinogenic power. But several new synthetic substances of the dibenzanthracene series have been found by Hieger in Kennaway's laboratory to be very strongly carcinogenic for mice. Now Cook and Dodds (1933) have made the remarkable observation that two of the most active of these carcinogenic hydrocarbons are also œstrogenic. Moreover, there is a close chemical relationship between carcinogenic hydrocarbons and certain substances, including œstrin and cholesterol, which are present normally in the body. Speculation is consequently rife as to the possibility of the elaboration of endogenous carcinogenic agents under the influence of certain stimuli, such as

light. In Chapter III. it has been shown that certain melanodermias are attributed to the sensitisation of the skin to light by the *absorption* of hydrocarbons by inhalation. It is likely that the same mechanism plays a part in tar-cancer.

Nævous Origin. When none of the above forms of irritation can be traced, one is inclined to invoke the nævous theory, especially for basaliomas. The idea is that the basal layer is originally plastic and capable of begetting not only the superficial layers of the epidermis but also the various annexa, and that sometimes there persist in it certain foci of cells (cell-rests) which at a later period, owing to some stimulus or alteration in their environment, make futile attempts at forming appendages of the skin, especially hair-follicles. Savatard states that in the vast majority of basal carcinomas examined by him there has appeared to be an attempt at producing hair-follicles, presenting a picture of adenoid or cystic masses, in some of which there is a peculiar striation, elongation and fibrillation of the cells which suggests abortive hair-shaft formation. Haythorn, from similar observations, goes so far as to trace all basaliomas to the hair-matrix. It is perhaps significant that basaliomas never occur on the palms or soles.

The origin of melano-carcinoma from moles has been discussed in Chapter III. Epithelioma adenoides cysticum seems to bear the same relationship to basal carcinoma as does the mole to melano-carcinoma.

Secondary Carcinoma

Metastatic cancers in the skin are rare, and perhaps for that reason can easily pass unrecognised. They may be disseminated by the lymphatics or the blood-stream from the breast, bones or internal organs. They are characterised by hard, red, mauve, or brownish elevations. At first they are isolated but later coalesce into irregular uneven sheets, which may resemble sclerodermia. Often they ulcerate, vegetate or fungate. A striking example of secondary cancer from the breast, reported by me, started as a sudden stinging sensation followed by acute inflammation at the top of the scalp and from there spread continuously down the face

and neck. The greater part of the top of the scalp was bald, the skin was red and raised into firm irregular lumps, which extended to the forehead and behind the ears. At the periphery of the affected area there were outposts of little, discrete, hard, deep, cutaneous nodules.

In 1924 Kuettner described another inflammatory form of secondary carcinoma under the title *erysipelas carcinomatosum.*



FIG. 43. — Carcinoma erysipelatodes acutum. (C. Rasch, *Brit. Journ. Derm. & Syph.*, 1931, p. 351.)

Rasch (1931) in describing a further instance proposed the better name *carcinoma erysipelatodes acutum.* In Rasch's case there was a progressive heaviness and swelling of one breast, and the overlying skin became bright red, hot, thickened and stiff, but remained smooth : she complained of smarting and pricking. The trouble eventually spread round to the back and over the whole of the chest and epigastric region. The edge was irregularly wavy, only very slightly raised, and of a flaring erysipelatous redness. Histo-

logically the blood-vessels were dilated and contained clumped masses of epithelial cells. The intima was everywhere intact (see Fig. 43). This condition differs from " cancer en cuirasse " in that in the latter the skin is more scleroderma-like and the cancer-cells are found mainly in the lymph-vessels and tissue-spaces. Parkes Weber in 1933 reported a further variety, which he called *carcinoma telangiectaticum* (see Fig. 44). In some parts the process spread by an advancing margin and in others by the formation of small telangiectatic islets. Both margin and islets were slightly elevated. The condition appears to spread mainly in the lumen of the cutaneous blood-capillaries.

Treatment

Prevention. Excessive exposure to sunlight must be avoided. Keratoses of senile type in atrophic skin, especially if occurring in men working with carcinogenic agents such as pitch-dust, should be treated early. If possible such men should be transferred to other work. In dangerous trades the worker's skin should be cleaned before he returns home and clothes put on which are free from the irritating substances. Some protection is afforded by rubbing bland ointment on all exposed surfaces before starting work.

Biopsies. These are of some practical value in prognosis and in the selection of treatment. Epstein considers that experience has proved them free from danger; but Paul warns against them, especially in the naso-facial and naso-labial regions, where excision is sometimes followed by the development of the severe terebrant form; even when performed elsewhere they should be followed by immediate treatment. Drops of clear fluid exuding from some depth point to the involvement of cartilage.

Radiotherapy. For the majority of cases in which bone or cartilage is not involved Paul prefers *radium* in such dosage that a single treatment is effective. He considers a marked and prolonged inflammatory reaction is essential; it appears in 7–10 days, reaches its maximum in about 14 days, and then subsides with



FIG. 44. Carcinoma telangiectaticum. The telangiectatic spots do not lose their colour under glass-pressure, though the diffuse blush disappears. (F. P. Weber's case.)

the formation of crusts which fall off in about 6 weeks; the scar may be a little keloidal. For all other types than ulcers with flat borders he recommends preliminary removal of the projecting portion either by CO_2 snow, 1–5 minutes repeated in a week if

necessary, the radium being applied 1 or 2 weeks later, or else by ablation with a knife. The radium must cover a larger area than the surface-lesion, as the growth tends to spread laterally in the corium. From his experience Gardham disagrees that radium is contraindicated when cartilage is involved, but the dose must be kept at the lowest limit compatible with the arrest of the growth.

X-rays act similarly. They are considered by many to be somewhat inferior to the beta-rays of radium. But we shall see in the next chapter that one of the most efficient ways of using radium is by means of radon, so filtered that only the gamma-rays (which closely resemble X-rays) are operative. But it is probably chiefly a question of dosage and technique. In Germany, where radium is scarce, X-ray therapy has been greatly developed. Hintze in Bier's Clinic has obtained with X-rays alone over the period 1921–29, 50–60% of cures. The cases included all types, such as growths affecting the trunk, complicating lupus, prickle-celled epithelioma, deep and completely incurable cases, and those with glandular enlargement. No cases were considered cured if any carcinomatous lesion was still present anywhere in the skin after 5 years. The highest published percentage of cures on the 5 years' basis for operative procedures had been 37·3% (Leeds Infirmary), and for radium 41·5% (Forssell). Moreover, X-rays have the advantage over radium of being more convenient for large areas, more rapid in application, and perhaps more easily controlled as regards dosage. Molesworth also considers X-rays the method of choice for all basal-celled growths less than 4 cm. in diameter. For those exceeding this size he prefers implantation of radon-seeds. Further details of these methods will be given in Chapter XIII.

For early basaliomas Adamson recommends the following method. The major part of the growth is first scraped away under a local anæsthetic; this reveals its exact shape, size and depth, the surface-view and palpation often being deceptive. The erosion is then mopped out with trichloracetic acid, which stops bleeding and forms a dry crust; this is followed by one application of 3–5 skin-units of unfiltered X-rays. There is no

after-reaction. The wound is mopped twice daily with spirit till the crust falls off and heals within 14 days. A sound scar results without any tendency to telangiectasis.

For multiple superficial epitheliomatosis, though they are recommended by many authorities, I consider radium and X-rays inadvisable, in that relatively large doses are required, and it is exceedingly difficult to remember exactly which areas of skin have already been treated.

Though prickle-celled and metatypical growths are less responsive than basal-celled, this is only a matter of degree. I have seen many such growths completely healed by 2 or 3 doses of 3 skin-units at fortnightly intervals. Recently Busman and Woodburne reported a complete cure of typical Paget's disease of the glans penis, the centre of which had developed into prickle-celled cancer, with unfiltered X-rays, 1 skin-unit every 4 weeks, 5 exposures in all.

CO_2 Snow. Paul finds freezing alone particularly successful for growths of the eyelids and the inner canthi. Some suitable instrument has to be held inside the lid to obtain pressure. He gives about 60 seconds.

Graham Little recommended it for his variety of superficial epithelioma, giving 10–15 seconds. I consider this the best and safest method for all superficial varieties, if at all extensive. It is also eminently suitable for senile keratoses and early prickle-celled carcinoma.

Fulguration and Electrocoagulation. For superficial basalioma I have found fulguration with a small high-frequency machine perfectly satisfactory. The operation is very rapid, is not followed by any inflammatory reaction, the cosmetic result is excellent, and there is no danger of subsequent telangiectasis. For deeper lesions electrocoagulation following excochleation is useful. It is particularly valuable for destroying little recurrences after other treatments.

Martenstein and Epstein found that the combination of curetting and fulguration followed by radium yielded a higher percentage of cures after one session than single methods, and the cosmetic results were as good as with radium alone.

For Paget's disease of the nipple, which is nearly always associated with deep carcinoma, radiotherapy is inadequate, and removal of the whole breast is required.

Bibliography

ADAMSON, H. G. "Treatment of Early Rodent Ulcer," *Brit. Med. Journ.*, 1933, **2**, 994.

BUSMAN, G. J., and WOODBURNE, A. R. "Paget's Disease of the Glans Penis," *Archives of Derm. and Syph.*, 1931, **24**, 396 (*Abs. Brit. Journ. Derm. and Syph.*, 1933, **45**, 40).

"Cancer and Chemical Stimuli." Leading article *Brit. Med. Journ.*, 1934, **1**, 951.

COOK, J. W., HIEGER, I., KENNAWAY, E. L., and MAYNEORD, W. V. "Production of Cancer by Pure Hydrocarbons," *Proc. Roy. Soc.*, London, B., 1932, **111**, 455 (*cit. Brit. Med. Journ.*, 1934, **1**, 951).

DRAKE, J. A. "Paget's Disease of the Vulva," *Brit. Journ. Derm. and Syph.*, 1929, **41**, 177.

DUNN, J. S., and SMITH, J. F. "Self-healing Primary Squamous Carcinoma of the Skin," *Brit. Journ. Derm. and Syph.*, 1934, **46**, 519.

EPSTEIN, S. "Zur Klinik, Histologie und Therapie der Epitheliome der äusseren Nase," *Zeit. f. Hals-Nasen u. Ohrenheilk.*, 1932, **32**, 312.

FRASER, J. F. "Bowen's Disease and Paget's Disease of the Nipple: their Relation to Dyskeratosis," *Archives of Derm. and Syph.*, 1928, **18**, 809 (*cit.* Schürch).

GOLDSMITH, W. N. "A Case of Metastatic Scirrhous Carcinoma of the Scalp," *Brit. Journ. Derm. and Syph.*, 1929, **41**, 270.

GUGGENHEIM, L. "Multiple Präcancerosen (mit präcancerösem Exanthem) und Carcinome, zum grossen Teil von bowenoidem Typus, nach langjährigem Arsengebrauch," *Arch. f. Derm. u. Syph.*, 1933, **68**, 26.

HEWER, T. F. "A Case of Multiple Epitheliomata in an Albino," *Brit. Journ. Derm. and Syph.*, 1932, **44**, 469.

HINTZE, A. "Die Prognose des Karzinoms," *Münch. med. Wschr.*, 1935, **82**, 163.

HOOKEY, J. A. "Keratoma Senile and Verruca Senilis: Clinical and Histopathologic Study," *Archives of Derm. and Syph.*, 1931, **23**, 946 (*cit.* Schürch).

JADASSOHN, J. "Demonstration von selteneren Hautepitheliomen," *Bruns' Beiträge zur klin. Chir.*, 1926, **136**, 345.

JUON, M. "Visceral Metastases in Metatypical Cutaneous Epitheliomata," *Acta. Derm.-Ven.*, 1933, **14**, 4, 287.

KREIBICH, C. "On the Paget Cell," *Arch. f. Derm. u. Syph.*, 1931, **163**, 467.

LITTLE, E. GRAHAM. "Erythematoid Benign Epithelioma," *Brit. Journ. Derm. and Syph.*, 1923, **35**, 435.

MOLESWORTH, E. H. "The Treatment of Skin and Lip Cancer," *Derm. Woch.*, 1934, **99**, 1134 (*Abs. Brit. Journ. Derm. and Syph.*, 1935, **47**, 133).

PAUL, C. N. "Cutaneous Neoplasms," London, Lewis, 1933.

PUHR, L. "Ueber präcarcinomatöse Veränderungen des cutanen Bindegewebes," *Magy. orv. Arch.*, 1935, **36**, 163 (*Abst. Zbl. Hautkrank.*, 1935, **52**, 94).

RASCH, C. "Carcinoma Erysipelatodes," *Brit. Journ. Derm. and Syph.*, 1931, **43**, 351.

SAVATARD, L. (*a*) "Intra-epidermal Carcinoma of the Skin." *Brit. Journ. Derm. and Syph.*, 1931, **43**, 161. (*b*) "Psoriasiform Carcinoma of the Skin," *ibid.*, 1935, **47**, 51.

SCHÜRCH, O. "Die präcancerosen der Haut," *Zbl. Hautkr.*, 1934, **47**, 1.

SMITH, J. FERGUSON. "A Case of Multiple Primary Squamous-celled Carcinomata of the Skin in a Young Man with Spontaneous Healing," *Brit. Journ. Derm. and Syph.*, 1934, **46**, 267.

TAUBER, E. B., and GOLDMAN, L. "Multiple Benign Superficial Epithelioma," *Brit. Journ. Derm. and Syph.*, 1935, **47**, 21.

WEBER, F. PARKES. "Bilateral Thoracic Zosteroid Spreading Marginate Telangiectasis, probably a Variety of Carcinoma Erysipelatodes (C. Rasch), associated with Unilateral Mammary Carcinoma and better termed Carcinoma Telangiectaticum," *Brit. Journ. Derm. and Syph.*, 1933, **45**, 418.

CHAPTER XIII

RADIANT ENERGY

Ultra-Violet, Luminous and Infra-Red Rays

THE infra-red rays range from a wave-length of 610,000 A.u. to 7,600 A.u. and the ultra-violet from 3,750 A.u. to 100 A.u. There is a gap of about 10–40 A.u. between the shortest U.V. and the longest X-rays, the nature of which is unknown. There is a certain alternation in the *biological absorption* as one passes along the spectrum. The infra-red rays are more easily absorbed by the tissue than the more penetrating visible rays; then comes a region of greater absorption in the U.V., which is followed again by the deeply penetrating X-rays and gamma-rays. The long infra-red rays are absorbed by the most superficial layers, the short infra-red, red, orange and yellow penetrate deeply through the skin, even to the subcutaneous tissue. Sonne has shown that they can heat the tissues at 0·5 cm. depth to a temperature actually some degrees higher than the irradiated skin-surface. The blue-violet luminous rays do not penetrate beyond 20 mm., and are mostly absorbed by the hæmoglobin in the superficial blood-capillaries. The penetrativeness of U.V. rays is greater the longer the wave-length. Rays under 3,000 A.u. can hardly penetrate through the epidermis, and those under 2,450 A.u. cannot even pass the horny layer (Hill). Nevertheless, Lucas has shown that U.V. rays even short enough to activate ergosterol (*i.e.*, in the neighbourhood of 2,800 A.u.) can pass through the epidermis of a day-old rat.

The *biologically active* region of the sun's spectrum for the human skin is between 3,130 A.u. and 2,900 A.u., and is often referred to as the "Dorno rays." The sun's spectrum ends quite suddenly at this point: under no circumstances have shorter wave-lengths been detected. The spectrum of a mercury-vapour

lamp is relatively rich in the shorter-waved U.V.; its most potent erythema-producing rays are those around 2,967 A.u., which scarcely exist in sunlight. U.V. rays are absorbed by the cells and cause death by a specific action on the cytoplasm.

Anderson and Fraser estimate that the *thickness* of the human adult epidermis, which is considerably greater than that of young children, averages about 1 mm. Lomholt has shown that U.V. rays of wave-lengths short enough to produce erythema can penetrate through rat-skin of 1 mm. thickness. [Previous experiments had shown that the permeability of dead bloodless rat-skin is the same as that of living human skin made bloodless by compression.] Further, according to Bachem and Kunz, the longer-waved U.V.R. penetrate deep into the corium and in overdosage can produce a severe toxic action on the capillaries.

Under normal conditions the *infra-red* and *luminous rays* have only a heating effect of short duration. The blood-vessels *immediately* dilate. After cessation of irradiation the tissues begin to return to normal. These rays are seldom allowed to produce enough heat to blister or necrose, since their effect is *immediately felt.* Luminous rays, probably through absorption by pigment, produce a dark red, sharply circumscribed erythema; the infra-red rays only bring about a pale mottled non-circumscribed reflex erythema.

The Acute Actinic Erythema. Between the exposure to U.V.R. and the appearance of the erythema there is a characteristic *latent period*, generally thought to be 2 or 3 hours, but probably much shorter. Collin has observed within half an hour fine red spots around the follicular orifices. The maximum is reached in 6–12 hours. A "flare-up" (see p. 260) is sometimes observed several weeks after a single intense exposure.

Different parts of the skin vary greatly in their *sensitiveness*; the most sensitive regions are the inner side of the arms and thighs, the popliteal space and the sides of the chest and back. The difference seems to depend chiefly on the varying thickness of the horny layer; the skin remaining after desquamation is always extremely sensitive. The degree of erythema is also influenced to some extent by the depth of pigmentation, the fat-content of the

superficial layers and by the local circulation and temperature. Thus Shattock and Waller have shown that: (1) heating the tissues by any method after exposure to U.V.R. diminishes or suppresses and delays the actinic erythema; (2) heating before exposure increases it; (3) heating simultaneously acts as in (1); (4) the actinic erythema of heated skin is more vermilion than that from pure U.V.R., which is rather crimson.

HISTOLOGY. The first visible change is an increase of leucocytes in the cutis. These are attracted towards the epidermis. Here one can soon see in the stratum spinosum changes in the nucleoplasm and coagulation of the cytoplasm. The basal-cells do not degenerate except after a much more intense exposure, even those on the tips of the papillæ, which are actually nearer the source of light than the prickle-cells of the interpapillary pegs. There is also some exudation in the epidermis. These changes are observed before the development of the erythema.

THE MECHANISM OF THE ERYTHEMA. The evidence points to the erythema being at least predominantly due to changes in the epidermal cells, which secondarily affect the superficial blood-vessels; for exceedingly little U.V.R. penetrates beyond the adult epidermis. Moreover, it is striking that in children under 2 or 3 years of age, in whom the epidermis is thinner and therefore more easily penetrable, ultra-violet erythema is much less pronounced. Perthes demonstrated that even intense irradiation of skin entirely denuded of epithelium provoked no inflammatory response. Though it has been shown that melanin absorbs and stops U.V.R. (Hill and Campbell), it does not in its normal position entirely prevent erythema, even in negroes. The rays must therefore act on something superficial to the site of the melanin. This is clearly seen microscopically, the prickle-cells being damaged and the basal-cells, the nuclei of which are capped by pigment, escaping. The attraction of leucocytes towards the epidermis before the erythema begins indicates the setting-free of a substance from the epidermal cells which is diffused into the cutis. Nathan and Sack produced an erythema by the intracutaneous injection of an extract of irradiated epidermis, not obtainable with a similar extract of non-irradiated epidermis. Lewis's experiments demon-

strated the spread of erythema beyond the area irradiated, and this diffusion is often most clearly seen in the direction of the lymph-stream. The erythema due to U.V.R. differs from that produced by most irritants in the absence of the reflex nervous arteriolar halo. Actually this is only relative and is probably explained by the slow protracted nature of the trauma.

Chronic Actinic Effects. In dermatitis from natural sunshine the area beneath the chin, which is in shadow, escapes, and the radial side of the hands and forearms, rather than the ulnar, is attacked. This distribution does not apply when there is reflection from snow and ice. The earliest signs of chronic solar dermatitis are scattered pink or brown spots and then a slight scaliness or greyish keratoses from proliferation of the epidermis. The skin of the dorsum of the hands may become thick, tough and of a violaceous tint; rarely the changes may be so pronounced as to resemble radio-dermatitis.

The face and hands are normally redder than the rest of the skin. Finsen showed that this diffuse superficial capillary dilatation is the result of light. He also showed that skin which had been exposed to a single intense irradiation and from which erythema and pigmentation had disappeared still continued for a long time to redden abnormally easily on slight mechanical or other stimulation. It has since been demonstrated that if, many months after ultra-violet irradiation, 0·01 gm. of histamine is injected subcutaneously, the irradiated portion of skin will flush in vivid contrast to the non-irradiated area. This state renders a previously irradiated region a *locus minoris resistentiæ* for various diseases. Haxthausen points out that we can best see the chronic effects of sun alone in the sternoclavicular region of women who keep that area covered in cold weather and exposed in summer. Under such conditions one sees a permanent dilatation of the visible vessels. The arterioles are more easily dilatable than normally, but are not permanently dilated. This is in contrast with the skin of the legs, where we see the effect of prolonged cold, namely, dilatation of minute vessels, but contraction of arterioles; and with that of the face, where the effects of cold and of sunlight are combined.

Pigmentation. Increase of pigmentation is probably due to direct stimulation of the melanoblasts. It is increased by the erythema-producing rays, but also by longer-waved rays, including the luminous and infra-red (as well as by non-radiant irritants), so that it is possible to produce pigmentation without there having been any erythema. This is now made use of cosmetically, by oiling the skin before exposure to sunlight, most fats absorbing the erythema-producing U.V. rays; the intense pigmentation which now follows prolonged exposure lasts well because desquamation is avoided. It may be that chemical and mechanical irritation act partly by increasing the excitability of the melanoblasts to light, for Peck (1929) found that such agencies produce no pigmentation in the skin of rabbits kept in the dark but strong pigmentation in the light. Stahl and Simsch have shown that whilst hyperæmia at the time of exposure to U.V.R. intensifies both erythema and pigmentation, cold electively increases pigmentation. With the idea that cold might act through stimulation of the sympathetic, ephedrine was given by mouth for several days before irradiation; the effect was only a slight increase of erythema, but a conspicuous increase of pigmentation. Preparatory treatment with calcium diminished both. That an active blood-supply is not necessary at the time of exposure was proved by Meirowsky, who produced intense pigmentation by irradiating excised skin. Nevertheless, Urbach made the interesting observation that on a girl's forehead, deeply pigmented by sunlight, a nævus anæmicus remained unpigmented, though it gave an equal dopa-reaction. He concluded that some function of the capillaries was essential for super-pigmentation. It certainly tends to be less in anæmia. Gantenberg has observed that in the successful liver-treatment of pernicious anæmia the pigmentation of exposed parts is strikingly increased and runs completely parallel with the course of improvement. At the same time he demonstrated a correspondingly progressive increase of U.V. sensitiveness and of blood-cholesterol.

The chief *function* of pigment is probably to protect the blood from being overheated by the process of conversion of the deeply penetrating red, orange and yellow rays into heat. Dorno (1929)

has shown that the maximal absorption by pigment is in the region of the yellow rays. We have seen that in its normal position in the skin of white races it cannot protect efficiently against U.V.R., which act mainly on the prickle-cells superficial to it. But after a very recent irradiation it does protect, for Meirowsky has shown that the whole epidermis up to the horny layer is then full of pigment, which has been emptied out of the basal-cells; it is eventually cast off in the scales. It is only 8–14 days later that the true increase of pigment takes place in the basal layer. Miescher has, however, shown that the skin of an Abyssinian is, in fact, much less sensitive than white skin. As the breadth of the horny layer is about the same, he attributes the difference in sensitivity entirely to the copious pigment in *all layers* of the epidermis of the Abyssinian.

Thus, though pigment may not be a satisfactory protection against quartz-light, it is an important protection against natural sunlight. Moreover, Keller now recognises that the longer U.V.R., in addition to their obvious effect on the prickled layer, have a direct action on the cutis. That these can be caught and rendered harmless by pigment has recently been shown by the absorption-experiments of Miescher with dopa-melanin solution.

Berlocke Dermatitis. In 1916 Freund described finger-shaped vertical stripes of yellowish to dark brown discoloration generally from the front or back of the neck downwards (see Fig. 45). The colour is darkest at the lowest point and along the converging borders. The appearance suggests the track left by fluid trickling down. It was found that this disorder follows exposure to the *sun* after the application of *eau-de-Cologne*. Experimentally Freund was able to produce with eau-de-Cologne and also with bergamot-oil, which is a constituent, a light-dermatitis with strong subsequent pigmentation. Generally the pigmentation is preceded by inflammation, but often no inflammatory stage is noticed (Garzella): there was none in either of my cases. The spots usually appear very quickly, in 1 or 2 days, but rarely are delayed for 2 weeks. Of course the shape need not always be in the form of pendants ("Berlocke") and other names

have therefore been suggested, such as "perfume-dermatitis," or "dermatosis pigmentaria E. Freund," which is preferable.

Subsequent experiments with bergamot-oil and irradiation with sun or quartz-lamp have often been negative (Rosenthal and Goodman). Szántó tested the separate ethereal oils that occur in toilet-preparations and found that nearly all cause a distinct increase in light-sensitiveness, bergamot-oil being the most potent. According to Del Vivo only *bergamot* and *cedar-wood* oils are



FIG. 45.—Berlocke dermatitis. (R. Habermann, Jadassohn's *Handbuch*, IV., 2, p. 811.)

active, and it is only natural sunlight that brings about the pigmentation. Irradiation first and application of the essences afterwards produced no comparable effect. Treatment of excised portions of skin with eau-de-Cologne and sunlight had a negative result. It is probably the red-yellow rays that are responsible. Kurz did, however, succeed by daily application of eau-de-Cologne 4711 and exposure to suberythema-doses of the mercury-vapour lamp in producing stronger pigmentation than with pure alcohol. Histologically this was found to be due not to increase of basal-cell

pigment but to a deepened colour of the horny layer. In most cases there was no trace of inflammation.

Its frequent mention in Continental literature contrasts with its rarity in this country, and probably reflects a difference in custom. I have only had 2 cases. In one the discoloration was along the side of the neck, where it was touched by the fringe of the patient's hair, on which she had used brilliantine, which is frequently scented with bergamot-oil. But even allowing for differences in custom there must be some unexplained *individual chemical peculiarity of the skin.*

Habituation. Though pigment plays a part, the skin can be habituated to light in its absence, as has been shown in vitiligo-patches and other leucodermias by Rost and Jadassohn. Keller attributes increased tolerance to a change in the cell-membranes, which become less permeable. Perthes has shown that irradiation diminishes the sensitiveness of the skin to a subsequent exposure, even if the interval is as short as 5 hours and the first dose only strong enough to produce a faint erythema without subsequent pigmentation. He thought the immunity consisted in the formation of antibodies which counteracted the inflammation-producing substances set free from the epidermal cells. Lehner and Urban found that the loss of sensitiveness is not specific but applies to all those irritants that attack the epidermis. Meyer, Ledermann, Kropatsch and Linser have been able to demonstrate that there is, in addition, an increased sensitiveness, which generally intervenes between the phase of increased tolerance and the return to normal. These phases they attributed to alterations in the physiology of the light-sensitive cells. But may it not be that the increased sensitiveness depends on an exfoliation of a thickened horny layer, even if it is not macroscopically obvious ? The most recent work has been done by Miescher, who concludes from functional and histological investigations that the defence of the skin against short-waved U.V.R. is mainly the result of the increased formation of horn-cells, of which a thickness of 0·1 mm. acts as an almost complete barrier. They stop U.V.R. by virtue of the cyclic aromatic compounds, phenylalanine, tyrosin, and especially the sulphur-rich cystine.

This simple mechanism, important as it is, does not, however, quite explain some of Perthes findings, especially the very rapid development of immunity and his observation that the smallest degree consists, not in a diminution of the intensity of the erythema but in its more rapid disappearance. This might be explained by exudation. Saidman attributes the immunity to photoelectric fatigue.

Pathological Sensitiveness of the Skin to Light. There are several known substances which can sensitise tissues to certain rays. Animals injected with phthalein-dyes, such as eosin, or with hæmatoporphyrin can be killed by exposure to sunlight or artificial sources of luminous rays, but are not affected if kept in the dark. In non-fatal cases there ensue loss of hair, œdema and necrosis of the skin. Similar effects can be produced with some coal-tar derivatives, such as acridine. Bacteria can also be sensitised to luminous rays by many dyes. The action of the *photodynamic substances*, or sensitisers, depends on their union with tissue-proteins. After this union the luminous rays produce reactions similar to those evoked by U.V.R., but at a deeper level and therefore often of greater severity. Many sensitisers are readily soluble and rapidly excreted. Sensitiveness is only present as long as there is an adequate concentration in the irradiated tissues. Many diseases in animals, mainly white-skinned, during the summer are caused by their eating foods containing photodynamic substances, *e.g.*, buck-wheat, clover, maize or red mangel. The photodynamic substance responsible for buck-wheat poisoning is, according to Sheard, phyloporphyrin, which is closely related chemically to hæmatoporphyrin.

In man experimental sensitisation has been produced with erythrosin and hæmatoporphyrin.

Porphyrin. This is the only known chemical sensitiser that is produced endogenously and appears to have a relationship with light-dermatosis. *Hydroa æstivale* is sometimes associated with congenital porphyrinuria. The onset is often in the first year, usually after the first exposure to strong sunlight. The porphyrinuria persists throughout life, which is, however, often short.

Sometimes the inherited form only becomes manifest later in life. But in many cases of hydroa there is no demonstrable porphyrinuria: the lesions are, as a rule, less severe than in subjects of congenital porphyrinuria and, though sometimes familial, do not show the same preference for males.

Hausmann first showed the photodynamic action of hæmatoporphyrin, and later Ehrmann suggested the causal connection between light-sensitiveness and porphyrinuria.

Meyer-Betz (1913) injected 0·2 gm. of hæmatoporphyrin into his own vein; exposure of a portion of the skin a quarter of an hour afterwards to a Finsen lamp resulted in conspicuous swelling and redness, leading to deep infiltration and hæmorrhagic necrosis of the whole cutis. Two days later a short exposure to the sun produced immediate pricking and burning of the whole of the uncovered skin, followed by erythema, pain and swelling. Frei has succeeded, by means of intracutaneous injection of hæmatoporphyrin in great dilution, in producing wheals on subsequent irradiation.

But the relationship of porphyrin to hydroa is by no means a simple one. We have seen that in a great many cases porphyrin has not been demonstrated. This may, of course, be due to inadequate methods. It may be that in such cases there is an excretion of the colourless porphyrinogen discovered by Fischer, and that this only becomes converted into porphyrin in the skin, perhaps under the influence of light itself.

The porphyrins of the urine and fæces are not identical with hæmatoporphyrin. They are intermediate products in the conversion of hæmoglobin into bilirubin and due to a metabolic error. Attempts to sensitise with them produce milder symptoms or none at all. Several reduction-products of hæmin, *e.g.*, mesoporphyrin, *though giving the same spectrum*, have quite different powers of sensitising mice; mesoporphyrin having none. Hæmatoporphyrin taken by mouth is not absorbed (Fischer). In investigating cases of hydroa, it is therefore most important to determine the exact nature of any porphyrins discovered.

With regard to the failure to demonstrate porphyrin in any individual case, it is, however, important to remember that, in

animals injected with hæmatoporphyrin, sensitiveness to light is still present when porphyrin can no longer be found either in the blood, bile or urine. Meyer-Betz was still sensitive 2 months after the injection of porphyrin, though it had disappeared from the serum within 3 days.

It is even more puzzling that there are many instances of copious excretion of porphyrin without light-sensitiveness. While the eruption is common in cases of porphyrinuria of unknown origin, it has never been described in association with acquired toxic porphyrinuria of known origin, *e.g.*, from sulphonal, except in one case after ingestion of luminal.

Even the injection of hæmatoporphyrin does not necessarily sensitise to light. Vinchon and Bourgeois allude to the successful treatment of melancholia by this method. In severe forms they give about 10 intramuscular injections of about 2 c.c. of a 0·5% solution, and have never seen it sensitise to light.

In Meyer-Betz's experiments the reactions to the Finsen lamp had some resemblance to hydroa, but the effects of sunlight were neither so localised nor so deep and destructive. When injected intravenously hæmatoporphyrin is evenly distributed, and differences of reaction depend only on differences of exposure to light. In hydroa, on the other hand, Meyer-Betz suggested that possibly the hæmatoporphyrin is formed or deposited at certain points only, or that in the course of the disease some parts of the skin become desensitised.

Many recent observations point to porphyrinuria being due to impaired function of the *liver*. Suner, Perutz and Günther have shown that fresh, digested, acidified or alkalised liver can destroy porphyrin or remove it from solutions. Similar preparations of other organs cannot. Günther thinks that porphyrin is chiefly formed in the intestine, whence it is absorbed into the circulation and taken up by the normal liver. Carrié has shown that in rabbits porphyrinuria produced by sulphonal can be abolished by feeding with liver. Since in this respect watery extracts of liver are useless, it is probable that ingested liver destroys the porphyrin in the intestine before it can get into the circulation. Sulphonal is thought to produce porphyrinuria by damaging the liver in such

a way that it fails to take up the porphyrin reaching it from the intestine. In one case of hydroa Stein noted hepatic insufficiency by the galactose test : as the eruption receded the liver-insufficiency disappeared. In some cases of congenital porphyrinuria there are gross liver-changes. Urbach and J. Blöch describe 2 cases in which hydroa was associated with porphyrinuria and with impaired liver function.

Attempts to settle which are the rays responsible for hydroa have also been a little disconcerting. Scholtz, Moro and Pautrier could find no abnormal reactivity to U.V.R., and Arzt and Hausmann failed to reproduce hydroa-lesions even after repeated irradiation with Finsen and Kromayer lamps. But Scolari produced immediate characteristic pemphigoid lesions with U.V. rays and visible rays with wave-lengths shorter than 5,090 A.u. Eidinow states that the lesions are aggravated by the blue-violet visible rays. L. Freund found an abnormal reactivity to U.V. rays between 3,960 and 3,250 A.u. This was confirmed by Martenstein, who further showed that their potency increases as the wave-length diminishes. With rays shorter than 2,800 A.u. he found not only that the effect was abnormally intense, but that the incubation-period vanished, so that the earliest phase of the reaction resembled that of heat-rays. To alpha, beta, gamma and X-rays he detected no over-sensitiveness. But Epstein has reported that in a typical case of hydroa there arose, 6 days after application of thorium X ointment (when the usual erythema, which was actually somewhat weaker than in controls, was already subsiding), an eruption of characteristic hydroa-blisters, confined exactly to the irradiated area.

Thus such positive evidence as there is incriminates the U.V. rays, and possibly the blue-violet, as causative in hydroa ; whilst, on the other hand, in experimental sensitisation with porphyrin, it is the luminous rays, chiefly in the orange region, that are concerned (Hausmann, Campbell and Hill, and Dhéré). It is true that Hausmann and Sonne did sensitise red blood-cells to U.V.R., but mainly to the longer-waved about 3,655 A.u.

Whether porphyrin is demonstrable or not, experimental irradiation of hitherto unaffected areas of the skin of hydroa-

patients usually produces the first time only a normal reaction, repeated exposures being necessary to evoke hydroa. The mechanism is therefore not a simple general photodynamic sensitisation : the light itself must first produce certain changes in the skin. As a complement to this, Scolari reports a case in which exposure of the hands or face to U.V. or heat-rays, or even Finsen lamp with compression, produced no eruption, though severe characteristic lesions could be evoked on the skin of the back ; this points to the uncovered parts having attained some kind of immunity.

As opposed to the usual hypothesis that hydroa is due to a circulating substance sensitising the skin to light, Werther thinks that, on the contrary, light brings about physical changes in the skin-cells, rendering them more prone to disorder, and that then some circulating substance brings about the dermatosis. He was led to this view because the typical reaction cannot be produced experimentally on all areas, but only where light-stimuli have accumulated. An analogy is given by a salvarsan-erythema which was confined to, and exactly coincided with, an area previously X-rayed. Werther's view would help to explain Epstein's case, but is difficult to reconcile with Scolari's production of *immediate* lesions with U.V.R. on covered areas.

Yet another possibility is that porphyrinuria can be the result rather than the cause of dermatoses. Goeckerman, Osterberg and Sheard first showed that solar *eczema*, too, was sometimes associated with porphyrinuria. In their patient the hæmatoporphyrin in the urine was increased 250% after general irradiation with U.V.R. Similarly, Templeton and Lunsford experimentally produced porphyrinuria in 11 out of 16 non-light-sensitive persons by means of suberythema or mild erythema doses of U.V.R. In normal controls they could find no trace of porphyrin, but they did find it occasionally in patients with widespread dermatoses unrelated to light.

Eosin. Dermatoses have been described by Prime in patients who had for a long time taken eosin therapeutically. There was swelling of the face and hands, followed by pruritus and scratch-effects. The nails became loose and black, a symptom which has

also been observed in hydroa vacciniforme with porphyrinuria by Arzt and Hausmann. It sensitises to green rays.

ACRIDINE DERIVATIVES. In some cable-works where coal-tar and pitch were used, Lewins reported that the workers complained of burning and itching followed by erythema of the parts of the skin exposed to light. He considered that acridine was responsible, or possibly anthracene or anthraquinone bodies. I have seen severe vesicular dermatitis follow mild irradiation with the quartz-lamp after the use of crude coal-tar paste, and Herxheimer has described solar dermatitis after painting with carboneol fluid.

Recently Jausion has described frequent sensitisation following the treatment of gonorrhœa with *acriflavine* or gonacrine (euflavine). Within 48 hours of the injection an intense erythema develops on the uncovered parts and a few pruriginous spots at a distance. The whole body, but particularly the face and hands, becomes super-pigmented. This sensitisation actually starts immediately after the injection and begins to decrease after 48 hours and then rapidly disappears. The degree of sensitisation runs more or less parallel with the amount of flavine being excreted in the urine (Ambrogio).

Following these observations, Oppenheim suggested treating psoriasis by injecting acriflavine intravenously and then irradiating. But Haxthausen reported a case in which this treatment not only unfavourably affected the psoriasis, but also gave rise to a peculiar *persistent* supersensitiveness to daylight. Experiments proved that the sensitiveness was to the U.V.R. between 4,000 and 3,400 A.u., and that it was not confined to the face and hands. The sensitiveness was probably not due to retention of the acriflavine; for, according to Hausmann and Krumpel, acriflavine sensitises to luminous rays around 4,580 A.u. [It also has a second absorption-maximum at 2,650 A.u., but these rays would not be present in daylight.] The experiments were made 6 months after cessation of treatment and no flavine could be detected spectrographically in the serum or urine.

CHLOROPHYLL. Kitchevatz states that, if an area of skin is lightly scratched and treated for an hour with a solution of chlorophyll, it will in certain individuals become inflamed and

subsequently pigmented by exposure to red rays but not to U.V.R. It is, of course, to the red rays that chlorophyll renders plants responsive. Kitchevatz thinks this may explain the disease described by Oppenheim in Austria in 1926 under the name *dermatitis bullosa striata pratensis*. In his series of 40 patients, all of whom had been bathing in the river and had dried themselves by lying in the grass, there developed 24 hours later a characteristic rash, consisting of a criss-cross of bright red vesicular or bullous streaks, rather suggesting artefact, limited to those parts of the skin that had been in actual contact with the grass. Many cases have since been reported in other countries, and Corsi reported the first English case in 1933. After a week the inflammation subsides but leaves behind a marked pigmentation which persists for some months. It affects particularly those parts of the skin that have been super-pigmented by sunlight, and in a case of vitiligo the leucodermic areas escaped.

Salvarsan, Mercury, Gold. A patient of Juon's had a generalised dermatitis after treatment with salvarsan and mercury: following this, and lasting for 9 months after the treatment, there arose a supersensitiveness to natural sun and to the mercury-vapour lamp. Investigation revealed that he was also oversensitive to X-rays, thorium X, mercury, formalin and cutaneous application of salvarsan. The sensitiveness to mercury and salvarsan (the latter being the more pronounced) had arisen during the treatment. Percutaneous application of salvarsan in subliminal doses sensitised to subliminal doses of U.V.R. and *vice versâ*. This was therefore a case of polyvalent sensitisation, especially to salvarsan and light. The sensitiveness to both agents disappeared together after several months.

The peculiar pigmentation in exposed areas sometimes produced by gold has been described on p. 327.

Bacterial Sensitisers. Grosz and Volk have shown in animals that infection with tuberculosis, or even intracutaneous injection of killed bacilli, increases the sensitiveness of the skin to light. Colon bacilli can have the same effect. Eidinow has shown that some streptococci and some lactose-fermenting coliform bacilli contain substances which render red blood-

corpuscles or Paramecia vulnerable to the blue-violet visible rays. Frei has described an urticarial reaction in a consumptive produced by luminous rays.

OTHER POSSIBLE SENSITISERS. Barber and Howitt draw attention to the substance which is normally present in, and can be partly extracted from, the skin, and which gives a blue fluorescence in Wood's light. Its amount in the epithelium varies with the latter's sensitiveness to light and perhaps determines it. In summer-prurigo they nearly always found an unusual flora in the fæces, intestinal delay and hypochlorhydria. They thought the sensitiser might be either a decomposition-product of protein or a bacterial, probably streptococcal, toxin. Haxthausen finds that the serum of 60% of subjects of polymorphous light-eruptions sensitises red cells. The frequent coincidence of the attacks with monthly periods suggests that in some instances the sensitiser may be connected with the menstrual cycle. Barber has observed acquired sensitiveness to sunlight after a severe attack of food-poisoning and after a bout of dietary excess resulting in enlargement of the liver.

In cases of polymorphous light-dermatitis Haxthausen has found that it is possible to evoke the eruption with carbon-arc or mercury-vapour lamps. Sometimes the response is characteristic from the beginning, but in others there is at first a diffuse erythema, which is only gradually converted into a papular dermatitis. The most characteristic prurigo-like eruptions are obtained by repeated irradiation of the same portion of skin. Most frequently he found the only active rays to be the U.V., but a number of observers, including Barber, Howitt, Urbach and Konrad, have had cases in which the visible rays were responsible.

Duke and Ward have reported cases of urticaria produced by visible violet rays, the sensitiser being unknown.

There is no doubt that in many cases we are not dealing with a primary sensitisation to light, but with autosensitisation following an initial actinic erythema. Early experiments of Sellei and Liebner in summer-prurigo showed that irradiation of various regions of the body-surface resulted in the development of the characteristic eruption not at the treated sites but only at the

sites of election, viz., the face and extensor surface of the arms. Moreover, after irradiation of one arm the same degree of reaction appeared on the non-irradiated arm as well. Liebner thinks that products of the damaged epithelium are conveyed by the blood and cause inflammation of the cells at the sites of election, which presumably had become sensitised by previous and constant exposure.

It seems to be also possible for the products of damaged skin-cells to sensitise the rest of the skin to light. I have observed a high degree of temporary supersensitiveness to sunlight accompanying an autosensitisation-pruritus and urticaria, attributable to an itchy plaque on the leg persisting from an insect-bite.

Impairment of Natural Protection. Anderson and Ayres suggest the possible importance of disturbed sulphur-metabolism, leading to diminution of cystine in the hair and horny layer, where it is normally present in relatively high concentration. According to Ward cystine is the only amino-acid exerting any marked absorption of solar ultra-violet rays. This mechanism is thought to be especially likely in the ætiology of pellagra (Smith). It is interesting that just those foods found useful as preventatives of pellagra are exceptionally rich in cystine. It may also explain the value of sodium thiosulphate in its treatment.

Skin-diseases aggravated or provoked by Light. Being an irritant U.V.R. may be expected to aggravate certain skin-affections already present. Secondly, certain disorders to which an individual is liable can remain latent until evoked by some agency, such as light. Thirdly, the cutaneous changes produced by light may predispose to the subsequent development of other disorders.

Eczema. The seborrhœic type and the form developing from streptococcal pityriasis on the face are especially susceptible, and complete exclusion from light is sometimes an important part of the treatment.

Erythema Exsudativum Multiforme. There is no special photogenous form, but light is one of the determining factors of the attacks. The incidence is highest in June (Haxthausen).

Lupus Erythematosus. See Chapter IX.

ROSACEA. Most cases are made worse by U.V., luminous and heat-rays.

URTICARIA. Many observers have described immediate whealing confined accurately to areas exposed to U.V.R. After subsidence of the wheals the residual erythema is no stronger than normal. Now according to Lewis the development of erythema or urticaria depends respectively on the slowness or rapidity of the liberation of H-substance. This accords with the observation that in light-urticaria the latent period is absent, but it does not explain instances in which the wheals disappear and after the usual latent period a normal erythema develops. Probably the immediate wheals are produced by the longer-waved U.V.R. and visible rays, and the delayed erythema by the shorter U.V. acting on the epidermis.

FURUNCULOSIS, ECTHYMA, ACNE AND NEURODERMATITIS. These can also be aggravated.

The Diagnostic Use of U.V. and Infra-red Rays. ULTRA-VIOLET RAYS. Their chief diagnostic value is in the detection of *ringworm* of the scalp, and the method has been described on p. 359. Normal skin, viewed by Wood's light, is hardly illuminated, but the nails and all hyperkeratotic structures fluoresce bluish white. *Psoriasis* appears silvery and *seborrhœic dermatitis* rather more orange. Vaseline gives a brilliant blue fluorescence.

Wood's nickel-oxide glass filter only permits the passage of rays around 3,660 A.u., close to the visible violet. Goodman, using a filter which allows the passage of U.V.R. down to 2,400 A.u., has made some interesting observations. In cases of dermatitis some clues may be found as to the cause. Thus in dermatitis produced by *hair-dye* he noted that the usual dark shadow denoting erythema merged into an area of the scalp which, together with the hair upon it, fluoresced brilliantly. *Iodine* fluoresces yellowish grey many days after application. *Rouge* and *nail-polish* appear red or reddish brown, and *face-powders* some of them brilliant violet-blue and others reddish. Natural fair hair gives a variety of colours, yellow, brown, etc., while bleached fair hair is homogeneous except at the root. Pigmented areas look much darker than by ordinary light, so that *leucodermia* stands out by contrast

more conspicuously. The filtered U.V.R. not only show up *freckles* more clearly, but reveal the presence of many that are invisible in ordinary light. *Molluscum contagiosum*, unlike hyperkeratotic lesions, is very dark, except the central umbilication which is white.

Davidson and Gregory have devised a convenient hand-lamp for Wood's light, which can be fitted to any electric light plug. It consists essentially of a Mazda "photoflood" lamp and a filter consisting of two thicknesses of $\frac{3}{16}$-inch Corning Heat Resistant Red Purple Ultra glass No. 587.

INFRA-RED PHOTOGRAPHY. By this means Haxthausen has been able to demonstrate *varicose changes* in small and medium-sized subcutaneous veins that cannot be recognised by direct observation or by ordinary photography. The great majority of patients with ulcer or eczema of the leg, presenting no clinically recognisable varices but otherwise having the symptoms usually associated with them, were shown by infra-red photography to have changes in the small and medium-sized subcutaneous veins, more pronounced in the affected leg.

Treatment of Light-dermatoses. PROTECTION AGAINST LIGHT. Preparations for protection against U.V. rays include 2–4% æsculin, ultra-zeozone ointment, and naphthol sulphuric acid 2–4% in lanoline (antilux). Wettenhall recommends *quinine alkaloid* 1½% in vanishing cream. *Tannic acid* 10% in spirit, first suggested by Meyer and Amster, is an exceedingly effective and convenient prophylactic. If it dries the skin too much a little castor-oil can be added. Jausion and Pagès have proved the efficacy of *coconut-oil* in preventing erythema while, if anything, it increases pigmentation. Against luminous rays the best protective is *resorcin* 3% in zinc paste (Urbach and Konrad).

DESENSITISATION. For sensitisation to light induced by euflavine Jausion and Marceron found that 0·25 gm. of *resorcin* per day by mouth prevented relapses in patients already affected and protected new patients from any solar erythema. It is best given a quarter of an hour before the injection. But since resorcin can give rise to digestive disturbance and even occasionally a mild eczema, Jausion and Pecker gave it up in favour of *pyrocatechin*,

which, being soluble in water, can be injected intravenously and is perfectly tolerated. The average daily dose is 2 mgm., but it can be safely increased to 5 mgm. They probably act by virtue of their reducing power, which antagonises the oxidising action of light. Resorcin, 0·5 gm. internally, was also found useful in Urbach and Konrad's case of summer-prurigo, in which the luminous rays were responsible but the sensitiser unknown.

If porphyrinuria is present or any suggestion of hepatic insufficiency, it is well to administer *liver* by mouth. Goldschlag has had some successes with *insulin*. In acquired light-sensitiveness Barber and Howitt have found that improvement follows the correction of intestinal stasis and hypochlorhydria and the injection of a vaccine of intestinal organisms (mass-vaccine of Danysz).

Non-specific methods of desensitisation generally fail, but Castle had a success with peptone intravenously.

When there is much œdema, Teissier and Tanon recommend giving *xylol* for its dehydrating effect. The dose is slowly increased up to about 100 drops a day. It may, however, provoke hyperkeratosis and cicatricial melanodermia. *Red* and *infra-red rays* are also useful in aiding the resorption of inflammatory products, as well as of excessive pigment.

For solar eczema Jausion and Pagès give *hyposulphite of soda*, dried, 0·5–2 gm. and resorcin 0·05–0·2 gm. daily, preferably in the morning. If exudation is extreme, they administer two or three times a week sodium hyposulphite 5 gm., pilocarpine nitrate 0·005 gm. intravenously, and resorcin 0·25 gm. by mouth. If these measures are inadequate they recommend 5–10 intramuscular injections of the patient's freshly passed *urine* ½–5 c.c. at intervals of 3 days.

Actinotherapy. General Irradiation. The most exactly known general effect of exposing the skin to U.V. rays is through the production of vitamin D by the activation of ergosterol. This reaction probably takes place chiefly in the region of the stratum granulosum under the influence of wave-lengths in the neighbourhood of 2,800–3,100 A.u., but also to a slight extent in the subepidermal capillaries by means of somewhat longer U.V.

rays (Lucas). According to Hsiang Ch'uan Hou (1930) a large proportion is actually formed on the surface, for the healing of rachitic rabbits by means of a certain dosage of U.V.R. is delayed if the irradiated skin is previously cleaned with ether. Irradiation of a circumscribed portion of the skin causes some activation in non-irradiated areas.

But vitamin D is not the only substance absorbed into the blood-stream from irradiated skin. Physiologically the epidermal cell-walls allow only a small amount of material to pass in and out; light and other stimuli increase their permeability and a heightened cell-metabolism (shown by deeper staining and by certain nuclear foldings, such as are also observed in endocrine glands) results in a larger amount of substances being given off (Memmesheimer).

The tyrosin-level of the blood is distinctly raised after irradiation but falls again rapidly at the beginning of clinically appreciable pigmentation (St. Rothmans). The products of irritation of the skin, which appear to originate not from dead (necrohormones) but from young strong cells, as well as showing other resemblances to histamine excite the liberation of gastric juice. They also increase the number of eosinophil cells in the blood; this probably explains the frequent eosinophilia in so many extensive dermatoses.

Eidinow has demonstrated that exposure of a portion of the skin to U.V.R. increases the bactericidal power of the blood flowing through it; but the blister-fluid obtained by massive irradiation is not more bactericidal than normal serum. He further found that (1) previous prolonged irradiation of rabbits with combined infra-red, luminous and U.V. rays increased their resistance to injected virulent staphylococci; (2) identical irradiation after injection did not increase resistance; (3) the results were not related to the production of vitamins A or D. He finds that the maximal increase in hæmobactericidal power in man is obtained when minimal erythema is produced over one-sixth of the total body-surface. Accordingly, for short-ray-therapy, he recommends that such a dose should be given two or three times a week and that an interval of 10–14 days be allowed between irradiation of any one area.

In dermatology general irradiation is of most value for tuberculosis (see Chapter VIII.). Volk and Wichmann found that a combination of heat and U.V.R. produces the best results. Natural sunlight appears to contain the best mixture, especially on the sea-coast. Volk gives 15-minute exposures of the carbon arc, doubling them every other day up to a maximum of 1½ hours. Mercury-vapour lamps, so effective in rickets, are definitely inferior to the carbon arc for tuberculosis. At the Finsen Institute they have recently introduced the "Universol" lamp, in which pure carbons are replaced by Siemen's "Schneeweisskohlen," whose emission more closely resembles sunlight. This lamp produces erythema in a much shorter time and has better therapeutic influence. The light-baths are given to the patient lying down every day or every other day. The dose should produce a moderate erythema; it is increased gradually. It should not be continued uninterruptedly for more than 3 months, after which there should be a pause of about 1 month.

General irradiation is also sometimes of value in acne vulgaris, erythrocyanosis frigida, mild xerodermia and chronic relapsing erysipelas.

Local Irradiation. *Lupus Vulgaris.* The Finsen lamp produces a deeper effect than is theoretically to be expected: this is not due to the luminous rays; for if the U.V.R. are cut out the remaining rays have no noticeable effect on the skin. As Finsen already knew, a small content of blood will absorb practically all the U.V.R.; therefore effective compression is absolutely indispensable for a deep effect.

Lomholt examined the penetrating power and effects on the human skin of various portions of the U.V. spectrum by passing them through shaved newly killed albino rat-skin together with selective filters. He found that:—(*a*) the longest-waved U.V. rays, around 3,880 A.u., which are powerfully emitted by a carbon arc burning by continuous current, could penetrate 1 mm. of rat-skin, caused a weak but distinct erythema and had only a slight effect on superficial lupus-nodules; (*b*) the rays around 3,660 A.u., powerfully emitted by the Kromayer lamp, had similar properties to (*a*): acting through rat-skin ½ mm. thick they produced hardly

a noticeable effect, even after an hour; (*c*) the short-waved rays around 3,130 A.u., also emitted from a Kromayer lamp, had a much stronger biological action, producing erythema rapidly: a faint erythema was obtained even through rat-skin of 0·5 mm. Then why has the Finsen lamp an even stronger depth-effect than the Kromayer? Lomholt proved that it is due to the field between 3,200 and 3,400 A.u. These rays are produced in greatest quantity from nickelled carbons, whilst the mercury-vapour lamp has only one small very weak band in this field.

It is not practicable to make even moderate quantities of biologically active light-rays penetrate deeper than about 1 mm. The success in curing lupus deeper than this level is partly due to successive irradiations gradually raising the diseased tissue to the surface and destroying it in layers. Recent lupus hardly extends as deep as 1 mm. but relapses in old plaques are often as deep as 6 mm.

In Lomholt's new lamp he filters off not only the infra-red but also the luminous rays: efficiency has been increased by approximation of the carbons to the lens and replacement of natural quartz by fused silica; there is automatic control so that one nurse can supervise three treatments at the same time. He claims for it better as well as more rapid therapeutic results than with the older Finsen lamps. Each area, which must include a zone about 5 mm. wide around the diseased focus, is irradiated for $\frac{3}{4}$–1 hour, at least three to four times, in as rapid succession as possible, provided that it is covered with new-formed epithelium before the next treatment.

Friboes and also Konrad think there is advantage in injecting 5–10 c.c. of $\frac{1}{2}$–1% solution of acriflavine intravenously shortly before irradiation.

Erysipelas. Success was first reported by Petenyi and has since been amply confirmed. Ude and Platou in a large series found that U.V.R. led to recovery 3–4 days earlier than treatment with magnesium sulphate and glycerine pack and other methods, and in 92% of cases brought about clinical arrest after the first exposure. The dose was such as to produce a reaction just short of vesiculation. Davidson, using the air-cooled quartz-lamp, is

also convinced of its efficacy. He gives twice the erythema dose and includes a 1½-inch margin of normal skin.

Acne Vulgaris. U.V.R. have no specific effect but can be used to induce exfoliation, which seems to be an essential reaction for the cure of this disorder. Smaller doses are useless and may even aggravate. They are not quite so effective as sulphur and resorcin paste but are a pleasanter treatment where large areas are involved, for instance, over the back.

Telangiectasia. Port-wine stains and angioma serpiginosum sometimes yield satisfactorily to the Kromayer with compression or to the Finsen-Lomholt lamp.

Indolent ulcers can be stimulated to epitheliate by very small doses. Heald recommends the prior application of a very thin film of liquid paraffin.

Xanthelasma. See page 160.

Vitiligo. In addition to the methods mentioned on page 76. Jausion and Pagès have elaborated a method based on first stimulating the formation of pigment and then dispersing it. This has the effect of evening-out the achromic and hyperchromic areas, though not completely : the effect, however, is said to last at least 1 year. The first stage, which lasts 20 days, consists of 10 intravenous injections of 5 c.c. of euflavine 2%, inunction of coconut-oil and subsequent exposure to the sun or mercury-vapour lamp. This greatly exaggerates the contrasts, and the patient should be warned. The second stage follows after a fortnight's rest, and consists of 10–20 exposures to the highest tolerated doses of red and infra-red rays, preceded by injections of hypo-sulphite of soda 5 gm., pilocarpine nitrate 0·05 gm., methylene blue 0·01 gm., intravenously ; the object of the methylene blue being to sensitise to the infra-red.

X-rays

Measurement of Dosage. There is great confusion in the expressions used to describe doses. It is impossible to define the degree of erythema to be taken as the skin-unit. It should be realised that, whereas the erythema-dose as generally understood

by dermatologists is one which produces a just appreciable erythema, Winz's H.E.D. (Hauterythem-dosis) induces a strong erythema followed by pigmentation lasting for months or years. It is therefore much more exact to express dosage in " r " units. " r " is the absolute unit of quantity of X-rays fixed internationally in 1928 and determined electrically by their ionising effect on air. The older unit " R," calibrated against radium and called the Röntgen, is equal to 1·066 r. For X-rays generated at 100 kV. the dermatologist's erythema-dose is about 350 r, whereas Winz's H.E.D. is about 600 r (Epstein).

Miescher (1924), as the result of extensive tests on normal skin, concluded that within the range 60–180 kV. its sensitiveness is independent of their hardness. Schreus (1932) also considers that the tolerance-dose is about 600 r equally for hard and soft rays, up to a half-value layer of 3 mm. Al. Miescher has shown that for different wave-lengths the erythema-dose runs much more closely parallel with the iontoquantimeter readings than with S.N. pastille readings. The sensitiveness of the *pastille* decreases as the wave-length increases.

As regards *filters* Wucherpfennig has shown that the glass wall of tubes varies so much that the difference may even be equivalent to ½ mm. Al. At 100 kV. Epstein finds that the S.N. pastille tint B dose *with or without ½ mm. Al. filter* equals 300 r. Therefore for practical purposes this filter does not qualitatively alter the beam of rays, but merely entails a longer exposure.

Epilation. Using 100 kV. Epstein gives 240–270 r to each field, and he says that the margin between this and an erythema-dose may be very large, even up to double. This is fortunate, since Molesworth and Riddle (1935) conclude from theoretical and experimental data that the angle of incidence of a beam of X-rays has little or no practical influence on the dose actually absorbed in tissue lying immediately below the surface irradiated. Consequently in the Adamson-Kienböck technique, at any practicable focus-skin distance, the areas where overlap occurs receive a dose very considerably greater than that received at the centres of irradiation. Thus the margin between the smallest dose that will cause epilation and the largest which will just fail to prevent

regrowth must be very much greater than has been imagined hitherto. Epstein (1933) had also shown that the dose at areas of overlap is almost double the direct dose. Through an accident he was able to observe that an exposure of double the dose intended was in fact followed by no ill-effects.

Malignant Disease. Copeman and Gouldesbrough (1929) have introduced a method of sensitising the growth by painting it beforehand with soluble fluorescein 2–5% with the addition of sodium bicarbonate 2% and glycerine ½%. They state that the secondary rays responsible for the therapeutic effect are quite different from the secondary X-rays produced by metals subjected to X-ray bombardment and are best evoked by using fairly soft X-rays. Fluorescein has also been administered intravenously in solutions of similar strength in doses of 20 millilitres, or orally in powders or capsules of 1–3 gm.

Colwell and Creed, however, in experiments with mice, tadpoles and amphibian ova, found that sodium fluorescein made no difference to the effects of X-rays. But in the course of their work they noticed that it was an excellent antiseptic, inhibiting the growth of staphylococcus aureus and bacillus coli even in a concentration of 0·5%. Since it is known that septic changes militate strongly against the success of X-radiation, Colwell thinks it likely that in those instances where fluorescein has appeared to assist X-rays it has done so by controlling sepsis.

For basal-celled growths less than 4 cm. in diameter Molesworth recommends a single dose without previous curettage. If the depth does not exceed 0·5 cm. he gives 120 kV., 1 mm. Al., 1,200 r., and for deeper ones 140 kV., 4 mm. Al., 1,350 r.

Coste (1926) urges the following technique:—(*a*) *a medium wave-length*, thinking that efficacy depends on the total quantity absorbed and not on any superior selectivity of the hard (short-waved) rays; (*b*) *absence of any filter*; (*c*) *a single session*, for results indicate that the cells are fully sensitive even when not in a state of division and the connective tissue is much less gravely damaged than by repeated treatments. He uses a spark-gap of 16 cm. between points, and the dose varies from 1–8 skin-units, according to the type of lesion.

He uses a similar technique for the *verrucous forms of tuberculosis*. Though each given area is only X-rayed once, a larger surface should not be covered at each session than 30 cm.^{2}. The dose varies from 3,500–4,500 R., *i.e.*, about 8 skin-units.

The irradiated areas are subsequently douched every day with sterile physiological saline and then dressed with a zinc and bismuth ointment. When the diseased parts have begun to necrose, one may use some pressure to facilitate their separation. A consequent radiodermatitis is very rare and always quite mild.

Pruritic Disorders (see also p. 121). Irradiation of the spinal column has been introduced for pruritic disorders, including lichen planus. Different techniques have been used, corresponding to different ideas as to the actual structures it is intended to influence, whether spinal nerve-roots or the sympathetic chain. Originally the spine was irradiated perpendicularly, but better results were claimed with the cross-field technique of Bordier. Schoenhof gives the following method. According to the situation of the affection, either the thoracic cord or the lumbar cord alone is irradiated in two fields or the whole spinal column in four fields (two to each side), with an inclination of the tube to 45°. Each field receives one-third erythema dose of hard rays, filtered through ½ mm. of zinc and 1 mm. of aluminium. It is repeated two or three times with intervals of 2 weeks.

Hæmangiomata. Molesworth considers X-rays the method of choice, especially in the cavernous type, and advocates treatment within the first 6 months of life, preferably during the first month. At this period the nævus can, in most cases, be suppressed by a single "normal tolerated" dose, whilst between the ages of 6 months and 1 year this has to be repeated several times.

Radiodermatitis. HISTOLOGY. According to Wolbach (1925) swelling of the collagen of the corium and subcutaneous tissue begins in 48–72 hours and reaches its maximum in a week; connective tissue so altered does not regenerate but new connective tissue is laid down by the surviving and ingrowing fibroblasts. In the superficial layers of the corium minute necrotic foci are formed, leading to polymorphonuclear infiltration. Epidermal

changes, which only begin on the 4th day and consist of swelling of the cells and increased mitoses, he believes to be secondary to changes in the lymphatics and capillaries, caused by the swelling of the collagen. In established chronic X-ray dermatitis there are :—(*a*) loss of epidermal appendages ; (*b*) replacement of normal collagen by peculiarly dense fibrous tissue ; (*c*) obliterative changes in the blood-vessels ; (*d*) necrotic areas immediately beneath the epidermis, generally in the neighbourhood of thrombosed telangiectases ; (*e*) reparative proliferation in the epidermis in response to the necrosis in the corium : the proliferated down-growths are imperfectly keratinised ; as the degenerative changes in the deeper tissues are progressive there is a constant call for epithelial proliferation greatly in excess of the normal—a state predisposing to cancer.

TREATMENT. The early *erythema* should not be treated with either lotions or ointments containing aluminium acetate, lead, mercury or silver. Iodoform and iodine must also be avoided. Cocain and anæsthesin by contracting the peripheral vessels can lead to ulceration. It is best to use a bland fatty ointment for several months (Bandhauer). For *cracks* in the fingers and nails Colwell and Russ recommend collodion or a cod-liver oil ointment. For *warts* wide excision followed by skin-grafting is the ideal method, but more commonly CO_2 snow or electrocoagulation is preferred. It must be remembered that the destructive effect of these agencies is much greater and repair much slower in an area affected by radiodermatitis than in normal skin. Superficial *ulcers* may eventually heal, and at first treatment may be conservative. Colwell and Russ recommend the application of zinc stearate powder, covered with impervious material ; sometimes saline compresses similarly covered act better. If there is severe pain, excision and plastic surgery will generally be required, though electrocoagulation may succeed. The uses of plastic surgery for chronic radiodermatitis have recently been specially studied by Gillies and McIndoe. As it is absolutely necessary to reach healthy tissue in every direction and since the changes may appear very late, operation must not be performed too soon.

Bröcker has found that infra-red rays act very beneficially on already existent X-ray burns, though they have no prophylactic influence.

Any further irradiation with radium or X-rays is condemned by most authorities. Nevertheless, good results have been reported in late radiodermatitis by Rost and Uhlmann (1932) with emanation ointments (50–100 electrostatic units in 1 gm.). Similarly, thorium X ointment (1,000–2,000 electrostatic units in 1 gm.), first used for this purpose by M. Jessner in 1925, has proved very useful (Epstein).

Radium

Radon. The chief innovation in the employment of radium in dermatology is in the use of radon *seeds*, with which extremely satisfactory results are reported by Roxburgh in *keloids*, *cavernous angiomas*, *subungual warts*, *rodent ulcers* and *squamous epitheliomas*. Some of the cases of keloid and rodent ulcer had failed to respond to X-rays or radium-plaques (beta-rays). O'Donovan and Brain have found radon effective for *non-syphilitic leukoplakia*.

Radon, or radium-emanation, is the first degradation-product of radium, by the loss of one alpha-particle from the atom. In treatment by radium the supply of radon is replenished as fast as it is used up, whereas in treatment by radon the amount is always diminishing, but at a known rate. For practical purposes it may be reckoned to decay completely in 1 month, reaching its half-value in 3·825 days. The amount of radon in equilibrium with 1 mgm. of radium is called a "millicurie." The following table shows how the dosage of radon can be compared with that of radium :—

One millicurie of radon left in position for . .	1	2	3	4	5	6	7	8	9	10	30	days
Is equivalent to .	22	40	56	68	79	88	96	102	107	111	133	mgm. hours
								(O'Donovan and Brain)				

Roxburgh uses the glass seeds in little cylinders of platinum 6 mm. long and 1·25 mm. in diameter, the walls being 0·5 mm.

thick, thereby cutting off all alpha-rays and practically all the primary beta-rays. He attributes their efficacy to the fact that, being left in position for 7 days, they subject the growth to a small quantity of almost pure gamma-radiation for a prolonged period, which seems to be more effective than a big intensity for a short period, as in the case of radium or X-rays. If it is desired to use beta-rays, the glass seeds can be inserted bare or, for surface-application, can be attached to strapping or Columbia wax: a filter of 0·1–0·2 mm. of aluminium is interposed to cut off the softest beta-rays.

For a small growth the seed is inserted into a track made under it with a large intramuscular needle or double-edged tenotome, and the attached thread is fixed with collodion. If the growth is over 0·6 cm. in length, 2 seeds are used, parallel to each other, 1 cm. apart. For a larger growth they are arranged round the periphery, either radially or tangentially, always with an interval of 1 cm. between their centres. If it is too large to be dealt with from the periphery alone, an inner ring is used, but in no case should a seed be placed in the centre as it leads to an overdose. About 100 mgm.-hours of gamma-rays are required for each square centimetre of surface for rodent ulcers and 150–200 for squamous epitheliomas. These doses are obtained from 1·1 and 1·65 to 2·2 millicuries respectively, left in position for 7 days.

If platinum seeds are used for surface-application, they must be separated from the skin by at least two thicknesses of adhesive strapping or by several layers of lint or by ½–1 cm. of Columbia wax to cut off the secondary beta-rays given off by the platinum, which would ulcerate the skin. The distance also ensures a more even exposure. For *angiomata* in babies about ¼–½ a millicurie per cm.^{2} is enough. Experience with this method is still very small.

Radon has the following advantages over radium:—(1) it is relatively cheap and the methods of application and dosage flexible; (2) the seeds are small enough to be inserted into positions such as at the inner canthi, where there is little room for a needle; (3) the dose in each seed can be of any required size; (4) it is uniform along the length of the seed; (5) it is simple to store;

(6) owing to its decreasing potency and absence of permanent value the patient can safely go away with a number of seeds in position. Over radium in plaques they have the advantage that gamma-rays can be used ; plaques usually contain so little radium that they have to be used unfiltered, so that their effect depends on beta-rays. In Roxburgh's experience gamma- is preferable to beta-radiation, even for superficial growths.

Brain has made a careful comparison between the results of treatment of epithelioma with platinum radon seeds and with unscreened radium plates. The percentage of cures from a single treatment was higher in the case of radon, but the response to a second or third treatment with radium plates was very satisfactory. He refers to the extraordinary variation in radio-sensitivity even in a single type of lesion. As a rule healing is complete in 4–6 weeks.

The use of emanation-*ointment* for late radiodermatitis has been mentioned. It has also been suggested for *sclerodermia* by Strassburger. K. Linser, using an ointment of 200–300 electrostatic units per gm. at short intervals, has had good results in *eczema*.

Thorium X (Degea). This has a similar action to that of radium-emanation (radon). Bloch in 1916 was the first to recommend thorium X ointment for *sclerodermia*. Several subsequent authors have been favourably impressed. In a considerable series of cases of sclerodermia and *acrodermatitis chronica atrophicans* treated with thorium X at Breslau, Epstein reports beneficial influence in nearly all. In extensive cases it was easy to establish beyond doubt the causal connection between the improvement and the treatment. The best results were in sclerodermia circumscripta. In acrodermatitis chronica atrophicans it had a much better effect on the inflammatory and infiltrative manifestations than filtered X-rays, diathermy or other methods hitherto employed. He uses an ointment of 1,000–2,000 electrostatic units in 1 gm. It is applied with a wooden stick to the diseased area, covered with gutta-percha and bandaged. It is left for 18–48 hours, generally not more than 24. The treatment is mostly repeated at intervals of 6–12 weeks. Such doses are usually followed by vivid erythema and swelling and have sometimes been repeated

as often as ten times; yet late damage has never been observed, though it has been used at the Breslau Clinic for 15 years.

Borderline-Rays (Grenz-Rays; Bucky, 1925)

The borderline-rays are in the portion of the spectrum between the Röntgen and U.V. rays, but much closer to the former. They are composed principally of wave-lengths about 2 A.u. (the wave-lengths used in ordinary X-ray work range from 1·6 to 0·1 A.u.). They are obtained from a special hot cathode metallic tube at about 10 kilovolts. A window of Lindemann's lithium borate glass has to be used, as they cannot penetrate ordinary glass. They are absorbed to the extent of 50% by the first 0·4 mm. of skin and 20% by 10 cm. of air. At the depth of the sebaceous glands there is about 25% of the surface-intensity left, and at the depth of the hair-papillæ only 1%.

The usual therapeutic dose is followed by erythema. With small doses, according to Fuhs and Konrad, this only appears after several days, but after big doses it may appear within 24 hours. Its intensity only slowly increases with the dosage and generally lasts about 3 weeks. Such doses can be repeated every 3 or 4 weeks without harm: chronic radiodermatitis has never been observed. Very large doses may produce a bullous reaction. Even this heals with complete *restitutio ad integrum* without pain or late damage; at most, there may be some shifting of pigment, trifling atrophy and telangiectases. Slight changes such as these appeared on Fuhs's own forearm 2½ years after experimentally exposing it to 4,500 r. Neither temporary nor permanent epilation ensues. Small doses increase pigmentation without erythema.

According to the studies of Herxheimer and Uhlmann on the effects of borderline-rays on the human skin, their action is chiefly on the epidermis; in this respect they differ conspicuously from X-rays. Fuhs and Konrad after doses of 2,000 r were unable to observe histologically any serious damage to elastin, glands, vessels or connective tissue.

Owing to the considerable absorption by the air, the focus-skin

distance must not be more than about 15 cm. Till recently this meant that the diameter of a field could not be more than about 12 cm. But nowadays the Lindemann window is only 0·1 mm. thick and also wider : moreover modern tubes can be loaded with 20 mA., so that the emission is much greater and the beam broader. Owing to the rather deep pigmentation produced, it is best not to screen off the surrounding normal skin, except when high doses are used for circumscribed lesions. The sharp demarcation of the pigmentation is more conspicuous when the focus-skin distance is short and with a Siemens tube than with a Müller.

They have now been tried for the majority of affections of the skin. At Jena, Spiethoff reports that they have largely superseded X-rays. Their great advantage is that treatment can be safely continued as long as the symptoms seem to demand it, and can always be resumed for recurrences. They also have an advantage in regions where it is important to avoid damage to underlying structures, such as hair-papillæ, sebaceous and sweat glands, testes and eyes. Wood and MacKee agree with Fuhs and Konrad that good results are obtained in :—perlèche, perionychia, subacute and chronic eczema, mycosis fungoides, basal-celled epithelioma, angioma cavernosum, plantar warts, psoriasis, lupus vulgaris, *tuberculosis verrucosa cutis*, severe cases of *acne necrotica*, *Darier's disease*, *port-wine stain* and *poikilodermia*. Indeed, Fuhs and Konrad consider that in the last five conditions, and also for *pityriasis lichenoides chronica and varioliformis acuta* and the ulcerated type of *erythema induratum*, borderline-rays are superior to any other method.

Spiethoff from a very large experience stresses the need of elasticity in technique. Higher voltage together with a filter are used for reaching greater depth, and are also required in hairy regions and when longer distance is employed, on account of absorption by the hair and the air. He has had excellent results in the following conditions, for each of which short notes are given of his technique :—

Alopecia Areata. He uses borderline-rays when U.V.R. have failed. The technique is 9 kV., 2,300–4,600 R, every 4 weeks. This produces a strong erythema.

ANGIOMA. In all forms treatment has to be prolonged. In the cavernous variety he considers the results superior to those of radium. The technique, according to the size of the tumour, is 10 kV., 2·5 cm. w/s (window-skin distance), 1,150–1,800 R, or 13 kV. + 0·03 mm. Al. filter, 15 cm. w/s, 690–920 R, intervals of 4–8 weeks. For flat forms 9 kV., 2·5 cm. w/s, 460 R, every 4–8 weeks. If there is no reaction the dose is increased up to 1,150 R. The reactions sometimes only happen after 2 weeks. For *port-wine stain* Spiethoff, Fuhs, Konrad and Samek all agree that this is superior to any other treatment.

CHILBLAINS. 9 kV., 2·5 cm. w/s, 920 R, every week or fortnight.

DARIER'S DISEASE. 9 kV., 15 cm. w/s, 115 R, every week. If there is much hyperkeratosis larger doses may be needed. For the scalp 13 kV. + 0·03 mm. Al., 15 cm. w/s, 115 R.

ECZEMA AND LICHEN SIMPLEX CHRONICUS. They are contra-indicated in acute cases and should not be repeated if they provoke an eczematous type of reaction. In general, the dosage is 9 kV., 2·5 cm. w/s, 230–4,600 R or 15 cm. w/s, 230–2,300 R. For extensive sheets he recommends 15 cm. w/s, 460 R, and subsequently at weekly intervals 230 R, or if there is much infiltration, 460 R. He aims at desensitising the skin against relapses, continuing treatment after apparent healing; generally about 10 exposures. The higher doses are only used for circumscribed areas, *e.g.*, vesicular eczema repeatedly occurring in the same place, and also for hyperkeratotic and vesicular eczema of the palms and soles.

FOLLICULITIS BARBÆ STAPHYLOGENES. 9 kV., 2·5 cm. w/s, 1,610 R. The good effect is enhanced by exposure immediately beforehand to infra-red rays. Fourteen days later, when the reaction to the borderline-rays is generally still present, he repeats the infra-red rays, and after a further 14 days gives another combined treatment and continues in this way till cure is achieved.

LICHEN RUBER PLANUS. For circumscribed or localised forms 9 kV., 2·5 cm. w/s, 230–460 R, and for hyperkeratotic forms 920 R weekly till cured.

LUPOID OF BOECK. For the deep form 13 kV. + 0·03 mm. Al.,

15 cm. w/s, 950–1,900 R, every 2–4 weeks. Superficial forms are treated like lupus vulgaris.

Lupus Vulgaris. Spiethoff considers this the method of choice; 9 kV., 2·5 cm. w/s, 4,600 R, every 4 weeks. If the reaction is inadequate the dose can be increased even up to 22,000 R. The efficacy is enhanced by an immediately preceding exposure to infra-red rays; with this preparation the dose of borderline-rays need seldom be more than 4,600 R.

Mycosis Fungoides. For flat infiltrations 9 kV., 15 cm. w/s, 460 R, once a week. For tumours 13 kV. + 0·03 mm. Al., 15 cm. w/s, 3,800 R, every 4 weeks.

Pigmented, Hairy and Fibromatous Nævi. For these, too, Spiethoff considers borderline-rays the method of choice, but a long course is needed; 9 kV., 2·5 cm. w/s, 4,600 R, every 4 weeks. If there is no reaction it is increased up to 11,000 R, but if more than 6,900 R are used, there ensues some atrophy and occasionally telangiectases.

Plane Warts. 13 kV. + 0·03 mm. Al., 15 cm. w/s, 460 R. The effect may be delayed a few weeks.

Pruritus Ani. 13 kV. + 0·03 mm. Al., 15 cm. w/s, 460 R, after 1 week's interval 230 R; further repetitions once a week till cured.

Pruritus Vulvæ. 9 kV., 15 cm. w/s, 115–230 R, once a week. If this is inadequate, it should be dealt with in the same way as pruritus ani.

Psoriasis. 230–1,150 R; either 2·5 cm. w/s and 9 kV., or 15 cm. w/s and 11 kV., according to the size of the lesions; intervals 1–3 weeks. For the scalp, where they are especially useful (no epilation), 13 kV. + 0·03 mm. Al., 15 cm. w/s, 460–690 R, every 1–2 weeks.

Tuberculosis Indurativa Subcutanea. 13 kV. + 0·03 mm. Al., 15 cm. w/s, 460 R, every 14 days.

Bibliography

Anderson, N. P., and Ayres, S., Jun. "Light Sensitive Dermatoses," *Journ. Amer. Med. Assoc.*, 1934, **103**, 1279.

Anderson, W. T., and Fraser, H. D. "The Penetration of Ultra-violet Rays into Live Animal Tissue," *Brit. Journ. Phys. Med.*, 1931, **6**, 170.

BACHEM, A., and KUNZ, J. "The Transmission of Ultra-violet Light through the Human Skin," *Arch. Physic. Ther.*, 1929, **10**, 50 (*cit.* Habermann).

BARBER, H. W. "The Significance and Pathogenesis of certain Dermatoses," *Practitioner*, 1932, **128**, 209.

BRAIN, R. T. "Radon in Dermatology," *Brit. Journ. Derm. and Syph.*, 1933, **45**, 247.

BRÖCKER, W. "Treatment of X-ray Burns by Long-waved Radiations," *Strahlentherapie*, 1931, **42**, 551 (*Abs. Brit. Journ. Phys. Med.*, 1932, **7**, 222).

CARRIÉ, C. "Hydroa Vacciniforme and Porphyrinuria," *Arch. f. Derm. u. Syph.*, 1931, **163**, 523.

COLWELL, H. A., and RUSS, S. "X-ray and Radium Injuries," 1934, London. Oxford Univ. Press.

COSTE, J. "Roentgenthérapie des épithéliomas cutanés et cutanéo-muqueux," *Arch. d'électric. méd.*, 1926, **34**, 257.

DAVIDSON, A. M., and GREGORY, P. H. "A Convenient Source of Wood's Light for the Diagnosis of Ringworm of the Scalp," *Can. Med. Assoc. Journ.*, 1932, **27**, 176.

DAVIDSON, J. M. "Phototherapy in Erysipelas," *Brit. Med. Journ.*, 1932, **1**, 929.

DEL VIVO, G. "A proposito dell'azione di alcuni olii essenziali sulla pigmentazione," *Giorn. ital. di Derm. e di Sifilo.*, 1930, **71**, 223 and 467 (*cit.* Habermann).

EIDINOW, A. (*a*) "The Local Origin of the Increased Bactericidal Power of the Blood following Ultra-violet Irradiation of the Skin," *Lancet*, 1927, **2**, 963. (*b*) "The Effect of Radiation on the Resistance of Rabbits to Infection with Virulent Staphylococci," *Brit. Med. Journ.*, 1929, **2**, 293. (*c*) "Photo-dynamic Sensitization," *Brit. Journ. Derm. and Syph.*, 1935, **47**, 277.

EPSTEIN, S. (*a*) "Zur Behandlung von Sklerodermie und Acrodermatitis chronica atrophicans mit Thorium X (Degea)," *Arch. f. Derm. u. Syph.*, 1933, **167**, 533. (*b*) "Experimentelle Eruption bei Hydroa vacciniforme durch Thorium X," *ibid.*, 1933, **168**, 67. (*c*) "Die Bedeutung der Ueberschneidungen für das Zustandekommen von Röntgenspätschäden in der Oberflächentherapie," *Arch. f. Derm. u. Syph.*, 1933, **168**, 548.

FREUND, E. "Demonstration von Lichtbildern," *Arch. f. Derm. u. Syph.*, 1928, **155**, 261 (*cit.* Habermann).

FUHS, H., and KONRAD, J. "Dosierungsangaben für die Strahlenhauttherapie," Urban and Schwarzenberg, Berlin, 1933 (*Abs. Brit. Journ. Derm. and Syph.*, 1934, **46**, 112).

GILLIES, H. D. T., and MCINDOE, A. H. "Plastic Surgery in Chronic Radiodermatitis and Radio-necrosis," *Brit. Journ. Radiol.*, 1933, **6**, 132.

GOLDSMITH, W. N. "Berlocke Dermatitis (Pigmentation)," *Proc. Roy. Soc. Med.*, 1933, **26**, 1306.

GOODMAN, H. "Fluorescence: particularly in Dermatology," *Brit. Journ. Derm. and Syph.*, 1928, **40**, 105.

GRAY, A. M. H. "Hæmatoporphyria Congenita with Hydroa Vacciniforme and Hirsuties," *Quart. Journ. Med.*, 1926, **19**, 381.

HABERMANN, R. "Paratypische Pigmentanomalien," *Jadassohn's Handbuch* IV/2, 1933, 796.

HAUSMANN, W., and HAXTHAUSEN, H. "Lichterkrankungen der Haut," Urban and Schwarzenberg, Berlin, 1929.

HAXTHAUSEN, H. (*a*) "Infra-red Photography of Subcutaneous Veins," *Brit. Journ. Derm. and Syph.*, 1933, **45**, 506. (*b*) "Persistent Hypersensitivity to Light after Intravenous Injections of Trypaflavine," *ibid.*, 1933, **45**, 16.

HILL, L. E. "The Penetration of the Skin by Radiation," *Trans. St. John's Hosp. Dermat. Soc.*, 1930, **19**, 66.

JAUSION, H. "Les applications thérapeutiques de la photosensibilisation," *Compt. rend. de la 1ère Conf. de la Lumière*, Lausanne, 1928, 219.

JAUSION, H., and MARCERON, M. "Le 'coup de lumière' acridinique: son traitement préventif par la résoreine," *Bull. Soc. franç. Derm. et de Syph.*, 1925, **32**, 358.

JAUSION, H., and PAGÈS, F. "Les Maladies de Lumière et leur Traitement," Paris; Masson, 1933.

JAUSION, H., and PECKER, A. "Pyrocatechine intraveineuse et désensibilisation à la lumière," *Bull. Soc. franç. de Derm. et de Syph.*, 1927, **34**, 350.

JESIONEK, A. "Licht Therapie des Lupus," *Strahlentherapie*, 1933, **48**, 659 (*Abs. Zbl. Hautkrank.*, 1934, **47**, 604).

JUON, M. "Sensibilisations- und desensibilisationsversuche mit UV," *Strahlentherapie*, 1928, **28**, 180.

KELLER, P. "Ueber die Wirkungen des Ultra-Violetten Lichtes auf die Haut," *Strahlentherapie*, 1928, **28**, 152.

KITCHEVATZ, M. "Dermatitis Bullosa Striata Pratensis: its Pathogenesis," *Ann. de Derm. et de Syph.*, 1934, **5**, 293 (*Abs. Brit. Journ. Derm.* and *Syph.*, 1935, **47**, 42).

KURZ, R. "Untersuchungen ueber die Kölnische-Wasser-Pigmentationen," *Dermat. Woch.*, 1930, **91**, 1614.

LIEBNER, E. "Desensitization experiments in prurigo simplex chronica recidivans æstivalis," *Dermat. Woch.*, 1928, **86**, 799.

LOMHOLT, S. (*a*) "The Effects upon the Skin of Concentrated Ultra-violet Light and its use in Dermatological Therapy," *Brit. Journ. Derm. and Syph.*, 1931, **43**, 385. (*b*) "The Treatment of Lupus Vulgaris," *Brit. Med. Journ.*, 1934, **2**, 291.

LUCAS, N. S. "The Production of Vitamin D by Irradiation of Ergosterol through the Epidermis of a Rat," *Biochemical Journ.*, 1933, **27**, 132.

MACKEE, G. M. "Ultra-violet Therapy in Dermatology," *Journ. Amer. Med. Assoc.*, 1932, **98**, 1553 (*Abs. Brit. Med. Journ.*, 1932, **2**, 67).

MEMMESHEIMER, A. M. "The Skin as an Organ of Protection and Immunity," *Trans. St. John's Hosp. Dermat. Soc.*, 1929, **18**, 67.

MEYER-BETZ, F. "Untersuchungen ueber die biologische (photodynamische) Wirkung des Hämatoporphyrins und anderer Derivate des Blut-und Gallenfarbstoffes," *Deutsch. Arch. f. klin. Med.*, 1913, **112**, 476.

MIESCHER, G. (*a*) "Das Röntgenerythem," *Strahlentherapie*, 1923–24, **16**, 333. (*b*) "Die Schutzfunktionen der Haut gegenüber Lichtstrahlen," *ibid.*, 1931, **39**, 601 (*cit.* Habermann).

MOLESWORTH, E. H. "Importance of Early Treatment of Vascular Nævi," *Med. Journ. Austral.*, 1933, **2**, 217 (*Abs. Brit. Journ. Derm. and Syph.*, 1934, **46**, 445).

MOLESWORTH, E. H., and RIDDLE, A. R. "The Effect of the Angle of Incidence upon the Dose of X-rays absorbed by the Skin," *Brit. Journ. Derm. and Syph.*, 1935, **47**, 152.

O'DONOVAN, W. J., and BRAIN, R. T. "Radon in Dermatology," *Brit. Journ. Derm. and Syph.*, 1931, **43**, 217.

PERTHES, G. "Ueber Strahlenimmunität," *Münch. med. Wchnschr.*, 1924, **71**, 1301.

ROXBURGH, A. C. "Radon in Dermatology," *Practitioner*, 1932, **128**, 242.

SCHOENHOF, S. "Ueber indirekte Röntgenbestrahlungen bei Hautkrankheiten," *Arch. f. Derm. u. Syph.*, 1928, **155**, 73.

SCOLARI, E. T. "Researches and Observations on Hydroa Vaccineforme," *Giorn. ital. di Derm. e Sifilo.*, 1933, 242 (*Abs. Brit. Journ. Derm. and Syph.*, 1934, **46**, 41).

SPIETHOFF, B. "Der Stand der Grenzstrahlentherapie in der Dermatologie," *Zbl. f. Hautkrank.*, 1933, **46**, 401.

TEMPLETON, H. J., and LUNSFORD, C. J. "Eczema Solare and Porphyria," *Archives of Derm. and Syph.*, 1932, **25**, 691.

UDE, W. H., and PLATOU, E. S. "Erysipelas: Comparative Study of Recent Methods of Treatment," *Journ. Amer. Med. Assoc.*, 1930, **95**, 1.

URBACH, E., and BLÖCH, J. "Hydroa vacciniforme, Porphyrinopathie, Hepatopathie," *Wien. klin. Woch.*, 1934, **47**, 527.

URBACH, E., and KONRAD, J. "Ueber eine durch den langwelligen Anteil des Sonnenspektrums erzeugte Lichtdermatose vom Typus der Prurigo æstivalis Hutchinson. Die Lichtschützende Wirkung des Resorcins," *Strahlentherapie*, 1929, **32**, 193.

VOLK, R. "Light Therapy in Lupus," *Brit. Journ. Actino. and Physio.*, 1930, **5**, 139.

WOOD, F. C., and MACKEE, G. M. "Therapy with Long Wave-length X-rays (Grenz Rays)," *Journ. Amer. Med. Assoc.*, 1931, **96**, 111.

CHAPTER XIV

MISCELLANEOUS

Exogenous Dermatitis

THE actual pathological mechanism has been described to some extent in Chapter VII. But it need hardly be said that many cases do not depend on sensitisation but on direct physicochemical action. The following substances are among those to which attention has recently been drawn as occasional causes :—*oranges*, the common weed *tansy*, *ragweed*, *ground-ivy* (hedera terrestris), *celery; cinnamon*, *sodium evipan*, *butesin picrate*, *podophyllum resin* (the dust of which is still more liable to attack the mucous membranes of the conjunctivæ and nostrils), *nupercaine* ointment, *calmitol*, *quinine* (used as a denaturant of alcohol in some toilet-waters); thimble made of *white composition* and *nickel* (Scott, Greenhouse and Sulzberger, Pascher and Sulzberger, Robertson, Tulipan, Peterkin, Fox, O'Donovan, Sulzberger and Kerr, Burgess and Usher, Goldman).

SUPERSENSITIVENESS TO QUINONE-BODIES. Cox reports that the examination of 216 furs, all alleged to be dyed furs which had caused dermatitis, revealed that 45·4% had been dyed with paraphenylenediamine, 12·5% with metaphenylenediamine, 9·3% with vegetable colours, and that 17% were natural undyed furs containing no trace of any irritant chemical.

Cox blames only the free unoxidised paraphenylenediamine. But according to Mayer the sensitiveness to *pellidol* (diacetylaminoazotoluol), to the fur-dye *ursol* (paraphenylenediamine) and to certain hair-dyes and photographic developers depends on a common basis, namely, sensitiveness to bodies with quinone-structure. In eczema-producing furs there are formed, by oxidation of the ursol during the process of dyeing, quinone imines

and di-imines, which constitute the irritants; but irritation can also be produced by intermediate bodies, the tissues being able to finish the oxidation.

Substances of the class of azo-dyes are, on the contrary, reduced in the living cells, giving rise to aminophenols and phenylenediamines, which in turn by subsequent oxidation give quinone-bodies. It is only by this indirect route that allergen is formed from, for instance, pellidol. Within this group-sensitiveness there are individual differences; thus one individual may be specially sensitised to quinone imine and another to quinone di-imine. This sensitiveness has nothing to do with the toxic property of these substances of forming methæmoglobin.

Rubber Dermatitis. A physician developed vesicular dermatitis from the use of rubber-gloves. The irritant was believed to be formed during the process of cold-cure vulcanisation, probably as a result of the combination of sulphur monochloride with unsaturated molecules of crude rubber. If the rubber-gloves were treated with an alkali, such as sodium hydroxide 4%, they no longer caused any irritation.

Leather Dermatitis. Beerman comments on its complex ætiology. The literature contains examples of specific irritation from almost every substance used in its manufacture. All hat-leathers do not cause irritation in all sensitive persons. One irritating substance was found to be soluble in ether and not present in all leathers. He thinks it is favoured by fungous infections.

Industrial Dermatitis. According to Horner, in the majority of cases, even among french-polishers, stainers and painters, the cause is not an irritant essentially connected with the work, but *cleansers* used afterwards. One such cleanser recently examined proved to be largely white spirit with cresylic acid. Other harmful cleansers are crude paraffin, turpentine and methylated spirit; but the worst offenders are alkalis, such as washing-soda, soda-ash and chloride of lime; the last two are popular for their bleaching effect.

The best and most widely applicable *preventative* is to apply some oil, such as cotton-seed oil, or waterproof grease before work.

This not only protects against the action of irritant substances but also allows them (as well as harmless stains like printers' ink) to be removed by gentler methods. In some factories they have introduced with success an "industrial skin-soap" composed of soft soap mixed with lanoline. It is rubbed into the skin before work and the excess rinsed off with a little water.

Turpentine Dermatitis. This gains interest from the recent recognition that the irritating property of oranges, lemons and celery is due to the same substance, namely, *limonene*, which is a terpene. *Pinene*, which is believed to be responsible for the irritant quality of turpentine, is closely related to limonene and is present in lemon-oil. Steam-distilled turpentine contains an ingredient which is decidedly more irritating than the other constituents. It can be removed by fractional distillation and is probably a saturated hydrocarbon with a boiling-point between that of alpha-pinene and dipentene.

Oil Folliculitis. Some success has been achieved in preventing it by the use after work of *Dakin's solution*, which both removes the oil and acts as an antiseptic (Bridge).

Sugar Dermatitis. There is nearly always some infection. In sugar-refiners *boils* are met with, and in those engaged in making sweets and candying fruits subacute *perionychia* (see p. 342).

Bakers' Dermatitis. Recent work in Australia threw blame on improvers, chiefly ammonium persulphate. But in England the amount of ammonium persulphate used for this purpose is very small; moreover, examination of those employed in its manufacture revealed no instances of disorders resembling bakers' dermatitis. According to the calculations of the Dermatitis Committee of the flour-milling industry, workers in flour-mills are actually affected with dermatitis to a smaller extent than the average population. There is a definite relation between the occurrence of dermatitis and *hand-kneading of dough*, which is hygroscopic. Coarse abrasions easily result from the removal of the dried hardened dough, especially from hairy regions, which is generally performed with a rough sacking-towel or a blunt instrument.

Woodworkers' Dermatitis. This usually shows itself first on

the face and neck with great swelling; the hands are affected subsequently. Sweating is an important factor. *Teak* is the best-known culprit, but other woods occasionally responsible are *Brazilian walnut* and *Roumanian pine*, which is used for the sound-boards of pianos, and *rosewood* used for xylophone-keys. The irritant action is thought to be exerted by non-saturated resinous acids and alkaloids.

PLANT DERMATITIS. Overton has reported peri- and hyponychial inflammation in those handling tulips, whether the bulbs or the cut flowers. She proved it to be due to the juice. Daffodils and narcissi, on the other hand, give rise to a sparse vesiculo-papular eruption on the forearms.

RUBBER INDUSTRY. Severe dermatitis is known to have been caused by some of the chemicals used to accelerate vulcanisation. Among these "accelerators" are "hex" (hexamethylene tetramine) and "B.B." or "montana syrup" (the butylaldehyde concentration-product of dimethyl p-phenylenediamine). Protection against hex is claimed by soaking the working-clothes in a concentrated solution of *acid sodium phosphate* and then drying them. The same solution is applied to the exposed skin and allowed to dry on.

CALCIUM CARBIDE. Torsujew divides sufferers from this industry into 3 groups:—(1) workers engaged in breaking-up the raw material may have frequently recurring dermatitis, especially on the inner surface of the thighs, the back of the hands, front of the neck, the volar aspect of the lower third of the forearms and the dorsum of the feet; (2) those engaged with the carbide-furnaces get hyperhidrosis and necroses on the back of the hands, and punctate or horizontal linear blackish depressions on the anterior aspect of the incisor teeth; (3) the sorters of the finished carbide may present bird's-eye ulcers, scars, and, less often, dermatitis.

PRINTERS' DERMATITIS. This is never due to printing-ink itself (Horner). It sometimes follows "making-up" or "making-ready," and Horner attributes the trouble to *formaldehyde* in the flour-paste, to which it is added to prevent the formation of moulds.

ARTIFICIAL MANURES. *Calcium Cyanamide.* Mayer has shown that this occasionally causes eczema as a result of a high degree of specific sensitisation. This is to be distinguished from its well-known caustic effects, which are not really due to the cyanamide but to calcium oxide, contained as an impurity.

Calcium ammonium nitrate can also lead to extreme sensitisation, resulting in conjunctivitis and eczematous swelling of the eyelids and neighbouring skin. Tests show that the sensitiveness is common to many manures containing NH_3.

Calcium nitrate is practically harmless on intact skin, but at the site of abrasions causes necroses, which heal very slowly. Its action is due to the calcium-ion.

Treatment of Strepto- and Staphylococcal Infections

It should be emphasised that it is difficult to make a strict clinical differentiation between staphylococcal and streptococcal infections. In many ordinary boils streptococci are found, especially if anærobic cultures are set up, and in one case of boils on the buttocks I have met with them in pure culture. Conversely, in a little epidemic among ward-nurses of superficial bullæ on the hands containing clear or milky fluid, I obtained from all the lesions a pure growth of staphylococcus aureus.

Specific Methods. VACCINES. The disappointing achievements of the ordinary methods in *sycosis* were sought to be improved by Gougerot and Meyer in 1925, by injecting staphylococcal vaccine *intracutaneously* in very large doses. Throne and Myers (1926) obtained better results with a mixed stock-vaccine of staphylococci, streptococci and B. coli than with an autogenous one : it had to be of high bacterial count - at least 6 billion per c.c. But Aolan intracutaneously gave them about the same percentage of cures and they recommended combining the two. These experiences throw great doubt on the specificity of the method. Barber and Forman (1933) have not noticed any advantage in making the injections in the infected neighbourhood. They use active strains of staphylococcus aureus, and sometimes streptococci concurrently if streptococcal lesions are associated. Their dosage is much

smaller, beginning with 10,000,000–25,000,000 and only increasing when the local reaction becomes negligible. Overdosage produces exacerbation. Improvement, they find, only sets in when 250,000,000–500,000,000 can be tolerated, whereafter it proceeds rapidly. Barber has not been successful with Aolan.

I have had poor results with staphylococcal vaccines given by any route, and however prepared. They are feeble antigens: even actual infection leads to little alteration in the sensitiveness of the skin. Thus in a man who had had severe staphylococcal sycosis of all hairy regions for some years, I found that his skin was neither more nor less sensitive to a vaccine of his own cocci than the skin of healthy controls.

There is a little experimental support for the production of local immunity. The observations chiefly refer to erysipelas and streptococcal inoculations. They suggest that a local may exist in the absence of a general immunity, and that when repeated local injections lead to a general immunising response, the level of immunity may be higher near the site of inoculation. But the severe inflammatory reaction associated with an attack of erysipelas is more effective in inducing local immunity than the relatively trivial reaction following the injection of killed hæmolytic streptococci (Topley).

Antivirus. The theoretical basis propounded by Besredka has not been substantiated. The preparations contain neither a living virus nor a specific product of the microbes which inhibits their growth. An "exhausted" broth will again allow the bacteria to grow in it after a mere restoration to its original *p*H (Miller, Jessner).

But in spite of its theoretical basis being false, it could still be useful in practice. But here again the evidence is against any good effects being specific. Mallory and Marble (1925), by injecting filtrates of cultures of staphylococci and streptococci into the skin of rabbits, produced a strictly localised but non-specific immunity lasting 5–6 weeks; but it was not appreciably greater than that conferred by uninoculated sterile broth. Freedlander and Toomey (1928) also proved the local prophylactic efficacy of compresses of sterile broth against subsequent injection

of staphylococcus aureus. Histological observations revealed that the broth acted by provoking an inflammatory response and in particular a mobilisation and concentration of histiocytes. Immunity of this type is confined to the area so inflamed and does not affect the skin as a whole.

The prophylactic power of broth (as well as of other irritants) is therefore certain, but opinions on its value in treating established infections are very conflicting. Neither Jessner nor Pick ever had a success. I have occasionally known spectacular improvement in *eczematised sycosis* to follow the use of sterile broth containing 0·2% of formalin.

Bacteriophage. The theoretical basis of bacteriophage-therapy is also not universally accepted, but it rests on incomparably more convincing evidence than that of antivirus. The phenomenon of lysis described by Twort is indisputable, though d'Hérelle's explanation of it as due to a living virus is uncertain. Staphylococcus bacteriophage was first demonstrated in 1921 by Gratia. Reports of its usefulness in practice are accumulating. Raiga claims to have obtained an immediate improvement and rapid cure in 95% of his cases of *boils* and *carbuncles*; 87% of *whitlows* completely healed in 3 weeks. In the majority he used a combination of local instillations (maximum of 3) and subcutaneous injections of 2 c.c. at intervals of 2 days, not more than 4 times. It is interesting that a pure staphylococcal phage gave much better results than polyvalent preparations which contained it in smaller quantity. He attributes the occasional failures or relapses to the presence in the serum of "antiphage," which he appears to believe can be got rid of by autohæmotherapy. Crutchfield and Stout were very successful with it in deep-seated *furunculosis*, pyogenic follicular lesions of *acne varioliformis* type and *sycosis vulgaris*. No improvement was obtained in acne vulgaris. In comparison they found Besredka's antivirus quite without action. They consider that their own observations, together with those of Rice, Larkum and others, strongly support the specific action of bacteriophage on the infection, and that it is superior to any other method for this class of disorders. They found their success was proportional to the degree to which the

phage used did in fact lyse the organisms cultured from the lesions. In a few instances they gave as many as 30 subcutaneous injections of 1 c.c. at 48-hour intervals without any bad effects. Cipollaro and Sheplar made cultures from the lesions to be treated and tested the susceptibility of the bacteria to stock phage. Only when lysis was complete and the solution had been clear for 24 hours was it considered satisfactory for use. They estimated that by this method furuncles and carbuncles were more speedily cured than by other treatments. Sycosis and *perionychia* also responded, while acne vulgaris showed no improvement (see p. 474). Gougerot and Peyre, though they had little success in sycosis with subcutaneous injections, found it useful to instil phage into each pustule and apply it as a compress.

Streptococcal Antitoxin. It is only recently that the importance of the soluble exotoxins elaborated by staphylo- and streptococci has been appreciated and efficient antitoxins prepared in the form of concentrated antitoxin-globulins. According to Parish and Okell all hæmolytic streptococci, independently of the clinical disorder from which they are obtained, elaborate the same toxin ; but the *amount* of antitoxin they call forth in horses varies greatly, the most active being the scarlet fever streptococcus. According to O'Brien, antitoxic serum from one strain of scarlet fever streptococcus protects rabbits not only against all strains of scarlet fever cocci but also against hæmolytic streptococci from *erysipelas* or other diseases. Indeed, in his hands better protection against erysipelas is afforded by the Burroughs Wellcome scarlet fever antitoxin-globulins than by any antierysipelas serum. Different results have been obtained with different makes of sera. Symmers, using an antitoxin made by the Lederle Antitoxin Laboratories, reckons from a review of 1,300 cases that the mortality is thereby at least halved. Thomson, while agreeing with Roberts that in the majority of cases serum is quite unnecessary, considers the Burroughs Wellcome preparation is of definite value. On account of a (possibly exaggerated) fear of anaphylaxis, he advises its restriction to cases severe enough to carry a grave prognosis ; in these it should be given without delay. The doses must be large, particularly in very young infants,

and must be continued for at least 3 days after apparent recovery.

Staphylococcus Toxoid. Staphylococci, too, produce an exotoxin: it kills rabbits when given intravenously, produces skin-lesions in rabbits and guinea-pigs, and is actively hæmolytic (Parish and Clark). The passive use of its corresponding concentrated antitoxin has not yet been proved of value in treating cutaneous lesions, but may be of value in toxæmia.

But this toxin, by the addition of formaldehyde, is rapidly converted into *toxoid*. Connor and McKie were able, by injecting toxoid subcutaneously, to protect rabbits completely, not only against toxin but against massive intravenous doses of the living germs. This immunity is accompanied by a marked rise in the antitoxin-content of the serum.

Superficial staphylococcal infections in man are generally accompanied by a slight but definite rise in the antitoxin-content of the serum compared with the average normal, measured by its antihæmolytic power (Bryce and Burnet, 1932). It is not certain that this is a perfect measure and that staphylotoxin is the same whatever its source. Thus Panton and Valentine state that the staphylococci of sycosis barbæ furnish a toxin strong in hæmolysin and weak in leucocidin, whilst, on the other hand, those from pyæmia give a toxin weakly hæmolytic but strongly leucocidic.

In treating human infections with toxoid all observers have noted a consequent rise in the antihæmolytic titre of the serum. Connor and McKie had good clinical results in *furunculosis* and *sycosis*. In 1934 Parish, O'Meara and Clark concluded from published work and their own results that toxoid is of value in subacute and chronic staphylococcal infections. Dolman (1935) from a large experience says it proved exceedingly useful in recurrent furunculosis and styes. Intractability, he thinks, is usually due to a concomitant infection in the nose. No alarming general reactions ever occur and focal reactions are inconspicuous. Recurrences of the lesion coincident with a significant fall in the antitoxin-titre often follow undue physical or mental fatigue, insomnia, or an intercurrent infection. A few of Gray's and my own patients have been treated with toxoid by Bamber. The

results in subjects of recurrent boils and carbuncles have been very encouraging.

The usual dosage of Wellcome's staphylococcal toxoid is to begin with 0·5 c.c. of a 10% dilution. If the local reaction is negligible, 0·1 c.c. of the full strength is given, and followed by gradually increasing doses up to 1 c.c. at intervals of 4–7 days. Then there should be a few weeks' rest, as the amount of antitoxin is not increased by continued injections beyond a certain number, and sometimes it is during this rest-period that improvement is most rapid (Murray). The tolerance which adults develop to large doses is soon lost, and after the lapse of more than 1 month the initial dose of a supplementary course should not exceed 0·1 c.c. Intramuscular injections are less painful than subcutaneous.

But the majority of English dermatologists are not impressed with this method, and Ferguson Smith finds that though toxoid pushes up the antitoxic titre the latter has no correlation with the course of furunculosis and that cure can be attained by means of local treatment alone just as easily as with the help of toxoid.

Non-specific Methods. GENERAL. White and Cooney treated 20% of 500 cases of *carbuncles* with *non-specific foreign protein* injections only. They found that the course was shorter in these than in those treated by surgery or a combination of surgery and protein injections. They used Aolan, Omnadin and Activin (purified 5% casein in combination with organic iodine, *i.e.*, similar to Yatren casein). All were satisfactory but their preference was for Aolan. Though the dosage naturally varied, overdosage seemed impossible. The injections were given daily; for the largest carbuncles an average of 4 were needed; a 5th was sometimes given 4 or 5 days later.

Furunculosis. I am convinced of the great value in some cases of a mixture containing solution of *arsenic* m. 3 and dilute *hydrochloric acid* dr. ½ three times a day.

"*Chronic Erysipelas.*" A case under my care of severe persistent œdema and redness, chiefly involving the neighbourhood of the eye, consequent upon erysipelas, which had not responded at all to streptococcal vaccine, X-rays, autohæmotherapy or injections

of sulphur and milk, yielded immediately and completely to *fever*-treatment with T.A.B. vaccine. The previously mentioned substances had not caused any febrile reaction.

Local. *Erysipelas.* Bormann has found *X-ray* treatment so efficacious that 3 months after its introduction it was possible to close an erysipelas-department which had hitherto been constantly occupied by 25–30 patients. He gives on the first day $\frac{2}{3}$ E.D. to the whole area and after 24 hours $\frac{1}{3}$ E.D. The temperature falls after the first dose and after 48 hours is normal.

Eczematoid Pyodermias. It is still unsettled whether a pyococcal infection *per se* can produce eczema. Clinically a typical eczema often appears to be a consequence of *staphylococcal* folliculitis. For this condition the following have seemed to me valuable :—solution of *aluminium acetate*, B.P.C. dr. $\frac{1}{2}$, water to $\frac{3}{3}$ 1 ; sterile nutrient *broth ;* or *resorcin*, *ichthammol*, glycerine, of each 1% in liniment of lime.

Kinnear agrees with Sabouraud that *streptococci* are responsible for certain forms of *intertrigo*, especially retroauricular, a form of *dermatitis* of the scalp which may extend to other parts, especially the folds, and *pityriasis alba* which forms circumscribed scaly patches on the face or scalp. The streptococci cultivated by Kinnear from impetigo were hæmolytic, whilst those obtained from these disorders were anhæmolytic. He thinks retroauricular intertrigo is always due to anhæmolytic streptococci, as he obtained them in every case, frequently in pure culture. But the technique used was designed to favour streptococci at the expense of other organisms. "Streptococcal dermatitis" presents over the whole area a red glazed appearance and gives rise from its entire surface to an abundant exudation of serum which dries to form crusts. With Sabouraud he seeks to distinguish it sharply from impetiginous eczema : but this distinction is not generally accepted ; a similar clinical picture can probably be produced by other infections and even I think by flexural psoriasis. The treatment he prefers is to rub in *iodine 1% in carbon tetrachloride.* In rebellious cases of streptococcal dermatitis of the scalp he has resorted with success to the rather unattractive method of covering the whole scalp with strips of *elastoplast.* They are removed after a week, when

there is usually an abundant accumulation of pus ; but after being cleaned the skin is found less inflamed. Six such dressings are usually enough to bring the scalp to the dry scaly stage when iodine completes the cure. In my experience iodine in carbon tetrachloride is both painful and unhelpful, even when a pure growth of anhæmolytic streptococcus is obtained. I have found *Monsol* of great value, at first in a 1 in 500 watery dilution and later in a strength of 4% in zinc paste or, for the scalp, in cold cream.

Impetigo Neonatorum. Guy and Jacob propose the following method of prophylaxis, which has greatly reduced the incidence at a large institution. As soon as possible after birth the infants are thoroughly cleaned with sterile paraffin and rubbed all over with 2% ammoniated mercury ointment. Subsequently they are cleaned daily with cotton-seed oil ; soap, water and powder are avoided.

As regards treatment, most authorities now advise keeping the skin dry with a mildly antiseptic powder. Finkelstein recommends opening the blisters and painting the base with 3–5% silver nitrate.

Boils and Carbuncles. Operative measures either electrical or with the knife are now generally condemned except when there is an obvious accumulation of pus. Tachau recommends early *X-rays*, especially for those on the face and for axillary (sweat-gland) abscesses, in doses of 10–20% E.D., *i.e.*, 50–120 r, at intervals of 10–14 days ; but sometimes one exposure is enough. The field should be large.

Turrell, Wilson and Russell are impressed with the powers of the new *ultra-short-waved diathermy* introduced in 1933 by Schliephake.

Läwen in 1933 introduced the method of packing the tissues around and under the lesion with the *patient's blood*, of which about 30–40 c.c. may be required. The method has proved valuable especially for axillary abscesses.

A useful *dressing* for boils suggested by Kissmeyer consists of alternate layers of a paint of ichthammol 70% and flexile collodium 30%, and of wisps of cotton-wool. It is changed 2 or 3 times daily.

The whole skin-surface should be regularly cleaned with disinfectant solution.

Sycosis. Tachau emphasises the importance of thorough manual *epilation.* It has generally appeared to me harmful unless the hairs are absolutely loose. No surface-applications are reliable: Scott especially advocates *75% ichthammol in water*: it is, however, not suitable for eczematised cases. *X-rays* are frequently very effective, but I agree with Barber and Jadassohn that they should be given only in fractional doses; I have often observed exacerbation following epilation-doses. In some X-ray-resistant cases Jadassohn and Jessner have succeeded with thorium X. (For Grenz-rays, see p. 453.)

Verrucose Pyodermia. Not very uncommonly pyodermias take on a verrucose form resembling blastomycosis. I have seen several cases, always on the hands and forearms of men, usually gardeners, and published one in 1935 (see Fig. 46). Ferguson Smith in 1929 attributed this "form of chronic pyodermia" to a special reaction to staphylococcus aureus; but in my case this organism was absent and streptococci and B. proteus were recovered. I find the best treatment to be freezing with CO_2 *snow.*

Biotropism

Milian (1929) invented this word to express the idea that some drugs possessing a special affinity for organisms have the effect, at any rate in certain dosage, of stimulating their activity. Sequeira quotes as an instance an old subject of syphilis and malaria, who was admitted to hospital with impetigo contagiosa. An injection of 0·45 gm. of 914 caused a febrile reaction; 5 days later a second dose was followed by severe general symptoms. On the 9th day after the first injection a scarlatiniform eruption appeared and a large bleb full of pus, which contained streptococci in extraordinary abundance. It was thought that the 914 stimulated the streptococci already present in the impetigo-lesions.

Morbilliform Eruptions. Sequeira mentions an instance of a morbilliform rash developing on the 8th day after the first of a course of injections of sulfarsenol; it disappeared in 5 days and did not recur on further treatment with increased doses. In

another instance a woman developed a morbilliform rash after treatment with 914. Two infants in the same ward subsequently developed typical measles. It was assumed that the patients



FIG. 46. Verrucose pyodermia. (Author's case.)

were suffering from latent measles and that the virus was activated by the arsenical compounds.

Stomatitis. Evidence is adduced in support of the view that

mercurial stomatitis is actually the result of a specific infection with Vincent's organisms which are activated by the drug.

Bromide and Iodide Eruptions. It is suggested that the acne-like lesions are due to activation of staphylococci dormant in the pilosebaceous follicles. This appears to me improbable on clinical grounds, since on withdrawing the drug the lesions regress and have no tendency to spread. Moreover, in a case of iodide-acne I made cultures from several of the pustules and found them quite sterile.

Aurides. D'Asdéry attributes many eruptions during gold-treatment to biotropism, and "focal reactions" are so interpreted. In patients treated with gold for tuberculides, isomorphic eruptions may be provoked or other tuberculous manifestations. The occasional exanthems occurring 8 or 9 days after gold-injections in lupus erythematosus are interpreted as biotropic outbreaks of exanthematic lupus and not as gold-intoxications. Similarly, scarlatiniform and morbilliform eruptions are thought to be not toxic, but the genuine specific infective diseases provoked by the drug. Even eruptions of a type not known to have an infective cause are so "explained."

Biotropic manifestations are said to be characterised by:—(1) Acute appearance on the 9th day. [It is difficult to understand why the same "incubation-period" should be required for all kinds of infective agents in all degrees of latency and stimulated by all kinds of drugs.] (2) Clinical aspect, generally belonging to the group of the disease under treatment, or resembling other infective dermatoses or dermatoses of unknown but "supposedly" infective origin. [Cannot non-infective diseases be made worse by drugs?] (3) They clear up if the drug is continued, and are therefore not an indication to stop treatment. [This applies to some of the rashes observed after gold and neosalvarsan injections but is certainly *not* true of bromide-acne or mercurial stomatitis.] (4) Intracutaneous tests with the drug are negative. [This does not disprove the toxic or even the allergic action of the drug; cf. phenolphthalein eruptions (see p. 217)].

Biotropism is a very important conception, and that such a

process may occur is hardly disputable. But the coining of this new attractive word has resulted in a great variety of phenomena being attributed to it without an approach to proof.

Acneiform Eruptions

Sulzberger, Rostenberg and Sher are impressed by the similarity of acneiform eruptions, whether produced by external agents, such as chlorine-gas, tar, oils, waxes and greases, or by internal noxæ, such as bromide, iodide, the products of tubercle-bacilli or the unknown agents responsible for acne vulgaris. That halogens (and certain other endogenous substances) cause *follicular* eruptions seems to be due to (*a*) the rich convolution of blood-vessels around the follicles (Jadassohn), (*b*) their excretion through the sebaceous glands (Stein), and (*c*) their special capacity for irritating the pilosebaceous apparatus. Sulzberger supports the third explanation by showing that in acneiform eruptions due to halogens the response to a patch-test not infrequently has a distinctly follicular rather than a diffuse eczematous character. Put in another way, the individual's pilosebaceous apparatus is over-sensitive to the halogen. They view the acneiform eruptions of tuberculosis, lichen scrofulosorum and rosaceous tuberculide analogously; and state that in these patients a follicular type of reaction to patch-tests with old tuberculin is the rule.

In addition to iodide, bromide and tuberculin, Sulzberger finds that trichophytin has an intrinsic tendency to affect the pilosebaceous apparatus selectively in certain individuals, even when externally applied.

Acne Vulgaris. ÆTIOLOGY. Bacterial infection is still widely blamed, at any rate for the pustulation, but on very inadequate grounds. As regards staphylococci, I did some systematic investigations in 1925 with the following results:—(1) I found no definite qualitative difference between the staphylococcal flora of acne-pustules, comedos, the surface of skin affected by acne and the surface of normal skin (over 90 strains were studied). No variety of staphylococcus was found in acne-pustules that was not present in equal or greater numbers on normal skin. From several pustules no staphylococci whatever could be grown and from

others very few. (2) The flora consists preponderantly of white cocci; only a very small percentage were coloured, mainly golden yellow or brown. (3) None of these coloured strains proved to be staphylococcus pyogenes aureus; (thus in cultures from the surface of the cheek in 14 normal persons and 19 acne-patients, as well as in cultures from the acne-lesions themselves, I did not once meet with a staphylococcus pyogenes aureus or citreus). Whether among my white cocci some should be regarded as staphylococcus pyogenes albus cannot be definitely decided, but they did not conform to the usual definition. (4) A small series of intracutaneous tests with a mixed vaccine of staphylococcus albus strains derived from acne-pustules did not reveal any difference in the sensitiveness of persons with and without acne.

Sabouraud is also opposed to the view that the pustules are caused by staphylococci. Whitfield excised a papulo-pustule and stained serial sections. In the granulation-tissue of the wall he found small colonies of staphylococci. In the centre was a macerated comedo containing masses of the microbacillus. This led him to think that the microbacillus was the cause of the comedo and the staphylococcus of the suppuration. But I found more white staphylococci in comedos than in pustules and still more on the surface, even of normal skin.

My view of the innocence of the staphylococci is perhaps to some extent supported by the fact that even enthusiastic users of staphylococcus bacteriophage and toxoid claim little success in acne.

The claims of Sabouraud's microbacillus or acne bacillus or, as it is now called, the *corynebacterium acnes* are little, if at all, stronger. It is distinguished from nearly all the other diphtheroids by preferring anaerobic conditions. According to Ketron and Burky (1925) it grows best on a medium with *p*H between 6·2 and 6·8 to which is added some enriching substance, *e.g.*, dextrose or glycerine. Gilchrist at the end of last century obtained agglutination by the blood of patients with severe acne. The bacilli to which he referred were, however, grown aerobically, and later he was unable to repeat his findings. Civatte showed that these bacilli are always to be found in the pilosebaceous orifices of

normal skin, but Gilchrist maintained that they were present more abundantly in acne-lesions. The bacillus is not pyogenic in animal-experiment and only pathogenic to mice on intraperitoneal injection. It has never been possible to produce acne-lesions in man by rubbing in cultures. A systematic investigation of this question by modern methods is lacking.

Bloch has shown from statistical observations that there exists between the start and course of acne and puberty (in so far as the latter is determined by the appearance of menses and of pubic and axillary hairs) not only a chronological but also a causal connection. The process responsible for "puberty," by inference, likewise determines the appearance of comedos. This process is the function of the gonads. The comedo appears at a determined age and is so common (in some degree) that it can almost be regarded as physiological. So he believes that acne in its first phase is a *consequence of the physiological function of the sexual glands* and that variations in degree are due to the *follicular apparatus of the skin differing individually in its sensitiveness to the hormone.* As Sharlit emphasises, the pilosebaceous complexes concerned, though otherwise well-developed, are *vestigial* as regards hair-growth or not yet ready to form hair. They respond instead by hyperkeratosis of the orifice, which blocks them. After being blocked, if abnormally sensitive, they may be provoked even to suppuration by further stimulation or irritation. Lawrence and Feigenbaum noticed that four women being treated for menorrhagia with Antuitrin "S" (pregnancy urine extract) lost their acne as menstruation became normal, and they had encouraging results from giving it in other cases of acne vulgaris. They think that perhaps the sex-glands of acne-patients are functioning *immaturely*, and that the beneficial effect of Antuitrin "S" may depend on its maturative influence upon them.

That the follicles of subjects of acne vulgaris are in fact, at any rate in one respect, supersensitive, appears from the demonstration by Sulzberger that in 100% the ingestion of iodide gr. 5 t.d.s. causes, after 2–3 days, exacerbation of existing lesions and the formation of many new ones. Such supersensitiveness may easily be or become *polyvalent.* This would harmonise with Whitfield's

observation that there is frequently abnormal intestinal digestion and that certain *foods* are harmful, such as cheese, chocolate and cocoa. Wise and Sulzberger think that white bread may offend, because of the potassium bromate in the improver, which is reduced in the baking-process to bromide. They also warn against iodised salt and foods rich in iodine. But the latter include green leaf vegetables, which are, on the contrary, specially recommended by Whitfield.

TREATMENT. Whitfield finds *calx sulphurata*, not less than 2 gr. thrice daily, specially useful in cases with constipation and acrocyanosis. Often he has been very pleased with intestinal antiseptics, particularly *creosote*, not less than m. 6 thrice daily. Wise and Sulzberger give *sodium chloride* 8–15 gm. a day, to aid elimination of bromide and iodide: this has sometimes proved beneficial even when their intake has not been obviously excessive. Doktorsky and Platt report great improvement in nearly all cases from *vitamin D* in the form of viosterol, 20 drops daily. In an unusually severe case with numerous scrofulodermia-like abscesses, I achieved astonishing success with *arsenical solution* m. 3 thrice daily by mouth, after failing with U.V.R., X-rays, manganese and lopion. Lawrence and Feigenbaum suggest *Antuitrin* "*S*" three times a week, except during menstruation, beginning with 1 c.c. and proceeding to 2 c.c.

As to external measures I entirely disagree with the prevalent generalisation that all grease-containing applications are contra-indicated. In fact, I find far the most efficacious to be a paste containing sulphur and resorcin in such strength as to produce *mild exfoliation*. The right strength must be found for each patient. Representative formulæ for a weak and a strong paste are:—precipitated sulphur dr. ½, resorcin dr. ½, zinc oxide dr. 3, hydrous wool fat dr. 1, vaseline dr. 3; and precipitated sulphur dr. 2, resorcin dr. 2, hydrous wool fat dr. 1, vaseline dr. 3.

The necessary exfoliation can also be attained by adequate doses of U.V. rays, which are more convenient for extensive eruptions on the trunk.

In the deep nodular forms fractional doses of *X-rays* may be required. If large amounts are used, Whitfield warns against

exposure to the sun for 4 weeks after the treatment; it has resulted in telangiectasis exactly limited to the exposed areas.

Psoriasis

There has been little progress in the elucidation of its cause. Bizzozzero has made some interesting observations on the *Koebner phenomenon*, *i.e.*, the appearance of characteristic psoriatic lesions, in a subject of the disease, at sites of injuries. He showed that skin transfixed with a needle gives a positive Koebner only at the points of entry and exit and concludes from this and other tests that the phenomenon depends on damage to the superficial layers of the dermis. He further showed that a local "immunity to the sign" (refractoriness) existed for a certain period within circinate lesions and also around a plaque that has ceased to spread. He points out the close resemblance of this localised immunity to the resistance to superinfection in similar lesions of trichophytic and syphilitic origin and argues (inconclusively) in favour of its parasitic nature. For this local refractoriness may not be specific. Lewis showed that vessels are refractory to histamine for varying periods after its injection, after exposure to U.V.R. and after many other types of injury, and Paterson has found that in psoriasis-plaques the vessels are refractory to histamine during the eruptive and chronic stages and that the return of the reaction is associated with clinical improvement.

Treatment. DIET. Schamberg (1932) refers again to his well-known investigations of 1913, in which he and his co-workers concluded that in psoriasis there was a "positive nitrogen-metabolism," *i.e.*, retention of nitrogen. He claims great success in a large majority of cases from the rigid administration of a *low protein* diet. He emphasises that the mere avoidance of meat and fish may not be enough, as there can still be an excess of vegetable protein. He gives tables of different types of diet containing enough calories for a man doing a moderate amount of work; for hard-workers he adds additional butter and cream.

It is, however, the lipoid metabolism which, according to the newest views, is at fault. In a patient suffering from psoriasis, diabetes and xanthomatosis, Grütz found on histological examina-

tion that in the psoriatic areas the widened papillæ of the cutis were packed with fine granules of lipoid. There appeared to be a stream of these fatty substances from the capillaries into the intercellular spaces of the epidermis, and they finally accumulated copiously in the superficial scales. This process cannot, however, be seen in by any means every case. A large series of psoriatic patients were therefore investigated by means of Bürger's test: cholesterol 5 gm. in olive oil 100 gm. is given orally to the fasting subject, after which 50 c.c. of blood are withdrawn after 4, 8 and 24 hours and examined for variations in the fat and lipoid. In subjects of psoriasis there was found to be an average of 40% increase of total serum-fat, of cholesterol and also phosphatides. Grütz thinks that the deposits in the skin depend on a similar mechanism to that of xanthomatosis. In a large number of cases he has been able completely to cure severe psoriasis by a *fat-poor* diet alone. Adults are only allowed a maximum of 20 gm. of fat daily, and children only 10 gm. The good effect of the treatment is only observed after about 3 weeks in children and 6 weeks or more in adults. Sometimes it is found necessary to diminish the total calories.

Semon considers the clinical results encouraging. Guthrie and others have found its action in many cases quite negative. Coke criticises the conclusions of Grütz and Bürger in that they were based on average findings in a small number of cases. He describes a simplified test, in which the opacity of the serum is measured with a photoelectric nephelometer.

If Schamberg's and Grütz's diets are both beneficial, possibly in both cases the virtue lies in reduction of *total* calories.

Injection of Extract of Scales. Campbell and Frost (1932) consider this method of value in generalised eruptions of long standing, but of no use in patients presenting only a few lesions. About 0·2 gm. of scales are ground down and suspended in 25 c.c. of absolute alcohol and allowed to stand for 24 hours. The injections are given intramuscularly twice a week, the first dose being 0·5 c.c. and the fourth 1·5 c.c.

Autohæmotherapy. In Burgess's experience it is the acute cases that respond best to this method. It is interesting that

these are also the ones in which he has obtained positive skin-reactions to urinary proteose.

MERCURY SULPHIDE. Benedetto has found this compound in colloid form (Mercolloid) to have a more pronounced and lasting effect than other methods, including other forms of mercury and sulphur. 0·01 gm. is injected intramuscularly 2 or 3 times a week ; about 20 injections may be required. It has been of definite service to me in intractable cases of psoriasis of the nails.

GOLD. Ingram has found gold the only effective remedy in those rare cases that resemble pityriasis rubra pilaris. Incidentally in true pityriasis rubra pilaris Twiston Davies has seen remarkable recoveries following its use.

Pustular Psoriasis. Originally this name was applied by MacLeod to typical plaques of psoriasis which become beset with pustules, a change sometimes foreshadowing a generalised exfoliative dermatitis.

Recently, however, the name has also been used for a not uncommon eruption affecting symmetrically the feet and hands, and which was formerly looked upon as a " chronic mild localised type of acrodermatitis perstans " (Dore, 1928). In 1925 Strandberg had suggested that acrodermatitis perstans (without further distinction) was a pustular form of psoriasis. In 1930 Barber and Ingram attempted to show that the chronic mild localised type was psoriasis and to be distinguished from true acrodermatitis perstans. The latter usually begins on the extremity of a digit, either as an infective traumatic sore or as a whitlow. From this localised unilateral site it spreads, either remaining unilateral or involving the other extremities or, rarely, becoming generalised. The nails are affected just as in ordinary whitlow. There is good evidence that this condition is due to infection with a resistant strain of staphylococcus pyogenes aureus.

In contradistinction to the above, the eruption which Barber calls *pustular psoriasis of the extremities* is eventually, and may be from the beginning, symmetrical. The sites of election are the thenar eminences and the inner portion of the hollow of the soles (see Fig. 47). The patches begin as reddish areas in which pin-head-sized endoepidermic pustules form. These are often

described as little lakes of pus, being flush with the skin-surface. Some of them may become confluent, but the majority dry up



FIG. 47.—Pustular psoriasis. (R. Klaber's case.)

in situ to form minute brown scabs which are eventually exfoliated. The eruption is subject to periods of quiescence and exacerbation. The sides of the toes can be involved, giving rise to sodden peeling,

resembling ringworm, and the big toes are sometimes swollen, red and scaly. The nails, as a rule, are unaffected, or show changes similar to those of ordinary psoriasis. In a few instances it is associated with ordinary psoriasis elsewhere. The pustules and scales contain *no demonstrable bacteria or fungi.*

The *histology* is essentially the same as that of ordinary psoriasis, the main differences being a far denser stream of leucocytes from the dermis into the rete, which is disintegrated by literal abscess-formation, and a correspondingly denser infiltration of the exfoliating parakeratotic masses with leucocytes. The differences, therefore, only amount to an exaggeration of the so-called micro-abscesses of Munro-Sabouraud, which are a feature of ordinary psoriasis.

It is not yet generally accepted that this eruption is psoriasis. It is curious that such a small proportion of these cases are associated with psoriasis (even if atypical) on other parts of the body and that extensive psoriasis (even the moist flexural type) when it involves palms and soles so seldom takes this form.

It is generally very intractable to *Treatment.* Some of Barber's cases after tonsillar enucleation have passed through a marked exacerbation and then cleared up. Some of my cases which had resisted ambulatory treatment responded with great rapidity to rest in bed.

Pityriasis Lichenoides et Varioliformis Acuta

This condition was first described in 1903 by Moeller and Afzelius and was given its present name in 1926 by Habermann. Wise calls it *parapsoriasis varioliformis.* Some cases start very acutely, some more gradually. Dore describes the original lesion as a small red spot with a yellow central point. This heralds the main eruption, which may be mistaken for chicken-pox rather than small-pox (Gray, Heath, Dore). Gray also notes its resemblance to malignant early secondary syphilis. Generally it later assumes the characters of ordinary pityriasis lichenoides chronica of Juliusberg (parapsoriasis guttata). But in a few instances it exhibits frequent relapses of the vesicular or necrotic form, so that it probably represents a specially severe or intense manifesta-

tion of the disease, rather than an acute phase. It seems to occur in epidemics.

Gross states that the first *histological* changes in parapsoriasis guttata and parapsoriasis varioliformis have the same features, viz., parakeratotic scutulum, permeation of the whole epidermis with leucocytes, œdema of the rete and papillæ and a characteristic infiltration in the corium.

TREATMENT. Successes have been reported by Goldschlag and Blatt with *X-rays to the spinal cord*, by Stühmer with *sweating-baths*, by Barber with *gold*, and by Konrad with *borderline-rays*. A relapsing case under Gray was quite resistant to gold. I have seen intermediate cases clear up well with *U.V.R.*, the mercury-vapour lamp apparently acting better than the carbon arc.

Papular Urticaria (Lichen Urticatus)

The cause is still elusive. Hallam's recent observations, though in a negative sense, are of great interest. In 1927 he recorded the fact that 14 children admitted to hospital during an attack recovered completely without any treatment. In 2 cases the whole of the food was brought from home, but both children remained well while in hospital though they relapsed after returning home. While still in hospital it was found that foods containing the proteins that gave positive skin-tests were innocuous, as were also sweets, cakes and ice-cream. In 8 out of 11 later cases the lesions healed and no new ones developed, as a result of the children sleeping at the hospital and going home during the day. In the three exceptions only a few sporadic papules appeared, and even these eventually cleared up. Bringing in the patients' own mattresses and bedclothes gave some suspicious positive results, but eventually failed to maintain the rash ; sprinkling into their beds dust from their home-bedrooms had no effect. Experimental biting with bed-bugs was also negative except for the usual temporary wheals. With the idea that warmth and bad ventilation might be responsible, some children were made to sleep in a small isolation-room with shut windows, heated above the normal temperature, but they developed no spots.

The converse arrangement, namely, spending the day in hospital and the night at home, did not have the same beneficial influence. With a view to eliminating any specific irritant in the children's beds, iron cots with sterilised mattresses, bedding and night-gowns were sent from the hospital and placed in the children's bedrooms for a week. There was an apparent improvement in all, but the small number of tests did not warrant firm conclusions.

From these experiments one can at least deduce that the exciting cause is not a food-factor, but is probably associated in some way with *home sleeping arrangements*.

Tate's more recent and extensive enquiry mainly confirms Hallam's conclusions. They both incriminate an exogenous allergen. Tate showed that it is not bedding or clothes, but can be carried in them. It is not vermin. The evidence as to house-dust and its contained moulds and bacteria is inconclusive; but it seems to me most unlikely that the dust of a hospital-ward should *never* contain the responsible substance present in home-dust, nor would children be less exposed to home-dust during the day than during the night. Tate says that the allergen cannot be derived from domestic animals or human beings, largely because some of his patients sleep in a separate bedroom at home. But he himself has shown that the allergen can be carried in bedclothes for a considerable time, in which case the allergen could be derived from the person who makes the beds.

He found no allergic diathesis, acidosis or alkalosis, but good evidence that the trouble is aggravated by an excess of carbohydrates in the diet and by heat.

Rosacea

Hachenburg states that in nearly every patient it is possible to demonstrate some disturbance or other of important bodily functions, generally concerning the vegetative nervous system as it affects the alimentary tract and the circulation. He mentions the frequency of a slight fine tremor of the hands, psychical lability, increased dermographism and spastic states in the smooth musculature. He and also Eastwood and Rulison have noticed

the frequency of *low blood-pressure*, and Rulison associates it with poor muscle-tone, a type of constitution in which hypochlorhydria is often found.

Ryle and Barber were the first in this country to employ the fractional method of gastric analysis in its investigation: in their first small series a strikingly high proportion had hypochlorhydria. In later studies of a much larger number of cases, Eastwood, as well as Brown, Smith and McLachlan, finds that the proportion of cases which have complete achlorhydria or marked hypochlorhydria is about 30%. This percentage is, however, according to Brown and his co-workers, actually lower than that given by a miscellaneous series of other dermatoses. It may therefore be concluded that marked subacidity is not a feature peculiar to rosacea. Moreover, the duration and severity of the disease did not appear in Brown's cases to have any close relationship to the gastric hydrochloric content. In the majority of cases in which the analyses were repeated several times over periods ranging from a few days to 10 years, they gave the same figures, though the clinical condition improved or got well.

The majority of patients are women with an average age of 35 years: the sex seems to have an influence on the gastric finding, as men have an excess of hydrochloric acid more commonly than women. Symptoms of gastric disturbance were present in 61% of Brown's cases, being practically constant in the hyperchlorhydria group. Eastwood found *digestive disturbance* in 95% in her series of several hundred cases. Correlation of clinical and X-ray findings, together with fractional gastric analysis, suggested that reflex flushing always means *a motor disturbance of the stomach*, and she found that the results of treatment were equally good whether dealing with low or high acid-curves, so long as smooth and regular peristalsis and emptying were achieved. The most promising cases were either those with a low acid-curve treated with hydrochloric acid or those with pyloric spasm and excessive acid treated with alkalis. In some cases it is best to give acid with meals and alkali 1½–2 hours afterwards. But both Eastwood and Brown note that the beneficial effect of hydrochloric acid is not confined to those cases showing low acid-curves, and it seems

certain that it has a more far-reaching action than the mere making good of a deficiency in the gastric juice. The chief dietary culprits Eastwood considers to be tea and excess of starch.

As regards other factors, 77% of Brown's cases had dentures or no teeth ; 55% had dandruff or seborrhœa, and 51% focal sepsis in the teeth or tonsils or both, the last being the same percentage as was found by Stokes and Beerman in 1932.

Ocular Complications. In nearly every case a mild *blepharitis* develops sooner or later, predisposing to the formation of *Meibomian cysts*. Some patients develop on the conjunctiva small greyish-yellow *phlyctenular* nodules near the corneal margin and erythema and telangiectasis of the exposed parts. Conjunctivitis generally portends *keratitis*. The corneal lesions usually occur as single or multiple localised infiltrates, generally starting at the limbus and eventually ulcerating.

The greatest relief, in Greeves' experience, is afforded by *X-rays*. A single early application may make an infiltrate disappear and a short course often heals old chronic ulcers. Most cases with ocular complications have appeared to Eastwood to be rather devitalised and to profit from *U.V. light baths* to the whole body except the face.

Vitamins

Vitamins influence resistance to infection, hair-growth and the colour of the skin. The skin is an important station for vitamin-synthesis. Vitamins can no longer be strictly separated from hormones, since it has been shown that vitamin " A " can be synthesised from carotin, and " D " from ergosterol, in the body. The action of vitamins is closely interrelated with that of the other hormones and also with the composition of foods, especially the proportions of proteins and catalysers, *e.g.*, iron, copper, manganese and zinc. Excessive intake of one vitamin leads to increased need of the others.

Vitamin " A." The liver converts the pro-vitamin, carotin, to " A," which it stores. " A " is antagonistic to thyroxin.

Excess. This can be fatal for rats ; lipoid accumulates in the

endothelium and epithelium, the coat becomes shaggy and the hairs of the snout fall out.

DEFICIENCY. This is reported by Frazier and Hu in Chinamen to cause, in addition to typical ocular disorders (xerophthalmia), a *follicular spinulous papular eruption* of the skin, with pronounced *superpigmentation* of every lesion and a milder darkening of other areas (see p. 71). Such changes are, however, not confined to the yellow races nor to instances of extreme deficiency (Pillat). Similarly, Löwenthal in Uganda has described *dryness* of the whole skin, with the exception of the face, associated with an irritable papular eruption, most apparent on the extensor surfaces, and Nicholls in Ceylon has observed a widespread incidence of a similar dermatosis. The clinical picture has been recognised by Goodwin in London. The cutaneous signs are generally earlier than objective ocular changes. *Histologically* one finds hyperplasia and hyperkeratinisation of the epidermis and hair-follicles and metaplasia of the epithelium of the sweat-ducts of keratinising type. All these changes disappear completely on giving " A."

Mackay observed that among a group of London babies, depending for their " A " solely on milk and table-foods, there was a greater susceptibility to *napkin-dermatitis*, *intertrigo* and *dribbling-dermatitis* than in a similar group which received supplemental " A." This susceptibility preceded any obvious changes in skin-texture.

Mackay and Goodwin think that mild degrees of deficiency of " A " are far from rare in this country.

Vitamin " B " Complex (B1 to B5 and Y). Yeast contains the most important members of the complex about equally. In maize-germs B1 predominates and in spinach and tomatoes B2, the only one present in ox-kidneys. B1 is antagonistic to thyroxin.

EXCESS. No effects are known.

DEFICIENCY. In experimental animals there are loss of hair and a dermatitis closely resembling that of human pellagra. The effects show sooner on a carbohydrate-rich than on a fat-rich diet (Randoin). The fall of hair due to lack of B2 can be cured not only by B2 but also by thyroid, lysine and cystine.

*Lack of B*1, which causes beri-beri, leads to no skin-changes.

*Lack of B*2 (*G*) is part of the cause of *pellagra*. The skin-changes consist chiefly of erythema and superpigmentation. The erythema affects the exposed parts, especially the back of the hands and wrists, face and neck, but also frequently the trunk and dorsum of the feet. It is probably provoked by sunlight. After a time there ensue pigmentation and lamellar peeling and the skin becomes gradually thickened, hardened and atrophic. On the nose are seen follicular hyperkeratosis and crusting. The pigmentation is general as well as local, resembling that of Addison's disease. In recent years a number of mild cases have been reported in Europe and even more in America. These mostly form a group which O'Leary distinguishes as *secondary pellagra*, in which there is a preceding non-pellagrous disorder, especially of the gastro-intestinal canal. The latter may operate either through inadequate diet or impaired absorption (see Fig. 48). But it must be remembered that colitis is a characteristic symptom even of endemic idiopathic pellagra.

The possible importance of disturbed sulphur-metabolism has been referred to on p. 436. Sabry states that in early cases *sodium thiosulphate* injections check the skin-lesions and in advanced ones cause their prompt disappearance. Ruffin and Smith report the excellent curative effect of aqueous extract of *liver*. *Desiccated stomach* has also been praised.

Vitamin "C." EXCESS. No effects are known.

DEFICIENCY. This causes *scurvy*. The resistance of the capillaries is lowered, leading to extravasation of blood, especially at points of mechanical stress, with consequent discoloration by hæmosiderin and hæmatoidin. The superficial hæmorrhages are closely associated with the hair-follicles. The subcutaneous tissue is œdematous. Even in milder cases the skin is dry and rough with powdery scaling. The hair-follicles are very prominent (nutmeg-grater skin).

Cases of symmetrical scorbutic skin-changes without manifest scurvy have been described by Nicolau as "scorbutides papulo-kératosiques folliculaires." Histologically there is an early hypertrophy of the keratohyaline-layer.

Some of the *pigmentation* suggests overproduction of melanin, as well as deposit of hæmosiderin. " C " occurs normally in the adrenal cortex and deficiency of " C " leads to hypertrophy of the cortex (Iwabushi) and diminished production of adrenalin (Ohata). Therefore, if adrenalin and melanogen are derived from the same source, there would be more melanogen reaching the skin. Szent-



FIG. 48.—" Secondary " pellagra. Skin-symptoms developed after prolonged mucous colitis. They were evoked when he was exposed to light on the balcony and regressed if shaded from the light. They were not prevented by a vitamin-rich diet. (T. R. Elliott's case.)

Györgyi further points out that " C," as a reversible reducing agent, is capable even in minimal concentration (1 in 0·000025) of completely inhibiting pigment-formation. He tells of subjects of Addison's disease who, when treated with " C " (pure natural ascorbic acid), lost some of their pigmentation, though other symptoms were uninfluenced.

In *Barlow's disease* there are symmetrical pin-head-sized

cutaneous and oral hæmorrhages and nutmeg-grater skin. The hairs are thin and dry and the nails thin, brittle and ridged.

Vitamin "D." Parathyroid is synergistic with "D" as regards tetany but not rickets.

DEFICIENCY. Rather surprisingly, this is not known to cause any skin-changes.

EXCESS. Rabbits get rough skin, falling out of the coat, calcification in the arteries and elsewhere, and severe general symptoms.

The *pigmentary changes* are described on p. 71. In Rodecourt's cases the skin also became rough and chapped.

No excess of "D" can be produced by means of U.V. rays.

Vitamin "E" (Antisterility). This substance is genetically related to ovarian hormone. Anterior pituitary and "E" can largely deputise for each other.

DEFICIENCY. The hairs of male rats become silky or woolly, as in castrates (Verzar and V. Kokas). The hair-papillæ and sebaceous glands become smaller. The disorder can be *cured* with *anterior pituitary.*

Lichen Ruber Planus

In 25 out of 28 cases of typical lichen planus Jacob and Helmbold isolated a *Gram-negative anaerobic bacillus* of the colon-typhoid group, which grew freely on a semi-solid dextrose human serum agar medium, containing pieces of human tissue. The serum must be inactivated between 56° and 60° C. for a number of hours. In sections of lichen planus lesions the organism could be demonstrated in the infiltrate but not in the epithelium. It was not found in normal skin nor in a number of other papular skin-affections. Inoculation of the skin of normal persons with this organism produced in a few instances lesions which both clinically and histologically resembled lichen planus.

TREATMENT. Biberstein successfully cured 70% of a series of cases, including some which had defied for years the usual treatment, by injecting *extracts of the papules.*

In cases resistant to the usual treatments, such as arsenic, ultra-violet rays and fever, Scherber recommends the careful trial

of *Germanin* (Bayer 205). Lichen ruber patients are much more sensitive to it than subjects of pemphigus. It is necessary to keep a careful watch on the kidneys. The initial dose is 0·25 gm., and 0·5 gm. is seldom exceeded. A feeling of tension in the palms and soles is a warning to intermit the treatment, and it must be definitely stopped if there is erythema here or elsewhere.

Pemphigus and Dermatitis Herpetiformis

IODIDE TEST. It is an old observation that *dermatitis herpetiformis* is made worse by ingestion of bromide or iodide, and there are several instances on record in which iodide actually seems to have originated the disease. Jadassohn (1912) showed that iodide causes aggravation not only when administered internally but also if applied externally in an ointment, especially if made with vaseline. Though this sensitiveness is not constant it is a very frequent symptom both in the florid and latent stages. The reaction appears within 24–48 hours and the new lesions so provoked mostly resemble the original ones. Often it is only the areas previously affected that react. The sensitiveness undergoes marked fluctuation, which sometimes runs parallel with clinical activity. Possibly it has an anaphylactic basis, since Lehner has been able to transmit it to a rabbit's ear by means of the blister-fluid, and Eisner has reported successful desensitisation by means of minute slowly rising doses.

In 1925 Jessner and Hoffmann sought to establish sensitiveness to iodide and bromide as a differential diagnostic test, since it is absent in pemphigus. Bromide is less often provocative than iodide. Internally 0·001 gm. of potassium iodide may be enough. If 1 gm. produces no reaction higher doses will not either. The ointment, generally in a strength of 20% or 50%, is smeared on, covered with battiste, bandaged and allowed to remain in place for 24–36 hours.

Perutz and Gutmann thought that the provocative action of iodide was due to poverty of chlorine and could be counteracted by giving sodium chloride. But Riehl, Jun., and Urbach dispute this and state that, in fact, a similar aggravation can be produced

by large doses of chloride ; the relative active doses being about 10 gm. chloride, 8 gm. bromide, and 2 gm. iodide.

TREATMENT. Various authors have had favourable results in *pemphigus vulgaris* with *acetarsol* (Oppenheim) ; Smith observed a recovery from *pemphigus foliaceus* following intravenous injections of *tryparsone*, 1 gm. at first and later 2 gm. weekly. In a series of cases of different varieties Scherber, who also has a high opinion of *blood-transfusion*, *salt-free diet* and the old combination of *arsenic* and *ultra-violet irradiation*, has produced striking improvement and often complete cure with *Germanin*. Germanin was first tried by Veiel. The dosage which has proved most satisfactory is 0·5 gm. on the first day and then four further injections each of 1 gm. every second day, intravenously. The treatment is liable to cause rashes or signs of nephritis. If these are allowed to disappear, another 2 or 3 injections of 1 gm. can be given at intervals of 7–14 days. I have found it extraordinarily effective in a severe case of the *pyodermite végétante* type of pemphigus vegetans.

Dermatitis herpetiformis responds less readily to Germanin (Scherber). Steiner in 4 cases succeeded with *sodium thiosulphate*, 10 intravenous injections, 3 each week, of 1 gm. ; at the same time ½ gm. was given orally thrice daily. The method was introduced by Wirtz. Possibly it depends on its power of reducing free iodine.

Scleroderma and Acrosclerosis

Sellei thinks that scleroderma and acrosclerosis are quite different diseases. He classifies this group of disorders as follows :—

Scleroderma Verum. *Characteristics.* It arises in different parts of the body and is an *infiltrative* process which eventually reaches homogenisation. Asymmetrical, round, ribbon-like or irregular plaques are formed, yellowish, alabaster-like, hard and *sharply defined* : pigment " displacement " (vitiligo) is frequent. There are no subjective symptoms or trophic disturbances. Healing may occur spontaneously, the plaques being replaced by greyish brown depressions and in some instances by white scars, or the disease develops into myosclerosis.

Functional disturbance of the *pancreas* is indicated by a positive atoxyl lipase resistance test.

Treatment. *Ferment* therapy is effective, especially the following :—(*a*) raw pancreas, 100–200 gm. daily ; (*b*) pancreatic ferments in the form of tablets containing amylase, lipase and trypsin, to be taken 1 hour before each meal ; these must be fresh ; (*c*) duodenal ferments in tablet-form, together with the pancreas ; (*d*) liver-extracts in tablets and injections. Continuous treatment for many months is necessary.

MORPHŒA. This is characterised by roundish sclerodermatous plaques, circumscribed with a lilac ring. The induration is relatively superficial and appears before the lilac ring. When the plaques heal, they leave atrophy and sometimes lustrous squamous patches. It may be associated with other forms of true scleroderma but never with acrosclerosis.

Acrosclerosis. *Characteristics.* It always arises *symmetrically* and simultaneously on the hands and feet and on the face. There are *vasomotor* symptoms, such as local syncope and asphyxia. Subjective symptoms are complained of, especially pain in cold weather. The process is one of *shrinkage*. On the finger-tips appear ulcers and stellate scars. The phalanges become pointed, the bones dry up and mutilation supervenes. In spite of its tautness, the skin may remain quite soft. The two distal phalanges are frequently hard to the touch. [He contrasts this condition with true *sclerodactylia* (a form of scleroderma), in which the induration spreads from the arm to the back of the hand and thence to the fingers.] The face becomes mask-like, the mouth gets smaller, the lips narrowed, and the teeth protrude. *Telangiectasia* is common, and there are frequently associated affections of the heart and aorta. After the disease has developed it remains in the same stage for decades. The great majority of patients are adult women. In most cases the skin is very sensitive to a 1 in 10,000 or 1 in 15,000 solution of adrenalin. The atoxyl lipase resistance test is negative.

Treatment. Ferments produce no objective cure but only subjective improvement. The best results have been obtained with vasodilators, such as *acetyl-cholin*, *padutin* and extracts of muscle and skin. Sellei especially recommends *glanducutin*, a skin-extract. *Histamine*, administered by iontophoresis or in

ointment, *parathyroid* and occasionally *sympathectomy* have also helped.

RAYNAUD'S DISEASE. He considers this distinct both from scleroderma and acrosclerosis. There may arise deep gangrenous processes of considerable extent, but skin-changes never appear in advance of the gangrene. He thinks it belongs to the group of hyperadrenalinæmias (see also pp. 12, 19).

Keratoderma Climactericum

Haxthausen gave this name in 1934 to what he considers a clinical entity, comprising *circumscribed hyperkeratosis* mainly of the *palms* and *soles*, occurring in women in association with the *climacteric* and accompanied by general disorders, of which *obesity* and arterial *hypertension* are the commonest and *arthritis* nearly as frequent. According to Gram, obesity, hypertension and arthritis form a very frequent "post-climacteric triad." Apart from age and sex I have found none of these associations to be constant. The hyperkeratoses appear as discrete, well-defined patches with superficial cracks, mainly on the parts most exposed to pressure, especially the centre of the palms, the ball and outer border of the feet, the heels and the knees (see Figs. 49, 50). They are not preceded by eczema. Histology shows marked parakeratosis but none of the micro-abscesses of psoriasis.

Of several of my cases whose blood uric acid was estimated only one had a raised figure. Her keratoderma, which was associated with spondylitis, responded well to cincophen.

Treatment of Cavernous Hæmangioma

Probably the most perfect results are obtained with radium or radon. But they have the disadvantages that they are not always easily obtainable, require great judgment in dosage to avoid disastrous damage, and, in the case of the scalp, produce baldness.

An excellent alternative is to bring about sclerosis by means of *injections*. I have systematically compared sodium morrhuate,

quinine and urethane, and *dilute hydrochloric acid B.P.*, and have found hydrochloric acid much the most satisfactory. The injection is made with a very fine needle as nearly as possible into



FIG. 49.—Keratoderma climactericum. (H. Haxthausen, *Brit. Journ. Derm. and Syph.*, 1934, p. 164.)

the centre of the tumour, the dose depending on its size. I generally begin with 0·2 c.c.; further doses are only given into any remaining soft areas when shrinkage has ceased. Silcock advocates the use of 2% sodium morrhuate *froth*. One c.c. of a



FIG. 50.—Keratoderma climactericum. (H. Haxthausen, *Brit. Journ. Derm. and Syph.*, 1934, p. 163.)

10% solution is mixed with 4 c.c. of sterile distilled water and drawn in and out of a syringe till the froth is formed. Enough is injected to produce moderate distension of the whole tumour.

Erythrocyanosis Frigida Crurum Puellarum

This condition, which has points of resemblance with chilblains on the one hand and indurative subcutaneous tuberculosis on the other, was first accurately described in 1921 by Thibierge and Stiassnie under the name "œdème asphyxique symmétrique des jambes chez les jeunes filles lymphatiques." But neither of these names is completely appropriate; for it can occur in men (Klingmüller and Fox), is occasionally unilateral, and may involve the arms as far as the shoulders (Pautrier). A firm bolster-like swelling begins as a horizontal band encircling the leg just above the ankle and may extend over the calf and, rarely, above the knee. There is no pitting. The skin is very cold to the touch and usually of a deep violet colour. There are no circumscribed deep lumps, as in Bazin's disease. It is often accompanied by keratosis follicularis rubra and hyperhidrosis of the hands and feet. I have, in several cases, observed on such a patch the development of bullæ containing clear fluid, which burst and leave superficial slowly-healing sores.

ÆTIOLOGY. Cold plays a much less obvious part in its causation than in that of chilblains; indeed, several of my cases have begun or been worst in the summer. It also differs from chilblains in the absence, as a rule, of itching. Moreover, it is seldom that it is accompanied by ordinary chilblains of the toes and fingers. Numerous authors blame endocrine disturbances, especially the ovaries and thyroids (Comby). Others assume an inborn dystrophy of the capillaries (Alexander). Microscopically the vessels are seen to have their endothelium damaged and to be dilated and surrounded by a small non-specific infiltrate (Klingmüller, Pautrier). There is no tubercular structure. But though there is no evidence that this condition is tuberculous, it may, when tubercle bacilli are mobilised, contribute to their settling at the affected sites.

TREATMENT. It has generally responded well in my experience to a combination of *carbon arc baths* and small doses of *thyroid* and *iodide*. Oldham in a typical case observed that during spinal anæsthesia the swellings became warm and the blue

colour was replaced by pink. *Lumbar sympathectomy* resulted in their remaining warm, pink and dry, for at least $1\frac{3}{4}$ years, though the swellings did not disappear.

Dermatitis due to Brucella Abortus

According to Tidy human infections are due to (*a*) consumption of infected milk (40% of raw milk is infected) and (*b*) contiguity to infected animals. A high incidence of mild or latent infection is revealed by the frequency with which the serum of apparently healthy persons in low dilutions agglutinates brucella abortus.

Urbach in 1928 drew attention to the fact that infection with B. abortus may be accompanied by skin-eruptions. Four types have been described:—(*a*) lentil-sized, red, itchy, follicular papules, which frequently become vesicular and then pustular and leave slight scars; they appear with little delay on the parts of the arms directly exposed to infection and subside without treatment within 3 weeks: (*b*) an exanthem on the chin, axillæ, thighs and dorsum of the feet, consisting of minute papules with a little scarring: (*c*) a bullous-hæmorrhagic dermatitis appearing first on the hands and arms a few days after exposure; later it breaks out elsewhere with severe itching and constitutional symptoms; the distribution may be that of erythema multiforme and the bullæ may leave behind criss-cross strands of scar-tissue: (*d*) pustules, vesicles and papules, at first at the site of exposure, but within 14 days covering almost the whole body: bullæ and erosions develop later and there is general adenopathy; such an eruption has been known to last at least 4 years with only short intermissions.

A patient of Urbach's so affected gave a positive intracutaneous reaction to a *vaccine* of B. abortus, graded doses of which led to cure.

He also described as a *diagnostic test* the "Immuno-Ballungsreaktion," which consists in the formation of a voluminous, ball-like, free-floating mass when the patient's serum is added in a test-tube to a suspension of B. abortus.

Recurrent Buccal and Vulval Ulcers

In 1923 Lipschütz drew attention to acute ulcers of the vulva. He thought they were due to *bacillus crassus*, which has since been identified with Döderlein's bacillus, an inhabitant of the vagina. In the last few years many of these acute vulval ulcers have been observed in association with acute and sometimes recurrent aphthous ulceration of the mouth. The clinical similarity between the genital and oral lesions is striking. Both are very painful and tend to recur. Often there are also skin-eruptions, especially in the form of erythema nodosum or papulo-pustules (Schnabl, Samek and Fischer and Whitwell). The fact that the bacillus crassus is not always found in the mouth-ulcers, though abundantly present in the vulval lesions, throws some doubt on its pathogenicity. Autoinoculation in several cases has been negative. On the other hand, it has sometimes been found in the blood and in a subcutaneous node (Samek and Fischer).

Kumer deduces from animal-inoculation that the superficial erosive type of recurrent mouth-ulcer is often an atypical herpes; but it must be remembered that the virus of herpes is very commonly present in the saliva of normal mouths.

Glossitis

Chevallier and his co-workers differentiate glossitis without anæmia as follows:—(*a*) *glossite rasée antérieure*: this smooth inflammation of the anterior portion is identical with Hunter's glossitis, an important symptom of primary anæmia. Treatment with *liver* and *iron* leads to cure. (*b*) *Glossite médiane losangique* has nothing to do with gastric disorders or anæmia. (*c*) *Glossite triangulaire postérieure* has no connection with blood-diseases, but indicates gastric disorder. They also describe under the name "glossite mamelonnée" a special non-syphilitic disorder of the posterior half of the dorsum, exhibiting painless warty growths; it is associated with similar changes in the stomach.

Cheilitis

Jordan and Tarabuchin distinguish cheilitis exfoliativa and Ch. glandularis as different diseases.

Ch. exfoliativa is superficial, appears late in life, is favoured by deficient oral hygiene (tartar, gingivitis, pyorrhœa) and is benefited by external and internal administration of *Lugol's solution.*

Ch. glandularis is a deep affection, occurs generally in the third and fourth decade, and is due to inflammation of congenitally abnormal accessory salivary glands. It can be successfully treated with *radium* and *potassium thiocyanate* externally.

Bibliography

ASDÉRY, H. "Les aurides biotropiques," *Rev. franc. Dermat.*, 1935, **11**, 33 (*Abs. Zbl. Hautkrank.*, 1935, **51**, 122).

BARBER, H. W. "Pustular Psoriasis of the Extremities," *Brit. Journ. Derm. and Syph.*, 1933, **45**, 113.

BARBER, H. W., and FORMAN, L. "The Results of Intradermal Tests in certain Dermatoses and the Therapeutic effect of Intradermal Vaccines," *Brit. Journ. Derm. and Syph.*, 1933, **45**, 4.

BIBERSTEIN, H. "Die Immuntherapie der Warzen und Kondylome," *Klin. Woch.*, 1932, **11**, 1021.

BIZZOZZERO, E. "On the Phenomenon of Koebner in Psoriasis," *Ann. de Derm. et de Syph.*, 1932, **3**, 510.

BLOCH, B. "Metabolism, Endocrine Glands and Skin Diseases," *Brit. Journ. Derm. and Syph.*, 1931, **43**, 61.

BORMANN, J. "Eklatante Effekte der Röntgenbehandlung des Erysipels," *Dermat. Woch.*, 1935, **100**, 181 (*Abs. Zbl. Hautkrank.*, 1935, **51**, 285).

BRIDGE, J. C. "Occupational Diseases of the Skin," *Brit. Med. Journ.*, 1933, **2**, 324.

BROWN, W. H., SMITH, M. S., and MCLACHLAN, A. D. "Fractional Gastric Analysis in Diseases of the Skin," *Brit. Journ. Derm. and Syph.*, 1935, **47**, 181.

BURGESS, J. F., and USHER, B. "Hypersensitiveness to Quinine," *Canad. M. A. J.*, 1930, **23**, 45 (*Abs. Archives of Derm. and Syph.*, 1930, **22**, 713).

CAMPBELL, H. S., and FROST, K. "A new form of Therapy for Psoriasis," *Archives of Derm. and Syph.*, 1932, **26**, 435.

CHEVALLIER, P., MOUTIER, F., STEWART, W., SEVAUX, A., and ELY, Z. "L'examen de l'estomac et la cure de fer dans les glossites dorsales," *Bull. Soc. franc. Dermat.*, 1934, **41**, 1736 (*Abs. Zbl. Hautkrank.*, 1935, **50**, 606).

CHEVALLIER, P., MOUTIER, F., COLIN, M., MOLINES, R., and SEVAUX, A. "Glossite mamelonnée et gastrite mamelonnée," *Bull. Soc. franc. Dermat.*, 1934, **41**, 1934 (*Zbl. Hautkrank.*, 1935, **50**, 606).

CIPOLLARO, A. D., and SHEPLAR, A. E. "Therapeutic Uses of Bacteriophage in the Pyodermias," *Archives of Derm. and Syph.*, 1932, **45**, 280.

COKE, H. "Psoriasis Treated by Low-fat Diet," *Brit. Journ. Derm. and Syph.*, 1935, **47**, 164.

CONNOR, J. I., and MCKIE, M. "Treatment of Superficial Staphylococcal Infections by Toxoid," *Brit. Journ. Derm. and Syph.*, 1934, **46**, 20.

CORSI, H. "Dermatitis Bullosa Pratensis Striata," *Brit. Journ. Derm. and Syph.*, 1933, **45**, 524.

COX, H. E. "The Chemical Examination of Furs in Relation to Dermatitis," *The Analyst*, 1933, **58**, 738.

CRUTCHFIELD, E. D., and STOUT, B. F. "Treatment of Staphylococcic Infections of the Skin by the Bacteriophage," *Archives of Derm. and Syph.*, 1930, **22**, 1010.

DOLMAN, C. E. "Clinical Uses of Staphylococcus Toxoid," *Lancet*, 1935, **1**, 306.

DORE, E. "Pityriasis lichenoides et varioliformis acuta," *Proc. Roy. Soc. Med.*, 1931, **25**, 212.

EASTWOOD, S. (*a*) "Gastric Secretions and other Digestive Factors in Rosacea," *Brit. Journ. Derm. and Syph.*, 1928, **40**, 91 and 148. (*b*) "Discussion on the Conditions common to Ophthalmic and Dermatological Practice," *Proc. Roy. Soc. Med.*, 1934, **27**, 1113.

FOX, E. C. "Exfoliative Dermatitis from Butesin Picrate Ointment," *Archives of Derm. and Syph.*, 1932, **26**, 44 (*Abs. Brit. Journ. Derm. and Syph.*, 1933, **45**, 372).

FRAZIER, C. N., and HU, C. "Cutaneous Lesions associated with Vitamine Deficiency in Man," *Zbl. Hautkrank.*, 1931, **37**, 677 (*cit.* Schaaf).

GOLDMAN, L. "Nickel Eczema," *Archives of Derm. and Syph.*, 1933, **28**, 688 (*Abs. Brit. Journ. Derm. and Syph.*, 1935, **47**, 73).

GOLDSMITH, W. N. (*a*) "Die Staphylokokken bei Acne Vulgaris," *Arch. f. Derm. u. Syph.*, 1925, **149**, 575. (*b*) "Verrucose pyodermia," *Proc. Roy. Soc. Med.*, 1935, **28**, 364.

GOODWIN, G. P. "A Cutaneous Manifestation of Vitamin A Deficiency," *Brit. Med. Journ.*, 1934, **2**, 113.

GRAY, A. M. H. "Pityriasis Lichenoides et Varioliformis Acuta," *Proc. Roy. Soc. Med.*, 1928, **22**, 92, and 1929, **23**, 351.

GREENHOUSE, E. A., and SULZBERGER, M. B. "The Common Weed Tansy (Tanacetum Vulgare) as a Cause of Eczematous Dermatitis," *Journ. Allergy*, 1933, **4**, 523.

GREEVES, R. A. "X-ray Applications in Superficial Keratitis," *Trans. Ophth. Soc. U.K.*, 1930, **50**, 111.

GROSS, P. "Pityriasis lichenoides et Varioliformis acuta," *Arch. f. Derm. u. Syph.*, 1931, **23**, 33 (*cit.* Juliusberg).

GRÜTZ, O. "Ueber eine neue Pathogenese und Therapie der Psoriasis," *Deut. med. Woch.*, 1934, **60**, 1039.

GRÜTZ, O., and BÜRGER, M. "Psoriasis als Stoffwechselproblem," *Klin. Woch.*, 1933, **12**, 373.

HACHENBURG, D. "Untersuchungen ueber Grundlagen der Rosazea," *Derm. Woch.*, 1931, **92**, 165.

HALLAM, R. "Further Observations on the Ætiology of Papular Urticaria (Lichen Urticatus)," *Brit. Journ. Derm. and Syph.*, 1932, **44**, 117.

HAXTHAUSEN, H. "Keratoderma Climactericum," *Brit. Journ. Derm. and Syph.*, 1934, **46**, 161.

HORNER, S. G. "Industrial Dermatitis," *Trans. St. John's Hosp. Dermat. Soc.*, 1934, **23**, 37.

INGRAM, J. T. "Acrodermatitis Perstans and its Relation to Psoriasis," *Brit. Journ. Derm. and Syph.*, 1930, **42**, 489.

JACOB, F. M., and HELMBOLD, T. R. "Bacteriologic Studies on Lichen Planus," *Archives of Derm. and Syph.*, 1933, **27**, 472.

JORDAN, A., and TARABUCHIN, A. "Ueber Cheilitis exfoliativa und glandularis," *Derm. Zeit.*, 1935, **70**, 249 (*Abs. Zbl. Hautkrank.*, 1935, **51**, 59).

JULIUSBERG, F. "Die Parapsoriasisgruppe," *Zbl. Hautkrank.*, 1933, **45**, 417.

KAHN, B. L. "Bacteriophage Therapy for Pyodermia," *Archives of Derm. and Syph.*, 1931, **24**, 218.

KETRON, L. W., and BURKY, E. L. " The Cultural Requirements of the Acne Bacillus," *Archives of Derm. and Syph.*, 1925, **11**, 354.

KINNEAR, J. " The Streptococcal Dermatoses," *Brit. Med. Journ.*, 1935, **1**, 291.

KLINGMÜLLER, V., and DITTRICH, O. " Perniosis or Erythrocyanosis," *Archives of Derm. and Syph.*, 1930, **22**, 615.

LÄWEN, A. " Ueber die Verwendung und Wirkungsart der örtlichen Eigenblutinfiltration bei der Behandlung schwerer fortschreitender pyogener Prozesse im Gesicht," *Immunität usw.*, 1929/30, **101** (*cit.* Tachau).

LAWRENCE, C. H., and FEIGENBAUM, J. " The Treatment of Acne Vulgaris with Pregnancy Urine Extract," *New Eng. Journ. of Med.*, 1935, **212**, 1213.

MACCORMAC, H. " A Note on Parapsoriasis," *Brit. Journ. Derm. and Syph.*, 1932, **44**, 576.

MACKAY, H. " Vitamin A Deficiency in Children ; Vitamin A Requirements of Babies ; Skin Lesions and Deficiency of Vitamin A," *Arch. Dis. Childhood*, 1934, **9**, 133.

MAYER, R. L. (*a*) " Die Ueberempfindlichkeit gegen Körper von Chinonstruktur," *Arch. f. Derm. u. Syph.*, 1928, **156**, 331. (*b*) " Ueber die Wirkung von künstlichen Düngemitteln, insbesondere des Kalksalpeters, auf die Haut," *Arch. Gewerbepath. u. Gewerbehyg.*, 1932, **5**, 808.

MURRAY, D. S. " Staphylococcus Toxoid," *Lancet*, 1935, **1**, 303.

O'DONOVAN, W. J. " Dermatitis due to Podophyllum Resin," *Brit. Journ. Derm. and Syph.*, 1935, **47**, 13.

O'LEARY, P. A. " Pellagra : a Study of 34 Cases in Localities where Pellagra is not Endemic," *Northwest Med.*, 1928, 320.

OLDHAM, J. B. " Erythrocyanosis Crurum Puellarum Frigida," *Lancet*, 1933, **225**, 1423.

OPPENHEIM, M. " The Use of Spirocid in Pemphigus Vulgaris Chronicus and Vegetans," *Derm. Woch.*, 1930, **51**, 1855.

PASCHER, F., and SULZBERGER, M. B. " Ragweed Dermatitis," *Archives of Derm. and Syph.*, 1933, **28**, 223.

PATERSON, W. G. C. " The Physiology of the Superficial Blood-vessels in Psoriasis," *Brit. Journ. Derm. and Syph.*, 1932, **44**, 310.

PETERKIN, G. A. G. " Contact Dermatitis due to Sodium Evipan," *Brit. Med. Journ.*, 1934, **1**, 456 (*Abst.*).

RAIGA, A. " Traitement des furoncles et des anthrax par le bacteriophage de d'Hérelle," *Presse Méd.*, 1929, **37**, 187.

ROBERTSON, W. G. A. " Poisoning by Ground Ivy," *Brit. Med. Journ.*, 1934, **1**, 1008.

RUFFIN, J. M., and SMITH, D. T. " The Treatment of Pellagra with certain Preparations of Liver," *Amer. Journ. Med. Sci.*, 1934, 512 (*Abs. Brit. Journ. Derm. and Syph.*, 1934, **46**, 444).

SABRY, I. " On the Chemical Nature of the ' Pellagra Toxin ' and the Discovery of the Sodium Thiosulphate Treatment of Pellagra," *Journ. Trop. Med. and Hyg.*, 1932, **35**, 164.

SCHAAF, F. " Ueber die Bedeutung der Vitamine in der Dermatologie," *Zbl. Hautkrank.*, 1933, **46**, 657.

SCHAMBERG, J. F. " The Dietary Treatment of Psoriasis," *Journ. Amer. Med. Assoc.*, 1932, **98**, 1633.

SCHERBER, G. (*a*) " Die Germaninbehandlung der verschiedenen Pemphigus-chronicus Formen," *Med. Klinik.*, 1933, **29**, 1739. (*b*) " Zur Behandlung verschiedener Formen von Lichen ruber planus mit Germanin," *Dermat. Woch.*, 1934, **98**, 797.

SCHLIEPHAKE, E. " Treatment of Patients with Ultra-short Electrical Waves," *Zbl. f. Inn. Med.*, 1933, **54**, 977.

SCOTT, J. A. (*a*) "The Treatment of Sycosis and Allied Follicular Infections of the Skin," *Brit. Journ. Derm. and Syph.*, 1933, **45**, 190. (*b*) "A Case of Orange Dermatitis," *ibid.*, 1934, **46**, 378.

SELLEI, J. "The Diagnosis and Treatment of Scleroderma and Acrosclerosis and some of their Kindred Diseases," *Brit. Journ. Derm. and Syph.*, 1934, **46**, 523.

SEMON, H. C. "Psoriasis Treated by Low-fat Diet," *Brit. Journ. Derm. and Syph.*, 1935, **47**, 164.

SEQUEIRA, J. H. "Biotropism (Milian)," *Brit. Journ. Derm. and Syph.*, 1931, **43**, 553.

SILCOCK, F. A. E. "Treatment of Vascular Nævi with Injection of 2% Sodium Morrhuate Froth," *Post-Grad. Med. Journ.*, 1935, **11**, 226.

SMITH, J. F. (*a*) "A Form of Chronic Pyodermia," *Brit. Journ. Derm. and Syph.*, 1929, **41**, 149. (*b*) "A Case of Recovery from Pemphigus Foliaceus," *Brit. Journ. Derm. and Syph.*, 1932, **44**, 588. (*c*) "The Factor of Immunity in Chronic Furunculosis," Paper read before Brit. Assoc. of Derm., July, 1935.

STEINER, E. "Sodium Thiosulphate Treatment of Dermatitis Herpetiformis," *Derm. Woch.*, 1934, **98**, 682 (*Abs. Brit. Med. Journ.*, 1934, **2**, 35).

SULZBERGER, M. B., and KERR, P. "Sensitisations of Eczematous Type," *Journ. Allergy*, 1933, **4**, 326.

SULZBERGER, M. B., ROSTENBERG, M. B., and SHER, J. J. "Acneform Eruptions," *New York State Journ. Med.*, 1934, **34**, 1.

SYMMERS, D. "Antitoxin Treatment of Erysipelas," *Journ. Amer. Med. Assoc.*, 1928, **91**, 535.

SZENT-GYÖRGYI, A. V. "Vitamin C, Adrenalin und Nebenniere," *Deut. Med. Woch.*, 1932, **58**, 852 (*cit.* Schaaf).

TACHAU, P. "Folliculäre Pyodermien I.," *Jadassohn's Handbuch IX*/2, 1934, 235.

TATE, B. C. "Papular Urticaria (Lichen Urticatus)," *Arch. of Dis. in Childhood*, 1935, **10**, 27.

THOMSON, M. S. "The Treatment of Erysipelas by means of Anti-Scarlet Fever Serum," *Brit. Journ. Derm. and Syph.*, 1929, **41**, 417.

TULIPAN, L. "Dermatitis from Cinnamon," *Archives of Derm. and Syph.*, 1932, **25**, 921 (*Abs. Brit. Journ. Derm. and Syph.*, 1933, **45**, 372).

TURRELL, W. J., WILSON, J., and RUSSELL, K. "Discussion on Short-wave Diathermy," *Proc. Roy. Soc. Med.*, 1935, **28**, 301.

URBACH, E. "The Significance of the Cuti- and 'Immunoballungs' Reactions for the Diagnosis of Dermatoses due to Bacillus Abortus (Bang)," *Derm. Zeit.*, 1932, **64**, 230 (*Abs. Brit. Journ. Derm. and Syph.*, 1933, **45**, 271).

WHITE, W. A., and COONEY, E. A. "A non-operative Treatment of Carbuncles," *New England Journ. Med.*, 1932, **207**, 398.

WHITFIELD, A. "Some Notes on Acne Vulgaris," *Brit. Journ. Derm. and Syph.*, 1934, **46**, 257.

WHITWELL, G. T. B. "Recurrent Buccal and Vulval Ulcers with associated Embolic Phenomena in the Skin and Eyes," *Brit. Journ. Derm. and Syph.*, 1934, **46**, 414.

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