Goulstonian lectures on modern views upon the significance of skin eruptions : delivered before the Royal College of Physicians of London / by H.G. Adamson.

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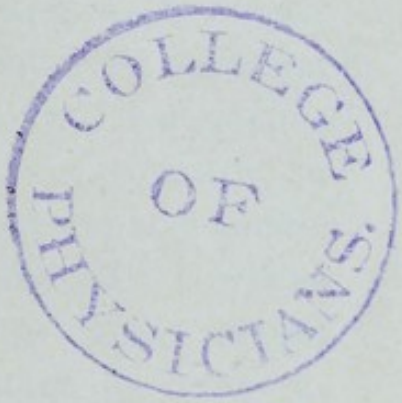

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Modern Views Upon the Significance of Skin Eruptions.

By H. G. ADAMSON, M.D.Lond., F.R.C.P.Lond.

Physician for Diseases of the Skin, St. Bartholomew's Hospital.

LECTURE I.

Delivered on March 12.

Mr. President and Fellows,—I thank you for the great honour you have done me in asking me to deliver these lectures. The office of Goulstonian lecturer has not been held by a dermatologist since Dr. Liveing gave his classical lectures on leprosy in 1873—now nearly 40 years ago. I feel, therefore, that this occasion is a double honour—to dermatology, as well as to myself. I believe that I have only to put before you some of the current aspects of this branch of medical science in order to reveal a subject full of interest, not for the specialist only, but for all who study medicine, and to show that dermatology is worthy of the honour you have conferred upon it.

It has been frequently said of dermatology that it is burdened with too many names and with names which are often too elaborate. It is true that a very large number of skin eruptions have been described and given

names—often long explanatory names; but this is perhaps not surprising if we remember that the skin is, from its position, not only exposed to all sorts of hurtful agencies from without and to numerous attacks or influences from within, but that this exposed position also makes possible the observation and description of details of the conditions resulting from these influences and assaults, which would be hidden from view if occurring in internal organs.

My purpose in these lectures is to inquire into the significance of some of these eruptions as interpreted by the light of our present-day knowledge, and to consider the reasons for their many differences in character and in distribution.

We now no longer regard them as natural objects, as did Willan, nor as pathological states, as did Hebra, but as the result of various hurtful agencies or abnormal influences affecting the skin. This is not to say that the accurate clinical and microscopical study of skin affections was not, and is not, essential, but that these studies are preliminary to that which we aim at—namely, the understanding of the real meaning of these eruptions.

This changed point of view is seen in the different manner of naming skin diseases formerly and now. The earlier names of skin diseases, such as eczema, acne, psoriasis, described the appearance or some clinical character of the eruption. Now, if we name a new disease, we try to indicate its origin and nature —as sporotrichosis, blastomycosis, toxi-tuberculide. But sometimes we are not able to go farther back than the pathological anatomy, as in parakeratosis, and sometimes, even now, we can only describe a clinical feature, as in granulosis rubra nasi.

Eruptions due to Physical Injuries to the Skin.

I propose in this lecture to deal mainly with those skin affections which result from the action of microbes, but I shall first refer briefly to one or two points concerning the reactions arising from local physical agents.

The action of all harmful agents upon the body tissues is first to cause degenerative changes (which may lead to death of the tissues), and these degenerative changes may give rise to reactive effects in the form of increased cell activity and serous exudation. But there are a few special features in regard to reactions of the skin to local physical injuries which deserve particular mention, because they give special characters to these reactions.

First, there is the part taken by the epidermis in these defensive efforts. This is well illustrated in the common corn. A long-continued slight friction or pressure will lead to a callosity or a *corn*, which represents a cell reaction confined to those parts injured—namely, the cells of the epidermis. It is a proliferation of the horny cells. It can hardly be called inflammation—yet it is a protective effort on the part of the tissues against injury.

But if the injury is somewhat more severe or more sudden, there is no time for proliferation of the horny cells, and damage is done to the more tender prickle cells, with the result that serous exudation is poured out from the vessels in the corium and a *blister* forms. Here it seems probable that the serous exudation is a protective effort against the poisons produced by death or damage of the epidermic cells, an effort to render the poisons inert by dilution, or perhaps by neutralization by antitoxins.

Another effect of local injury to the skin, which is not observed elsewhere, is the production of a *wheal* by a sudden blow or by some chemical action. Here there is

an exudation of serum into the deeper parts of the skin, which is often regarded as entirely the result of a reflex or vaso-motor disturbance. But it is also maintained that the wheal is mainly, if not wholly, the result of damage to the endothelium of the vessel walls, and that it, too, represents an inflammatory reaction rather than a vaso-motor disturbance.

So that all these disturbances which occur in the skin, as the result of physical injuries, represent protective reactions on the part of the tissues, and the nature of the disturbance, whether in the shape of corns, of blisters, or of wheals, varies according to the particular tissues which take part in the reaction.

An interesting and remarkable circumstance is the difference in length of time that elapses between the exposure to different kinds of injury and the resulting reactions. To a mechanical injury, for instance, the reaction may be almost immediate; to burns it is a little delayed; to freezing (as with carbon dioxide snow) still further delayed; after application of a strong light (as the Finsen light) it does not occur for several hours, and after exposure to X-rays not for some days. It will be noticed that the more unusual the kind of injury the more delayed the reaction. A possible explanation of this fact is that the tissues of the body have acquired a hypersensitiveness to damage done to them by the more common forms of physical injury. This is a view of which I shall have something further to say in my next lecture.

Eruptions due to Invasion of the Skin by Micro-organisms.

It has for long been taught that the inflammatory processes which occur in a tissue when it is invaded by

micro-organisms represent a local effort at defence against that invasion. In the same way are to be explained the eruptions of the skin which result from local microbic invasion—the eruption which we see and regard as the disease is really a beneficial occurrence and represents the local effort at defence against invading organisms.

Although these facts are commonly recognized they are not always sufficiently insisted upon, and more especially as an explanation of the many differences in type of the resulting eruptions. In works on pathology the only types of reaction to microbic invasion of the skin to which any attention is paid are pustules and granulomata, but if we recall some of those eruptions which we know to be due to microbic invasion, we find that they may be of very varied aspect. For example, there are the scaly patches and broken hairs produced by ringworm fungus, the vesicular and pustular lesions resulting from other ringworm fungi, the scaly macules of pityriasis versicolor, the black-head or comedo and the papulo-pustule of acne vulgaris, the follicular pustule of staphylococcic invasion, the vesicle or blister rapidly drying into a crust of streptococcic infection, the different types of eruption—papular, nodular, warty and gummatous—the result of infection by tubercle bacillus, *Spirochæta pallida*, sporotrichium, blastomycosis, actinomycosis, &c., and to these we may add the erythematous patches of a macular syphilide, the rose-spots of typhoid fever, and probaby other erythematous eruptions.

If we ask why the skin should react in such apparently different ways to microbic invasion, the answer is that the skin is made up of a variety of cells having different structure, and that any or all of these cells may take part

in these reactions. Sabouraud[1] has illuminated this matter by an idea which greatly helps to make clear the meaning of all these different types of reaction, and I have already given some hint of this idea when speaking of the reactions to physical agents. Sabouraud's view is that we are to regard each cell as reacting in defence against microbic invasion by the carrying out of its own special function. For example, the function of the epidermic cells is to produce horny cells, so that when the horny cells take part in the reaction we get hyperkeratosis and exfoliation or scaling; the function of the connective tissue cells is to produce fibrous tissue, so that the part of the connective tissue cells in the business of defence is that of fibrosis; and the function of the polynuclear leucocytes is phagocytosis, so that when they are active we get pus formation. To these three types of reaction mentioned by Sabouraud it may be added that the blood-vessels respond by dilatation and by the exudation of serum and leucocytes. And it is by a combination of these processes in different degrees that the different appearances of the various eruptions are produced. I will try to make this idea more clear by means of a few examples.

Reaction of Cells of the Epidermis.

(1) This photograph (fig. 1) is from a section of a macule of *pityriasis versicolor*, which is a superficial affection due to the invasion of the horny layers of the epidermis by a fungus named *Microsporon furfur*. In this section there is obviously a proliferation of the horny

[1] "La Défense de la Pean contre les Microbes," R. Sabouraud, *Annales de Dermatologie et de Syphiligraphie*, t. x, 1899, p. 729.

cells, and the grape-like masses of spores and mycelial threads of the fungus are seen between them. It represents very well a multiplication of the horny cells as a reaction to an invasion by the fungus. It cannot be called inflammatory, and yet it is a cell reaction to microbic invasion. It would appear to be an effort on the part of the horny cells to get rid of the fungus by exfoliation.

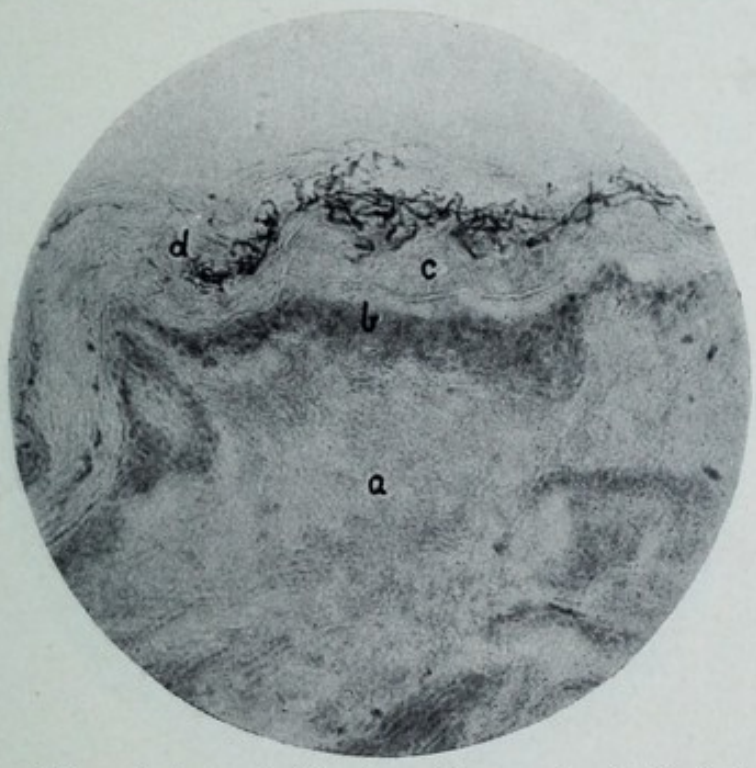

FIG. 1.—Micro-photograph of section of a macule of pityriasis versicolor. *a*, corium ; *b*, prickle cell layers ; *c*, thickened horny layer ; *d*, mycelium and spores of *Microsporon furfur*.

(2) The next photograph (fig. 2) represents the blackhead or comedo of *Acne vulgaris*, which is another example of local defence by the horny cells. The pilo-sebaceous follicle is plugged by a cocoon-shaped body, which is made up of concentric layers of horny cells encapsuling a mass of acne bacillus. It may be looked upon as a reaction upon the part of the horny cells to the invasion of the follicle by the acne bacillus. It is, perhaps, an

attempt to cut off the acne bacillus from the deeper structures.

(3) The next photograph (not here reproduced) is from a section of a common *wart*, which is almost certainly of an infectious nature, although the infecting organism has not yet been discovered. We may look upon the lesion as the reaction to invasion of the prickle-cell layers of the epidermis by some unknown organism. As a result

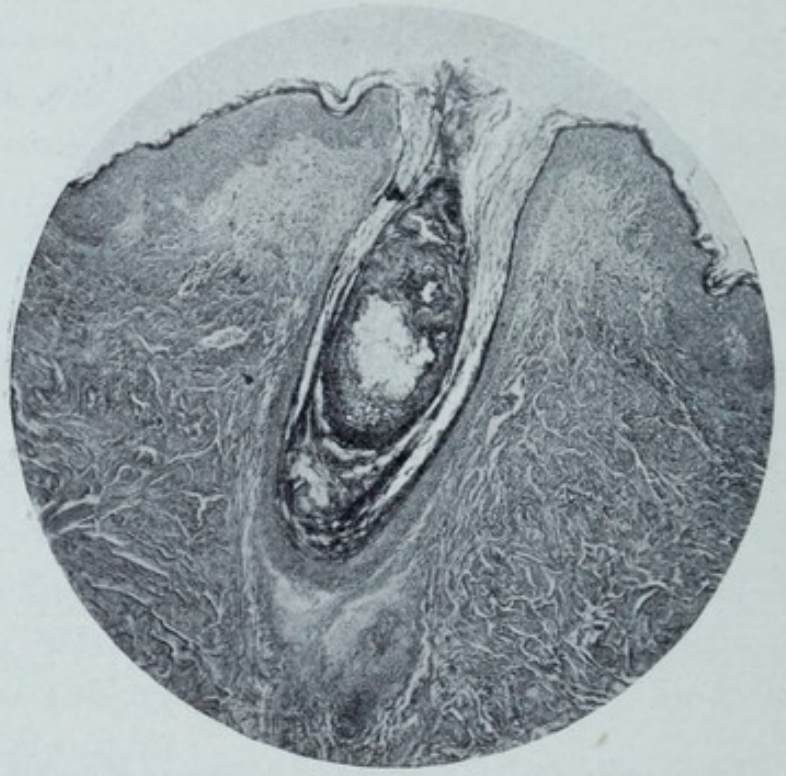

FIG. 2.—Comedo of *Acne vulgaris*, showing mass of micro-bacillus in the mouth of the follicle surrounded by layers of horny cells.

there is a responsive proliferation of the prickle cells, the prickle cells afterwards being transformed into horny cells as normally.

In *Molluscum contagiosum* (the next photograph, fig. 3) we see much the same conditions, but the prickle cells are somehow interfered with in their normal progress towards horny cells, and there results an irregular imperfect cornification, seen in the so-called molluscum

bodies. The photograph, which is from a very early lesion, shows that there is here also cellular proliferation in the cutis.

(4) In ringworm of the scalp we have, in the early stages, another example of reaction by proliferation of the horny cells. The earliest lesion produced on invasion of the scalp by ringworm fungus is a small, scaly patch, representing a reaction to the growth of the fungus in the

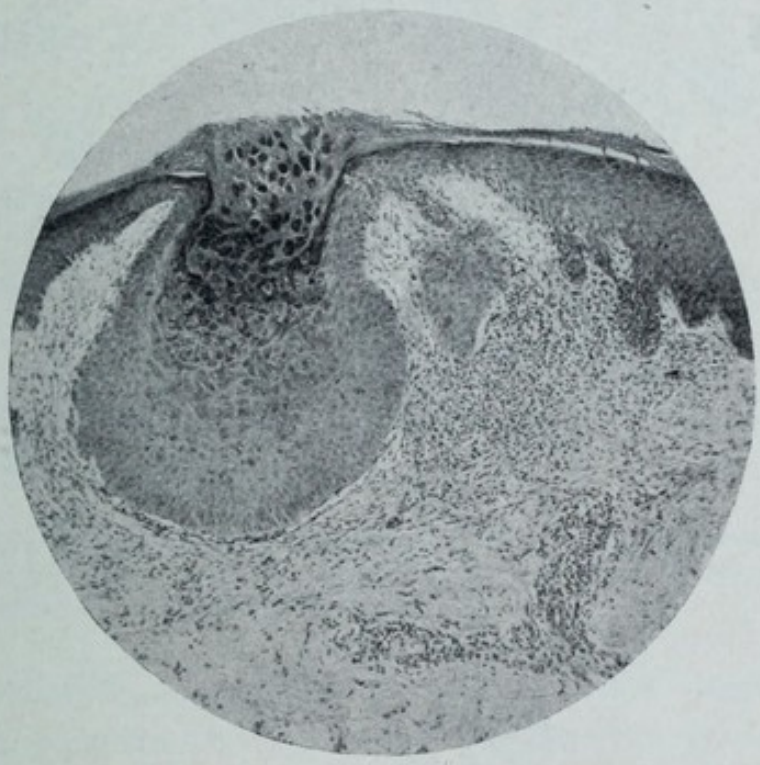

FIG. 3.—*Molluscum contagiosum*, showing a very early lesion.

horny cells. Very soon some of the fungus begins to grow down into the hair shafts, and eventually the hairs become filled with fungus, so that they become fragile and easily broken off. Thus we get a scaly patch covered with broken stumps. But in ringworm we have something more than a simple hyperkeratosis or horny-cell proliferation. For although the fungus remains confined to the horny cells of the epidermis and of the hair sub-

stance, upon which it lives, yet it has evidently an influence also upon the deeper tissues.

Deep-seated Reactions.

Dr. George Thin, so long ago as 1878, pointed out the fact that while the fungus of ringworm never penetrated

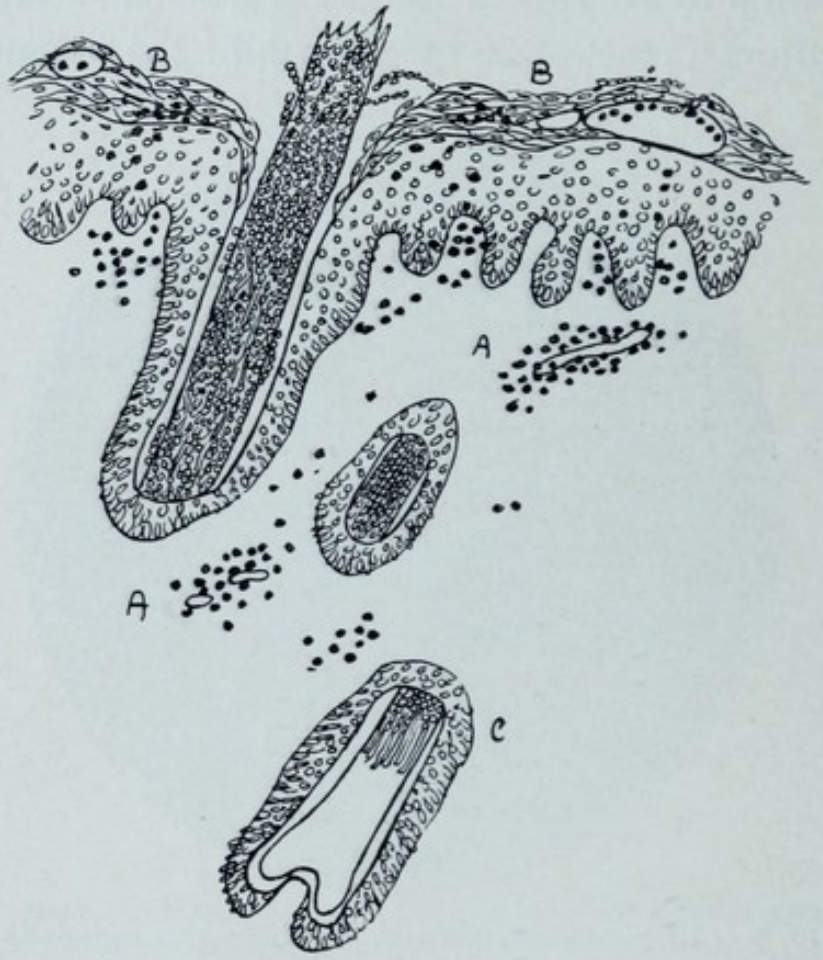

FIG. 4.—Section of ringworm showing fungus confined to the hair shaft, and yet giving rise to deep-seated reaction. A, cell-exudation round vessels; B, proliferation and œdema of horny cells; C, root of hair, showing that the fungus does not extend beyond the horny substance of the hair shaft.

beyond the horny layer and the hair, yet there were signs of deap-seated inflammation in the form of a leucocytic exudation round the blood-vessels, and he suggested that this was due to the escape of soluble products of decomposition of the hair substance by the fungus acting as an

irritant to the tissues, a view which nearly, though not quite, approaches the modern idea that the inflammation is a reaction to toxins secreted by the fungus.

Dr. Sabouraud has so shown that, even in the endothrix ringworms, where the fungus is entirely confined to the hair-shafts, there is evidence of cell exudation into the corium and of serous exudation into the epidermis around the mouth of the hair follicle. (Fig. 4.)

In the more inflammatory forms of ringworm vesicles or even bullæ may be formed on the surface of the skin,

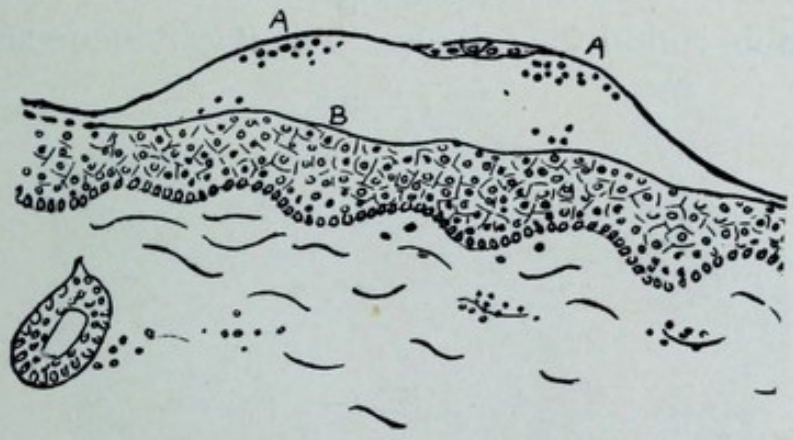

FIG. 5.—Section of impetigo contagiosa showing the vesicle resulting from streptococcal invasion. A, roof of vesicle, consisting of horny layer; B, base of vesicle, where the streptococci are found.

or deep-seated abscesses or granulomata may result without the escape of the fungus from the horny tissues.

We now come to two common eruptions, which are the result of the invasion of the skin by micrococci—namely, the streptococcic and staphylococcic impetigos.

Serous Exudations.

(5) In *streptococcic* infections the eruption is a superficial vesicle or blister. The vesicle is formed between the horny layers of the epidermis and the stratum lucidum by an accumulation of serum between these layers. There is only a very slight leucocytosis, the prickle-cell layer and

the cutis are œdematous, but there is little or no proliferation of the prickle cells. The main reaction here seems to be in the form of a serous exudation, attracted to the surface of the skin by the growth there of the streptococcus, and we must suppose, as in the case of the ringworm, that the serous exudation is in response to harmful toxins secreted by the streptococcus. (Fig. 5.)

Leucocytic Reaction.

(6) In *staphylococcic* impetigo the infection takes place *viâ* the pilo-sebaceous follicle and results in the formation of a pustule round the follicle. The staphylococcus gives

FIG. 6.—Early stage of follicular pustule (impetigo of Bockhart), showing collection of polynuclear leucocytes in and around sebaceous gland A and hair follicle B. (After Sabouraud.)

rise neither to an epithelial proliferation nor to marked serous exudation, but mainly to a reaction on the part of the polynuclear leucocytes which collect around the

growths of the staphylococcus and devour them. This drawing is from a section of a very early pustule, and shows the collection of pus cells within the sebaceous gland, and also around the mouth of the follicle. (Fig. 6.)

Connective Tissue Reactions.

(7) We must now consider some reactions due to microbic invasion of the deeper parts of the cutis, either

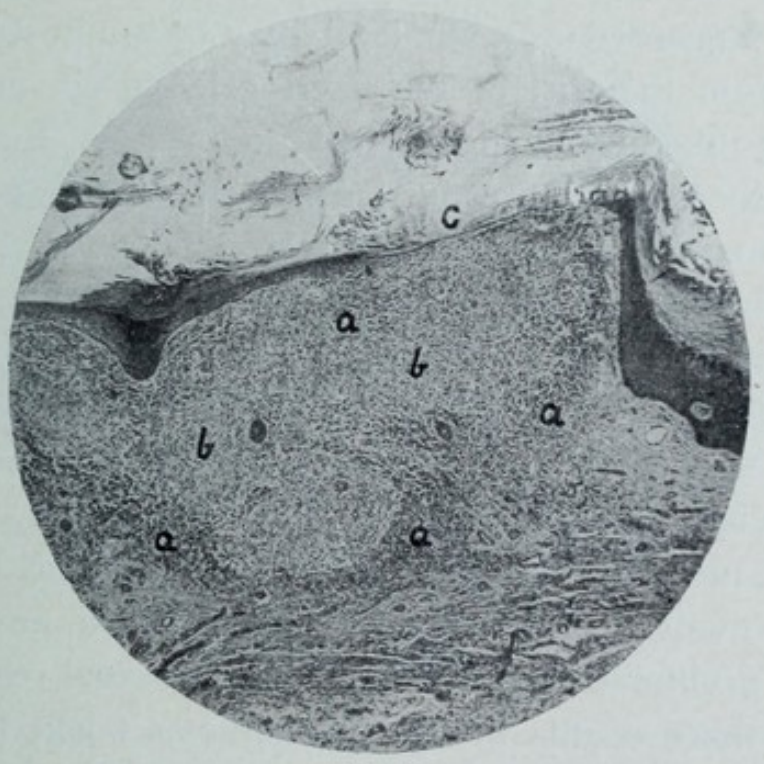

FIG. 7.—Section of lupus nodule. *a*, Mononuclear cells and plasma cells around the blood-vessels at margin of "tubercles"; *b*, epitheliod cells and giant cells; *c*, thinned epidermis stretched over the nodule.

by infection from without or by the blood-stream—namely, a type of reaction known as granuloma. As illustration of these reactions, two examples of different forms are seen in the granuloma of tubercle and of syphilis.

This photograph (fig. 7) is from a section of a *lupus* nodule. It shows a dense cell infiltration in the cutis,

which is seen to be made up of masses of cells arranged in groups or "tubercles." Each tubercle consists of a central zone of giant cells, around which is a zone of epithelioid cells, and outside this again a collection of plasma cells and lymphocytes. The whole infiltration is enclosed in a fibrous tissue capsule.

This lesion represents a reaction, mainly on the part of the fixed cells—the connective tissue and the endothelial cells—to the stimulation of the tubercle bacillus and its toxins. Regarded as a whole, it may be supposed to be an effort on the part of the fixed cells to surround the invading tubercle bacilli with fibrous tissue. But this is a slow process, and the fixed cells are perhaps poisoned by the toxins, for they do not straight away produce fixed cells of the same type, but they become converted into giant cells and epithelioid cells, which may be looked upon either as degenerate forms, which never reach the stage of fibrous tissue cells, or as modified forms taking on a special function under special circumstances. Sometimes we meet with lupus in which the epidermis has also become involved in the general tissue reaction, and shows decided proliferation, and when this epidermal reaction is marked there results the warty character taken by some forms of lupus—*Lupus verrucosus.*

(8) In *syphilitic granulomata* we find different appearances, according to the form of eruption, whether a primary sore, a secondary papule, or a tertiary nodule or gumma. In all there predominates a particular form of cell which is seen also in tuberculosis, but less abundantly—namely, the plasma cell.

In this section (fig. 8) of a syphilitic papule there are masses of plasma cells grouped around blood-vessels. There are no giant cells nor epithelioid cells, although

these may be present in very chronic forms of syphilide. Under a higher power some of the plasma cells show evidence of transition into connective tissue cells, and in many instances, especially in the primary sore, there appears to be direct proliferation of the connective tissue cells. Here the whole process again represents a fibrous tissue proliferation, but a more rapid one than in tuber-

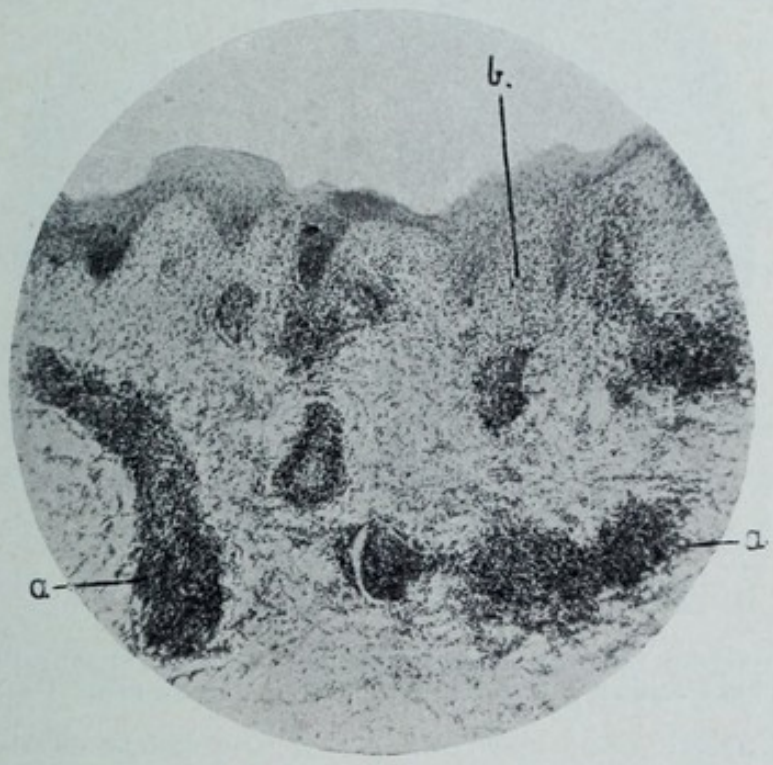

FIG. 8.—Section of a syphilitic papule. *a*, showing dense infiltration of plasma cells; *b*, direct proliferation of connective tissue cells. (Kindly lent by Mr. J. E. R. McDonagh.)

culosis. The plasma cells are no doubt the result of fibrous tissue proliferation and transition stages towards fibrous tissue cells. Less often we see the slower process with transition stages of epithelioid cells and giant cells, as occurs in tuberculosis.

The next photograph (fig. 9) is from a section of a syphilitic condyloma and shows the epidermis taking part in the reaction as in lupus verrucosus.

The granulomatous reaction is seen also in many other skin infections, notably in sporotrichosis, blastomycosis, and actinomycosis, and it may also occur in very chronic staphylococci infections.

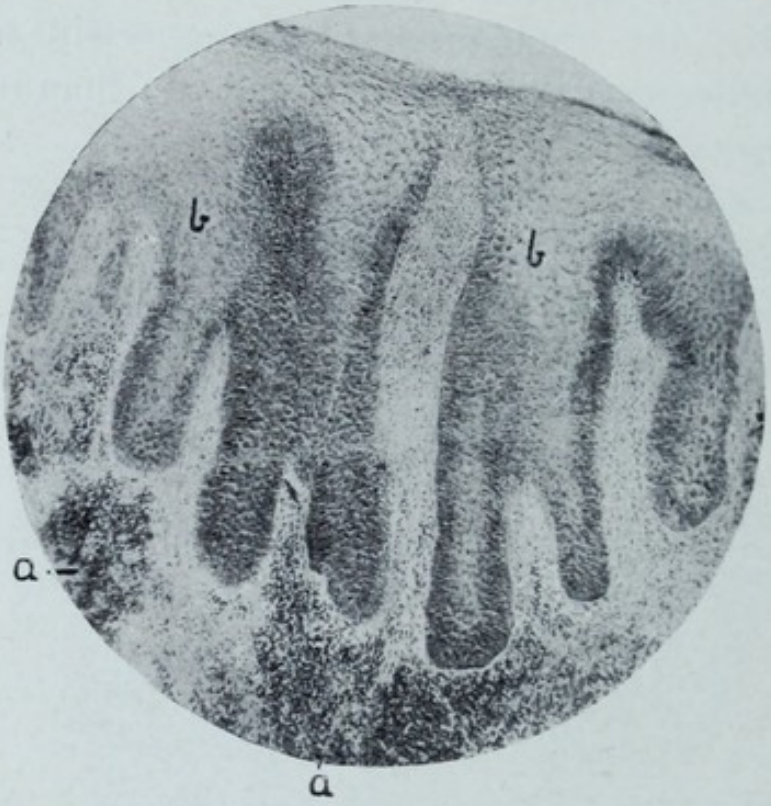

FIG. 9.—Section of a syphilitic condyloma. *a*, Dense mass of plasma cells round the blood-vessels; *b*, proliferation of the epidermis. (Mr. J. E. R. McDonagh.)

Dilatation of Blood-vessels.

(9) There is still one other form of reaction to be considered—namely, blood-vessel dilatation. It occurs in all the deep-seated reactions I have just discussed, but sometimes when a micro-organism attacks the skin from within the reaction may be confined to the blood-vessels and to the parts immediately around.

It is only recently that we have learnt that an organism invading the skin by the blood-stream may give rise to reactions confined almost entirely to the blood-vessels,

and unaccompanied as yet by any marked proliferation of the fixed cells. This is well seen in the roseola of syphilis, in which the presence of the spirochæta has been demonstrated, first by Veillon and Girard, in 1905, and since by other observers. Veillon and Girard's sections showed the capillaries dilated, engorged with blood, and, in some places, around them a commencing infiltration of mononuclear round cells, with spirochætæ in the terminal capillaries and also in the perivascular zones. In the same manner it has now been demonstrated that the rose rash of enteric fever results from the local presence of the typhoid bacillus, and also that in certain erythemas in pyæmic cases bacteria are present in the vessels.

The dilatation of the blood-vessels in these microbic erythemas may perhaps be looked upon as the result of damage to the vessel walls by the toxins of the micro-organisms; and possibly as an effort to carry protective bodies to the part attacked.

Eruptions regarded as Defensive Reactions.

All these eruptions are to be regarded, then, as efforts of defence against microbes and their toxins, each element in the skin helping in its own way. And with this idea in mind it is interesting to note how all the defensive structures disappear as soon as the attacking agent has been removed; they are no longer needed and they crumble away. We see this happen when we depilate ringworm hairs by X-rays; when we remove the crusts of an impetigo and apply an antiseptic to the eroded surface; when we evacuate a molluscum contagiosum or express an acne comedo: and one of the most striking examples is the disappearance of the

eruptions of syphilis when the spirochæte is destroyed by mercury or "606."

From the practical side of the correct diagnosis and treatment of these infective eruptions the recognition of the fact that each micro-organism gives rise to its own distinct type of reaction is of the greatest possible importance. For to be able to correctly diagnose ringworm, acne, impetigo, lupus, and so on, one must be familiar with the ringworm stump, the acne comedo, the streptococci vesicle, the staphylococci pustule round a hair follicle, the lupus nodule, and the rest—that is to say, with the primary or essential lesion of each eruption.

General Immunity in Skin Diseases.

So far these eruptions have been considered as representing the local defences of the skin against microbic invasion. We may now inquire to what extent the local lesions represent the body's effort of defence and to what degree, if any, they are supported by a more general effort, or in other words, we may study the question of general immunity in relation to infective skin diseases.

It is a question of great interest and a matter of considerable practical importance whether or not these skin affections do lead to the production of antitoxins or other antibodies in the blood—that is to say, whether they do or do not give rise to general immunity reactions. For if these defences were purely local it seems hopeless to try to cure such diseases by attempting to stimulate the general body defences by means of vaccines.

As we have just seen, in some skin eruptions we have to do with micro-organisms which do not penetrate beyond the superficial horny layers, as in ringworm, pityriasis versicolor, pityriasis capitis, acne, and possibly

warts and molluscum, and it is of particular interest to know whether these superficial infections lead to general defensive reactions.

In others, as in streptococcic impetigo, we have micro-organisms which, under other conditions, may invade the deeper tissues of the body, which, curiously enough, in cases of impetigo contagiosa remain as superficial infections. Here it would be of interest to know why the streptococcus in impetigo does remain as a superficial infection, and whether it is because the body is protected by a general defensive reaction. In others, as the tubercle bacillus, the *Spirochæta pallida*, and the sporotrichium, we have organisms which invade the deeper parts of the skin and yet do not give rise to sufficient general immunity to prevent infection of still deeper organs. Here it would be of interest to know to what degree of general immunity these deeper skin infections do give rise.

Evidence of some Degree of General Immunity.

In regard to certain eruptions we can at once call to mind evidence of the production of some degree of general immunity. I have already mentioned the streptococcal impetigos. Here, although there is not sufficient immunity to prevent local spread on the skin, there appears to be considerable protection against deep infection, for children with impetigo seldom or never get erysipelas or general streptococcal infections, and this although the streptococcus is apparently identical with the streptococcus of Fehleisen.[1] A clinical fact

[1] Sabouraud is of this opinion, and Mr. J. E. H. Roberts, who has kindly made many cultures for me from streptococcal skin eruptions, has found that they give the same reactions with the Gordon tests as does *Streptococcus pyogenes*.

which bears upon this question is that the younger the patient the more severe is the eruption, and the more likely the occurrence of deep infections. It would appear as though, while the child grows older, he gains some degree of immunity to the streptococcus, a circum-

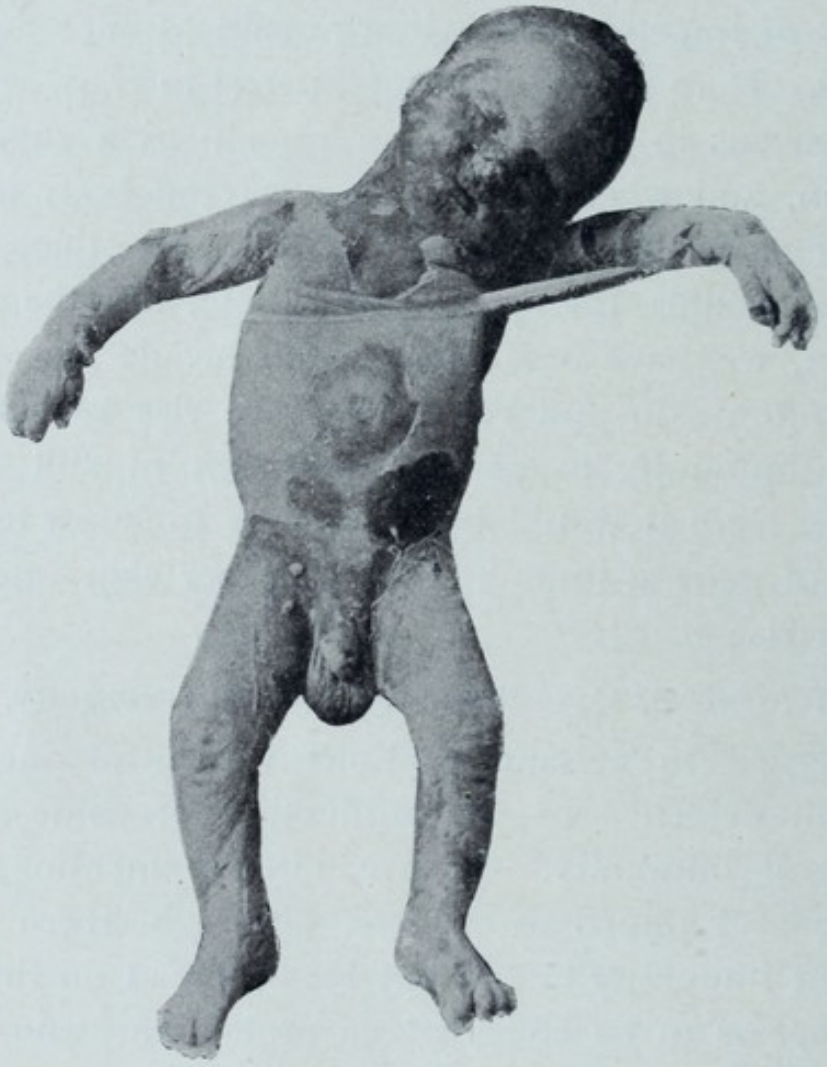

FIG. 10.—An infant who died from streptococcal bullous impetigo. The bullæ are large and the eruption is extensive.

stance which might be explained by slight repeated inoculations from the streptococci constantly present in the mouth or other mucous membranes in health. These three photographs (figs. 10. 11 and 12) illustrate the different power of resistance to the streptococcus at dif-

ferent ages. The first is of an infant who died from a streptococcal bullous impetigo. Here there are enormous excoriations representing large ruptured bullæ. In an exactly similar case recently in St. Bartholomew's Hospital streptococci were found in pure culture in the skin lesions, in the heart's blood, in the lungs, and in the

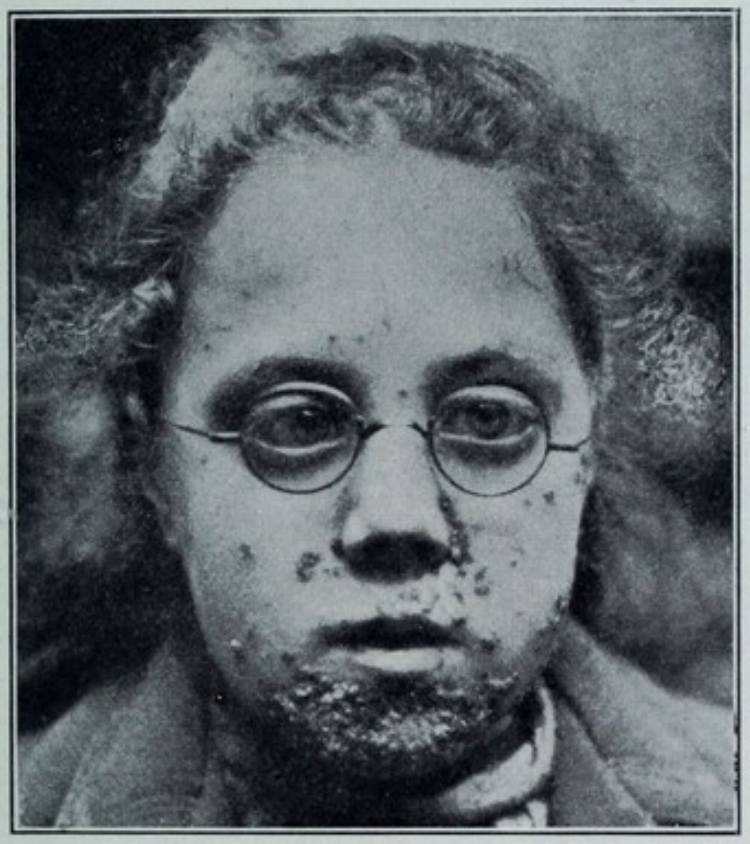

FIG. 11.—Typical case of impetigo contagiosa, showing the large "stuck-on" amber crusts.

peritoneal fluid. That it was the same affection as impetigo was seen from the fact that a nurse in attendance got a streptococci impetigo on the forearm.

The next photograph is from an ordinary case of impetigo contagiosa in a child and shows the large stuck-on crusts; and in these cases, as I have said, one never sees erysipelas or deep infections. The third is

an impetigo in an adult; and here it will be seen that the crusts are much smaller, indicating a still higher degree of protection. An interesting fact, which suggests that children who have had impetigo are "protected," was related to me by Dr. A. E. Stansfeld—namely, that in China the mothers like to see their

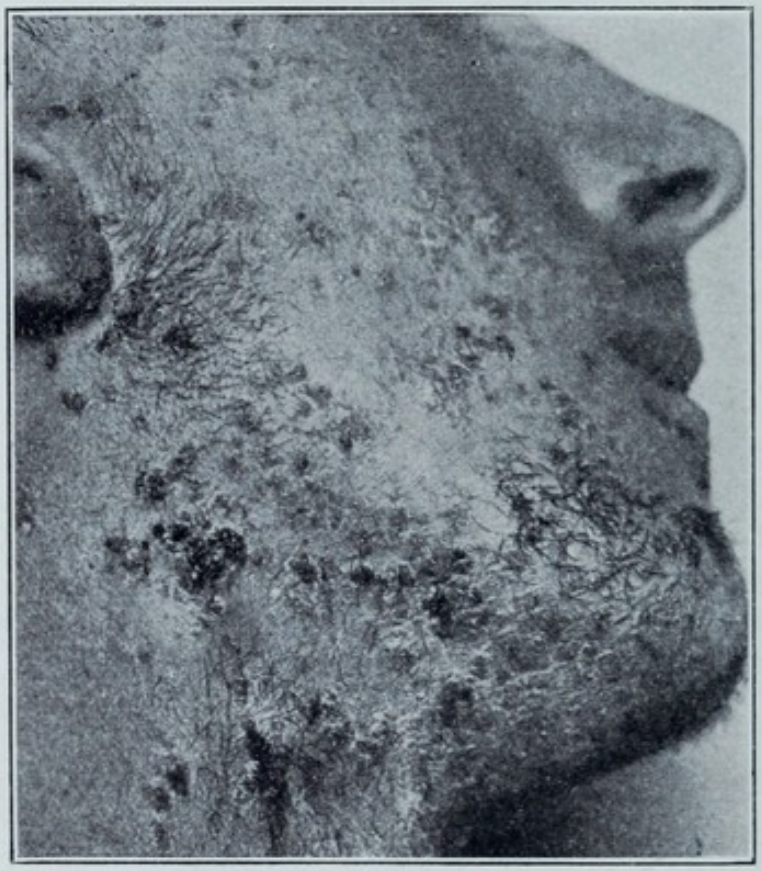

FIG. 12.—Impetigo contagiosa in an adult. The crusts are smaller than in a typical impetigo in a child.

children get impetigo, because they say that they then never have it in later life.

Other examples of immunity production are afforded by certain clinical observations in regard to ringworm. It is well known that a human being who once gets cattle ringworm never again becomes affected. And there appear to be different degrees of immunity pro-

duced according as the ringworm infection is of a more or less virulent type; for while an inflammatory cattle ringworm in a human being is generally single, the more superficial human ringworm continues to spread, although the new lesions are smaller than the parent patch. The same thing may be seen in staphylococcic infections—a carbuncle is usually single, boils are often multiple. That is to say, only in the more virulent type of infection is the patient protected against re-inoculation.

Lupus and General Immunity.

Lupus is another affection in which we have evidence of the production of general immunity. Clinically it is rare to see a patient with lupus who afterwards contracts tuberculosis of the lungs; at least, I think this is the general view, although recent statistics from the Finsen Institute at Copenhagen show that in those cases which were followed up tubercle had been found in the lungs in more than a third of those who had died. It cannot, however, be denied that patients with lupus often live many years, twenty or thirty or more, without contracting phthisis.

We have, indeed, experimental evidence of the production of antibodies in the positive—general and local—reactions to tuberculin which are given by patients with lupus. This reaction is, of course, well known, but as I wish to refer to it again later in another connexion I shall briefly recall it now. If we scratch the skin of a patient who has lupus and rub on to the scratch a little "old tuberculin," we see in the course of a few hours an inflammatory redness, sometimes with papulation, around the scratch. This reaction (well known, of course, as the von Pirquet reaction) is believed to indicate that the

patient has been rendered hypersensitive to the toxins of tubercle bacillus by the presence of certain antibodies in the blood. To use a modern word, the patient has become anaphylactic—anaphylaxis (or as the Germans say *Ueberempfindlichkeit*) being in all likelihood an indication of a stage towards the production of a general immunity.

Defensive Reactions in Syphilis.

Syphilis, too, is a disease which well illustrates these phenomena of local defence or of general immunity production.

In the first place there is the primary sore, which may be regarded as representing a local defence against the spirochæte. At the end of about one week there is evidence that some of the micro-organisms have passed this barrier in the enlargement of the glands of the lymphatics draining the area of the sore. But there is also proof of more general changes in the body, for it has been experimentally demonstrated by Queyrat, and it is known as a clinical fact, that a second infection may take place anywhere on the body up to the twelfth day after the appearance of the chancre, while after that a superinfection is impossible, unless, indeed, as in Pinard's experiment, a very large amount of virus be put into a subcutaneous pocket.

What has happened is that a general immunity has been produced sufficient to protect against a new inoculation, but not sufficient to destroy the spirochætes which are already in the body, and which have presumably become adapted to their surroundings. For presently there appear the secondary symptoms, which are local reactions against the spirochætæ which have

now become disseminated by the blood-stream. These secondary eruptions may perhaps be regarded as cuti-reactions in a hypersensitized person, the immunity production now having reached its acme.

After a varying period of weeks or months these defensive reactions, general or local, get the upper hand, and the patient remains free from symptoms perhaps for many years. Then the immunity begins to wane, and latent spirochætæ again become active and give rise to fresh efforts at defence. These fresh efforts are seen in the tertiary eruptions, every tertiary lesion being probably a revival of some secondary lesion which occupied the same spot, or, at any rate, the result of the awakening of latent spirochætæ deposited during the exanthem stage.

That this is something more than a fanciful explanation is borne out by the results of the Wassermann test. During the first days after the appearance of the sore it remains negative; it is invariably positive during the secondary stage; and it may again become negative when the secondary stage is passed. And here I may mention two other phenomena which are of great interest in this connection: first, that which is known as Herxheimer's reaction—namely, that at the beginning of a mercurial treatment the roseola may become more marked, indicating probably that the killing of some spirochætæ has liberated more endotoxins, and so produced a further local defensive reaction; and, secondly, that the Wassermann reaction may be changed from negative to positive in the late stages of syphilis by the administration of "606," presumably because the latent foci of spirochætæ become unlocked, and once more act as stimulants to the production of antibodies.

Field for Research.

There is then a good deal of clinical evidence that skin eruptions of microbic origin may be associated with general immunity production; and this suggests that in these eruptions there exists a field for experimental research on the subject of immunity.

Theoretically it would seem possible to determine by laboratory methods whether antitoxins, bacteriolysins, precipitins, opsonins, and other antibodies are present in the serum of patients with superficial skin eruptions, but practically there are many technical difficulties in carrying out such experiments. In one recently discovered fungus infection of the deeper parts of the skin —namely, in sporotrichosis—a good deal of work has already been done in this direction. Widal and Abrami and others have demonstrated the presence of specific agglutinins and of precipitins in the serum of patients with sporotrichosis, and positive results have been obtained by fixation of complement tests, using cultures of sporotrichium as the antigen.

But perhaps from the dermatologist's point of view some of the most interesting researches have been those which have to do with the question of general immunity production in ringworm and favus. To these researches I shall now briefly refer.

Immunity Production in the Skin Eruptions due to Mould Fungi.

The first experiments in this direction were those of Plato, a pupil of Neisser. Plato made a ringworm extract by pounding up the cultures from a virulent inflammatory ringworm and collecting the filtrate, which

he called "trichophytine." Patients who had a deep-seated ringworm were injected subcutaneously with "trichophytine," with the result that there occurred a general reaction with malaise, sweating and rise of temperature, and at the point of injection a local reaction in the form of papules or pustules. Moreover, the existing ringworm lesions became less active and gradually disappeared. These local and general reactions did not occur in patients affected by a superficial type of ringworm, nor in a healthy individual not suffering from ringworm.

Truffi repeated these experiments with similar results, and a few years later Bruno Bloch and Massini attacked the problem from another standpoint. They infected 70 guinea-pigs with different kinds of favus or ringworm, using mostly the achorion Quinckeanum or mouse favus, but also a dog ringworm (*Microsporon lanosum*) and a horse ringworm (*Trichophyton gypseum*). After successful inoculation with the favus fungus there appeared about the sixth to eighth day favus cups on an inflammatory base. From the time that the lesions were established the animals were found to be proof against further inoculation either with favus or with the two other fungi. This immunity lasted for at least eighteen months. With the dog ringworm and with the horse ringworm they got similar results and found that each fungus infection protected against all three.

These observers[1] also repeated Plato and Truffi's experiments with "trichophytine," with this difference, that they made their "trichophytine" from the filtrate

[1] "Studien über Immunität und Uberempfindlichkeit bei Hyphomyzetenerkrankungen," Br. Bloch und R. Massini, *Zeitschrift für Hygiene und Infectionskrankheiten*, Band lxiii, 1909, p. 68.

of broth cultures and not from the pounded-up cultures, and that they used it, not as a subcutaneous injection, but by rubbing it into a scratch, as in the cuti-reaction with tuberculin. They obtained with all forms of infiltrating trichophytosis a distinct reaction in the form of a papule with an erythematous halo, the reaction varying in proportion to the virulence of the ringworm.

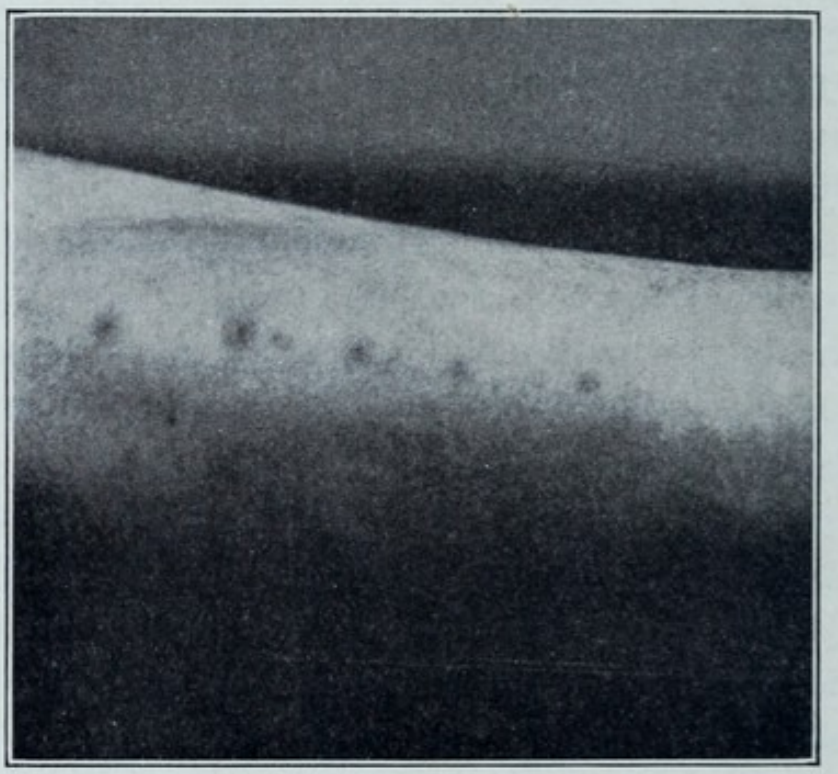

FIG. 13.—Cuti-reaction on forearm in a person previously inoculated with ringworm. The five patches from left to right represent the cuti-reaction to trichophytin (two sorts), microsporin (two sorts), and favin. The point to the right slightly lower than the five patches represents the control with no reaction. (Kindly lent by Dr. Bruno Bloch, of Bâle.)

But with ringworms which infected only the hair or nails, or in quite superficial ringworms, they got no cuti-reaction.

Bloch, who had successfully inoculated himself with a trichophyton two years previously, was able to obtain on his own arm a cuti-reaction from the same fungus,

from another trichophyton, from filtrates prepared from microsporon of the dog and from microsporon of human origin, and from a favus prepared from achorion Schönleinii. These reactions varied in intensity with the filtrates employed, being most marked against filtrates from deep-seated ringworms and least with favus and the common microsporon. Fig. 13 shows the cuti-reactions and the control—the latter without any inflammatory halo.

During the past two years these experiments have been again carried out by Bruhns and Alexander, and also by Lombardo in Italy. Bruhns and Alexander were not able altogether to confirm the results obtained by Bloch and Massini, for only in three-fourths of their cases was a second inoculation unsuccessful. They concluded that this was because they had used ringworm of a superficial type, in which it was probable that antibodies were thrown out only in small quantities.

Lombardo,[1] as a result of a large number of experiments with different varieties of ringworm fungus, found that he, too, could not entirely confirm Bloch's conclusions, because he could not obtain complete immunity. He did, however, get evidence of immunity reaction in so far as he found that a second and a third inoculation gave rise to reactions which appeared more quickly and which lasted a shorter time, indicating a supersensitiveness or anaphylaxis, and that this condition of anaphylaxis lasted for at least a year and a half. He further demonstrated a very interesting fact which had also been observed by Bloch—namely, that in order to obtain this

[1] "Ricerche sulla Ipersensibilità ed Immunità in Alcune Dermatomicosi," C. Lombardo, *Giornale Italiano delle Malattie Veneree e della Pelle*, vol. iii, 1911, p. 70.

immunity reaction it was necessary for the skin itself to be infected, and that subcutaneous injections of living or of dead fungus and intramuscular or intravenous injections of endotoxin, or of a filtrate of the culture in liquid media, would not produce it.

In some recent experiments of my own, made with an extract got from cultures from groin ringworm, I have been unable to obtain cuti-reactions either in cases of groin ringworm or of scalp ringworm, or in one case of a virulent inflammatory type of ringworm of the beard. This is hardly the result I had expected, since in groin and interdigital ringworms the eruption is often eczematoid, and is accompanied by itching—both circumstances suggesting the excretion of a toxic irritant. It must be noted, however, that the extract was obtained, not by Bloch's method of using the filtrate from a broth culture, but by grinding up the fungus itself and using the expressed juice, as in Plato's method. Further researches with the filtrate from broth cultures of this fungus and of the fungus from the virulent beard ringworm are in progress, the results of which I shall publish later.

The researches of Bloch and of others which have been quoted seem to indicate that it is only in those ringworms which produce distinct inflammatory lesions that general immunity reactions can be readily demonstrated. Yet there is some reason to believe that even the more superficial ringworms are not merely saprophytic in the horny tissues, but that they also give rise to some degree of general immunity reaction.

Relations of Immunity Production to Treatment.

From the point of view of the treatment of ringworm by vaccines or by trichophytines these observations on

immunity production do not greatly help us. If, as we are told, the principle of vaccine treatment is to prepare the invading micro-organisms for destruction by phagocytes, the good results sometimes obtained in staphylococcic infections are readily explained. But in the case of the ringworm fungus, which remains locked up in the horny tissues, and in the destruction of which the phagocytes take no part, it is difficult to understand how vaccines can be of use.

From this same point of view it is not easy to see upon what principle vaccines of acne bacillus are given in simple acne. It seems reasonable to suppose that staphylococcus vaccines would do good in pustulating stages of acne, but not that acne bacillus vaccines would clear up the comedones which form the basis of an acne eruption. And the ill-success which attends this treatment in the experience of many appears to confirm these misgivings.

Even if we go beyond the opsonin theory and suppose that vaccines help to stimulate all those forms of immunity reaction which are opposed to the micro-organisms in question, it is difficult to comprehend how they could be of help against ringworm invasion. For since it has been demonstrated that immunity reactions occur only when the ringworm fungus actually grows in the epidermis, how can we hope to stimulate the production of antibodies by the subcutaneous injection of vaccines? Indeed, it would seem, on reflection, that this observation of Lombardo and of Bloch, that immunity in ringworm occurs only when the skin is infected, has a very important bearing upon the whole question of immunity production and of vaccine treatment in general. Because, if it is found that certain micro-organisms can give rise

to immunity reactions only when they are actively growing in certain tissues, little result can be expected from the injection of these micro-organisms, dead or living, into the circulation.

Dr. F. W. Andrewes showed in his Croonian lectures[1] that certain non-pathogenic bacteria could give rise to immunity reactions when inoculated in a living state into rabbits, but this might, as he suggested, be due to some poisonous property of the protoplasm of those particular micro-organisms, for other non-pathogenic bacteria gave rise to no reactions. And it has yet to be proved that every pathogenic micro-organism gives rise to immunity reactions when injected in a non-living or even in a living condition into the circulation. And unless a micro-organism does this, how can it be of use as a vaccine?

In conclusion, it must be admitted that we are able as yet to make but little practical use of our knowledge of immunity reactions in the treatment of skin diseases, and with our present knowledge we generally do better to rely upon methods which aim at the removal or direct destruction of the micro-organisms which give rise to these eruptions. Nevertheless, this study of immunity production in skin affections of microbic origin is in itself of great interest, and in my next lecture I shall endeavour to show that it may also help us to understand the significance of many eruptions of non-microbic origin.

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[1] *Lancet*, July 16, 1910, p. 155.

LECTURE II.

Delivered on March 14.

Toxic Eruptions.

In my last lecture I discussed the significance of those eruptions which result from microbic invasion, and recalled the fact that such eruptions represent a local effort at defence against the microbes and their toxins. I showed how the various forms taken by the eruptions are to be explained by difference in the types of cell-reaction which produce them. I also referred to what we know of the occurrence of more general efforts at defence or immunity production in connection with these local reactions.

I propose now to consider another large group of eruptions which includes many of the well-defined and more common diseases of the skin, such as erythemas of various types, purpuras, urticarias, eczema, psoriasis, lichen planus, alopecia areata, pemphigus, scleroderma, leucoderma, pityriasis rubra, the tuberculides, and a number of others. As the result of many years of clinical observation these eruptions have been separated as having distinct and characteristic features which entitle them to be regarded as entities, each presumably having some specific origin. Their pathological anatomy has also been studied, and in most of them that, too, like the clinical symptoms, is distinct and characteristic. Yet as to the exact nature of perhaps the majority of these affections we still remain ignorant. It is to the question

of the possible toxic origin of some of these eruptions, and to the modern ideas as to the significance of toxic eruptions, that I intend to devote this lecture.

The Origin and Development of the Idea of Toxins in Dermatology.

The conception of eruptions as the result of toxins seems to have taken definite shape at the period of the introduction of old tuberculin injections as a means of treatment in 1890, when several cases were reported in which generalized erythemas occurred after injection of tuberculin. Hallopeau and Wickham had, however, at the Congress of Tuberculosis in 1888, already suggested that tuberculin could give rise to "toxinic and non-bacillary cutaneous eruptions." In 1891, Schwenninger and Brizzi claimed to have produced lichen scrofulosorum by local injection of tuberculin.

Then, with the advent of the antidiphtheritic serum for the treatment and prevention of diphtheria in 1894, it was observed that urticarial and erythematous rashes sometimes followed the injection of the serum. It was at first supposed that these eruptions were due to the antitoxin in the serum, but later it was shown that the serum and not the diphtheria antitoxin was responsible for them. Then it was discovered that snake-poison had like effects.

From this time we find the expression "toxic erythemas" coming into use, and drug rashes, shell-fish rashes, &c., being compared with the toxic erythemas resulting from serum injections. Rapidly this view gained ground, and then was evolved the idea of auto-intoxication, or that poisons manufactured by the body

as the result of defective metabolism or absorbed from the intestinal canal might act like toxins in producing skin eruptions. Tommasoli, one of the pioneers in this field, wrote a monograph suggesting the autotoxin origin of many forms of hyperkeratosis, and Carrocchi applied the same idea to alopecia areata.

In 1896 Hallopeau and Darier propounded the theory that many eruptions hitherto described as scrofulous, and known to be associated in some way with tuberculosis, were due not to the local presence of the tubercle bacillus, but to the toxins produced at a distant focus; and they invented for them the name of toxi-tuberculides. In 1897 Hallopeau contributed to the *Annales de Dermatologie* a paper entitled "Toxins in Dermatology," in which he insisted upon the importance of the *rôle* played by toxins in the production of dermatoses. The eruptions under consideration were mainly of an erythematous or urticarial type, but Hallopeau suggested that toxins might possibly also play a part in the production of acute eczemas, psoriasis, dermatitis herpetiformis, pemphigus, and other well-known skin affections. For many years some of these eruptions had been regarded as angio-neuroses, and it was now felt that the idea of toxæmic origin supported this view, for it seemed easy to explain the eruptions as due to the action of the toxins on the central vaso-motor apparatus. But discussions arose as to whether these so-called toxic erythemas and urticarias were really the result of vaso-motor disturbance, and evidence was brought forward to show that they were inflammatory in nature and due to the direct action of the poison on the smaller blood-vessels and on the tissues around them. Recent observations tend to confirm these views, and to suggest that there is a

close analogy between the eruptions due to toxins and the inflammatory reactions to microbic invasion.

I shall now consider some of these matters more in detail, first in reference to the toxic erythemas and urticarias, and afterwards as regards other supposed toxic eruptions.

What are the Toxic Bodies which may give Rise to Erythematous and Urticarial Eruptions?

When we speak of toxic bodies or toxins as the causative agents of eruptions, we generally use the term in a vague and a very broad sense to include all sorts of poisons, and not strictly toxins of bacterial origin. Amongst these poisons with which erythematous and urticarial eruptions may be associated are various drugs, including arsenic, antipyrin, arnica, belladonna, bromides, chloral, quinine, copaiba, ergot, mercury, iodides, iodoform, and opium; certain plants, as the nettle and *Primula obconica;* some articles of food, as strawberries, shell-fish, pork, cheese, and eggs in certain persons, and various forms of tainted meat; the venom or poison of certain insects, crustacea, molluscs, jelly-fish, anemones, &c., and snake poison; the fluid of a ruptured hydatid cyst and the antidiphtheric serum or simple horse serum, and tuberculin and mallein. Many of these agents produce rashes when applied externally, others when taken by the mouth, or administered subcutaneously.

It was suggested by Payne, in an article on "Fixed Erythemas" in the *British Journal of Dermatology* in 1894, that most of these poisons were of one class—namely, alkaloids, either vegetable or synthetical, or produced by the action of bacteria upon food.

Since then, we have learnt that besides the alkaloidal

ptomaines, which are often comparatively harmless bodies, bacteria also give rise to poisonous bodies which have characters quite distinct from ptomaines. These bodies, by the work of Roux and Yersin, Hankin, Wooldridge, Brieger, Martin, and others, were first separated as albuminoids, then as toxalbumins, and finally as toxins. These toxins are poisonous in infinitesimal doses to a degree very far beyond other poisons. Their chemical composition is quite unknown, for they exist in imponderable quantities. They have certain characters which do not belong to other poisons. They are sensitive to heat, and what is more remarkable, they produce symptoms of poisoning only after a more or less prolonged incubation period, and, above all, they have the property of exciting in the organism attacked the formation of specific antitoxins and antibodies.

A very interesting fact is that similar bodies to these bacterial toxins have been described as the result of cell activity in animals and plants. The former, called zootoxins, occur in snake poison, spider and toad poisons, and in eel blood. The latter, the plant toxins or phytotoxins, are ricin, croton, and a few others. And, too, there has been described a toxin secreted by muscles as a result of excessive muscular action—fatigue toxin.

Further experience has shown that this toxic action of living cells is only a matter of degree, and that any cell or fluid of animal origin may be toxic for an animal of another species to that from which it is derived if introduced into that animal's blood. Used, then, in this sense, the term "toxin" has a wider meaning than that of bacterial toxins, and would comprise many of the poisons I have mentioned as giving rise to these eruptions. In discussing drug eruptions, we shall see that

it is possibly not the drugs which give rise to the eruptions, but proteid poisons produced by the action of the drugs upon the living cells of the patient. So that there is some reason to suppose that the real poison in all these eruptions is a toxin or poison of living-cell origin.

How are these Toxic Erythemas produced?

I have already mentioned that for many years it was sought to explain these eruptions by the theory that they were angioneuroses, due either to central or peripheral vasomotor disturbance, and that after a time objections were made to this view, because it was found that the eruptions were inflammatory, and therefore not, it was thought, to be produced by simple vasomotor disturbance.

Payne, in 1894, in an article to which I have just referred, suggested that these substances circulating in the blood might act directly upon the tissues, and that this view seemed necessary to explain the more fixed types of erythema with which he was then dealing. Philippson and Jadassohn, in 1897, studied the anatomy of erythema multiforme, and maintained that the lesions were inflammatory. Philippson, in 1899, opposed the then current view of the vasomotor origin of urticaria on the ground that urticaria could be demonstrated experimentally to be inflammatory. He produced in animals urticarial lesions by injection into the skin of minute quantities of morphia, of atropin and of peptone, and of other substances, and these urticarial lesions were produced even when the sympathetic nerves were divided and the sympathetic ganglia removed.

Török and Vas, in 1900, showed that the exudation in

an urticarial wheal contained a very high percentage of albumin, suggesting an inflammatory exudation rather than a mere transudation of serum. In 1903 Török and Hari continued the researches of Philippson, and showed that different degrees of inflammation could be produced by various irritants. They injected into the skin warm water, weak potash solution, weak hydrochloric acid, and these produced no urticaria; but solutions of morphia, of atropin, of pepsin, and of trypsin gave rise to definite urticarial wheals, as also did cadaverin, urea, phenic acid, antipyrin, and the broth in which a staphylococcic culture had been grown. From these experiments they concluded that urticaria was an irritative phenomenon from a local cause and not an angioneurosis.

Meanwhile, in France, Leredde, in 1898 and in 1899, also wrote combating the view that these eruptions were angioneuroses, and maintaining that all erythematous lesions might be explained by the *direct* action of soluble poisons on the vascular elements (the cells of the vessel walls and the leucocytes) and on the connective tissue elements, without any part being played by the vaso-motor system. More recently Gilchrist, of Baltimore, has also demonstrated that urticarial wheals may be produced experimentally, and that they give evidence of inflammation, the histological picture showing the presence of enormous numbers of polynuclear leucocytes, increase in the number of lymphocytes, and in some sections a large number of mast-cells (fig. 14).

There is, then, a good deal of evidence in support of the view that these erythematous and urticarial eruptions which result from the action of poisons are actual inflammations and not merely vaso-motor disturbances. So that, for example, we may regard the wheal produced

by the sting of a nettle or by the bite of an insect as representing an inflammatory reaction to a local irritant rather than a reflex vasomotor disturbance. And it does not seem unreasonable to suppose that these local inflammations, produced by poisons, represent a defensive reaction analogous to that resulting from invasion by microbes and their toxins. There are other facts which support this view, and which point to a close

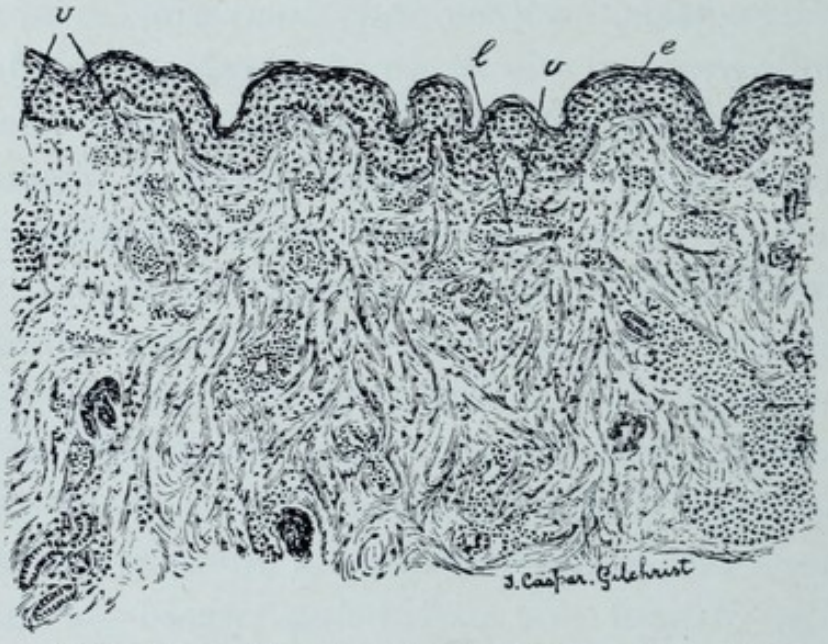

FIG. 14.—Urticaria—section of a wheal. Shows cell-exudation round the blood-vessels. *e*, epidermis; *v*, *v*, blood-vessels; *l*, lymphatic vessels; *s*, sweat-duct. (Reproduced by kind permission of Dr. J. C. Gilchrist.)

resemblance between these toxic eruptions and microbic eruptions. In some erythematous eruptions, as in roseola of syphilis, the rose rash of typhoid fever, and in some eruptions of erythema multiforme type occurring in cases of pyæmia, micro-organisms—spirochæta, typhoid bacilli, and streptococcus—have been found, showing that micro-organisms and their toxins may give rise to erythematous eruptions identical with those we call toxic erythemas.

General Immunity Reactions.

But perhaps the most striking resemblance of the action of these poisons to that of bacterial infections is in the property of giving rise to general immunity reactions. This is shown by the fact that, as with bacterial infections, there may be a more or less lengthy incubation period, and that pyrexia, joint pains, gland enlargements, and sometimes albuminuria may accompany toxic skin eruptions. This we know to occur with serum rashes, the incubation period being usually seven to ten days. Rather a striking example is that of a case of vaccination erythema which is pictured by Dr. T. Colcott Fox, in the last edition of Clifford Allbutt and Rolleston's "System of Medicine," in which an erythema multiforme type of eruption appeared eight days after vaccination with cow-pox. It is true that there is not always a long incubation period with toxic eruptions, but the reason for this I shall presently endeavour to explain.

It is particularly in the light of some recent ideas in regard to immunity production against various proteid poisons that these toxic eruptions seem comparable to eruptions of microbic origin. The ideas I refer to are those connected with the phenomenon of anaphylaxis. The history of the discovery of this phenomenon is now so well known that I shall here only briefly recall the main facts.

Richet and Hericourt, in 1898, in the course of some investigations on immunity, found that dogs injected with the zootoxic eel serum became very much more sensitive to subsequent injections. Instead of becoming protected from the effects of the poison (prophylaxis) the result appeared to be just the opposite (anaphylaxis). These experiments were repeated with similar results with

a poison isolated from mussels, and in 1903 Althaus showed that like effects could be produced by substances not usually regarded as poisons. He found that horse serum injected into rabbits rendered them so susceptible to a subsequent injection at the end of a week that they generally died. Now it had been observed already that the serum rashes and other symptoms—fever, joint pains, swelling of the glands, and slight albuminuria—which sometimes occurred after injection of patients with anti-diphtheritic serum, appeared much more rapidly and were often more severe after the second dose than they had been after the first injection. This so-called "immediate reaction" was now explained by the supposition that the patients had been rendered hypersensitive, or anaphylactic, to horse serum by the initial dose.

Various explanations have been offered for these phenomena which it is beyond my power to discuss, but upon broad lines it may be said that this condition of hypersensitiveness is an effort towards protection or immunity. Just as a patient who has been infected with tubercle bacillus becomes so hypersensitive that a general reaction is produced when he is injected with tuberculin, so a patient injected with serum is rendered hypersensitive to a second injection and a more violent and a less delayed reaction takes place. To complete this comparison, we ought to find that a patient made anaphylactic to serum would give not only a general reaction to a subsequent dose but also a local cuti-reaction to a small dose, comparable with the cuti-reaction to tuberculin and to trichophytin in tuberculous and in ringworm cases. And this has, indeed, been shown to be the case.

Moss, in the *Journal of the American Medical Association*, describes how he performed this test on thirty

persons. Nine who had not previously had serum injections gave negative results. The remainder gave positive results. Moss applied the test by injecting 0·01 c.c. of normal undiluted horse serum intradermically. A positive result consisted of an area of inflammation 1 to 2 cm. in diameter, which came on within twenty-four hours and disappeared in two to three days. In three cases a local urticaria was produced. Caillé has also described this test, and some animal experiments have been carried out by various observers lately on a very extensive scale by Coppolino in Italy. Coppolino sensitized animals with pig serum and obtained in them distinct cuti-reactions with serum from the same source. He also got bovine cuti-reactions with peptone in animals previously injected with peptone, and demonstrated by histological examination that the wheals produced showed evidence of inflammatory reaction in varying degree.

In a patient now under my own observation I have been able to demonstrate this cuti-reaction in a very striking manner. The patient is a girl who has been treated for a recurrent cellulitis of the face by injections, first of antidiphtheritic serum, on the supposition that the affection was diphtheria of the skin, and, since, of simple horse serum. On two occasions—now more than twelve months ago—she had severe anaphylactic symptoms after injections—collapse, sickness and profuse erythematous eruptions. Recently, in order to test her susceptibility to horse serum, I performed a cuti-reaction test by scratching the skin and rubbing in some horse serum, but with no result. Then I injected ½ minim of horse serum into the skin of the arm. Within a few seconds an erythematous blush appeared, and after a few minutes the puncture was surrounded by a hard raised

sixpenny-piece-sized urticarial wheal, with a halo of erythema 3 in. in diameter, which lasted for about an hour and a half (fig. 15). A control injection of ½ minim of horse serum into the skin of my own arm also gave at the time no reaction. But seven days later the site

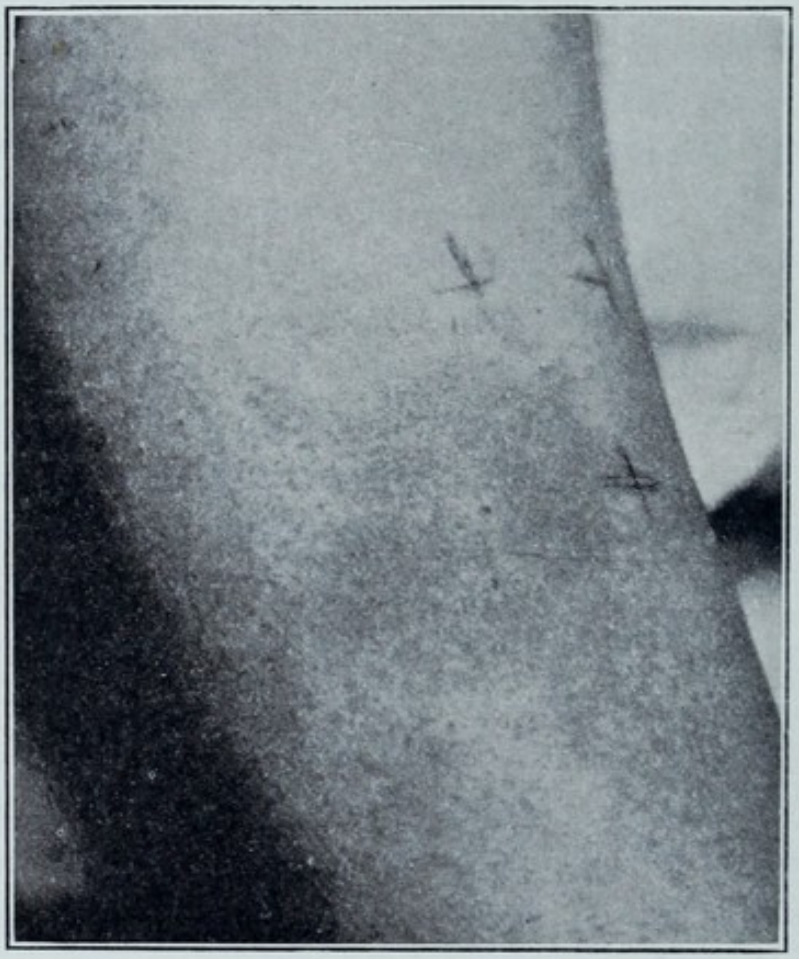

FIG. 15.—Cuti-reaction from intradermic injection of a minute drop of horse serum in a patient hypersensitive to horse serum. There is a large area of erythema, with a central wheal around the puncture.

of the injection began to itch and there appeared a raised urticarial wheal of the size of a two-shilling piece. The itching and the wheal were present on and off for four to five days.

Thus, in my own case there was a normal reaction, with incubation period of seven days, and the reaction

was slight and lasted long. In the patient's case the reaction was immediate, violent, and of short duration owing to the fact that she had become highly hypersensitive to this particular foreign proteid. So rapid and extensive was the reaction given by the patient that it appeared much more likely to be the result of a vasomotor disturbance than an inflammatory reaction.

In order to determine this point I excised a portion of the wheal fifteen minutes after the cuti-injection had been

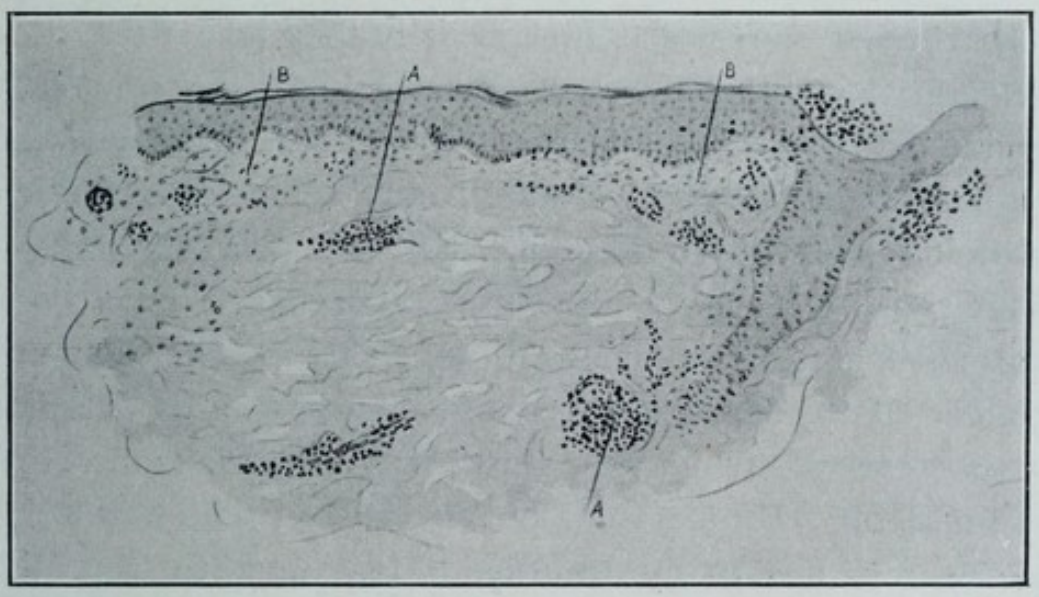

FIG. 16.—Cuti-reaction to serum. Section of the wheal shown in fig. 2. A, A, cell exudation round blood-vessels; B, B, proliferation of fixed tissue-cells.

made. The section (fig. 16) showed decided evidence of being an inflammatory reaction. Around the blood-vessels of the corium there were already dense mononuclear round-cell (fibroblast) infiltrations; in the papillary layer there was a proliferation of connective tissue or endothelial cells, and on the surface of the epidermis around the mouth of a hair follicle was a collection of mononuclear round cells which must have forced their way through the epidermis.

The Doctrine of Hypersensitiveness or Anaphylaxis applied to Skin Diseases.

The case I have just related is interesting as illustrating what I have said as regards the comparison of these toxic eruptions with bacterial eruptions. It is also a good example of the production of a high state of sensitiveness to a foreign proteid or, to employ the term used by German writers, to a heterogeneous albumin, and it serves to explain the clinical features of some cases of urticaria.

It is well known that certain persons are so susceptible to particular foods that immediately they take them they get an attack of nettle-rash. The explanation now suggested for these cases is that the patients have become highly susceptible, or anaphylactic, to certain foreign proteids—egg albumin, pork or veal, for example—which, owing to gastro-intestinal disturbance, have been absorbed, at some previous time, as toxic albumins unconverted by proper digestion. Everyone is familiar with cases in which an attack of urticaria has been brought on by some food poison, and in which there is afterwards for many months a tendency to repeated attacks of urticaria and pruritus. Such urticaria has been defined as a manifestation of hypersensitiveness to heterogeneous albumins, and the rapid improvement of many cases, when put on to vegetable diet, is to be explained by this point of view.

It is perhaps, also, by the phenomenon of anaphylaxis that is to be explained the circumstance to which I referred in my first lecture—namely, the variation in time elapsing between different forms of physical injury to the skin and the resulting reaction. It seems probable that the inflammatory reaction to physical and chemical irritants to the skin is a reaction to toxic bodies produced

by destruction of, or damage to, the cells of the tissues. If this be so, we can understand why the body should react immediately to common hurtful agents, such as mechanical injuries; less quickly to less common injuries, like burning; still less quickly to a less common injury, extreme cold; and only after a long incubation period of ten to fourteen days to a previously unknown injury by X-rays. It may be that the body has become anaphylactic or hypersensitive to the poisons produced by the more common forms of injury.

Professor J. T. Cash, of Dublin, has recently demonstrated in a very striking manner how extreme hypersensitiveness to a local irritant may be acquired. In one of Cash's experiments he applied an ointment of chloroxylonine (the principle of East India satin-wood) to his own arm for twenty-four hours without result. After ten days this was repeated. There was no immediate effect, but twenty-two days afterwards there appeared a dermatitis with itching which lasted several-days. Thirty-five days later a third application was made, the ointment being rubbed in only. Forty minutes afterwards the arm began to swell and get red, and an erysipelas-like condition remained for five weeks. After a prolonged rest the dermatitis was not only revived by a much weaker ointment, but it spread to the face, and the mucous membrane of the nose and throat became involved. This experience will recall the extensive dermatitis sometimes seen as a result of the application of a small quantity of some irritant lotion or liniment, and suggests that such patients have acquired an idiosyncrasy to such irritants by previous use.

The term hypersensitiveness, or acquired idiosyncrasy, is, of course, not a new one in dermatology. It has long

been known that repeated application of an irritant may in time give rise to a high degree of sensitiveness of the tissues irritated. It is only the idea that this is a manifestation of anaphylaxis that is new.

Drug Eruptions in their Relationship to Toxic Eruptions and to Anaphylaxis.

Before leaving this subject I wish to point out in what way these new ideas may help to explain some of the phenomena which occur in connection with drug eruptions.

It has for long been recognized that these drug eruptions are not necessarily the result of an excessive dose of the drug, but rather an indication of a peculiar hypersensitiveness, or idiosyncrasy, on the part of the patient. The production of an eruption by a drug seems to bear often no relationship to its physiological action. Some thirty years ago Behrend suggested that the eruptions produced by drugs were independent of the nature and of the physiological effects of those drugs, and that they were due to the action of foreign material, probably of chemical nature, generated in the blood by reason of the presence of the drug in the system. He thought that the smallness of the dose necessary to produce an eruption in many cases negatived the direct action of the drug. To-day we are reviving this idea; for the study of the phenomenon of anaphylaxis is suggesting that drug eruptions are produced by toxic albumins resulting from the action of the drugs upon living cells, and not by the physiological action of the drugs themselves.

The following experiment by Bruck supports this theory. Bruck injected guinea-pigs with the serum of a patient who had shortly before been affected by symp-

toms of iodoform poisoning. He then found that he was able to produce symptoms of iodoform poisoning in the guinea-pigs with small doses of iodoform. Something had been carried over in the patient's serum which rendered the guinea-pig hypersensitive, and Bruck concluded that it was an albumin compound.

In another way, too, modern ideas in regard to anaphylaxis have been anticipated by dermatologists; for Morrow, writing in 1887, said: "It has been observed that one attack of a drug eruption seems to confirm and intensify the susceptibility to subsequent attacks; while it may have required long and continued doses to determine the eruption in the first place, much smaller doses suffice to promptly redevelop a succeeding outbreak." And again, in regard to iodide of potassium, he writes that "while it may require several days to develop the eruption the first time, after its disappearance a single small dose may suffice to redevelop it in the course of three or four hours." These are now, of course, well-known facts, but I recall them in order to point out how closely they correspond with the phenomenon of anaphylaxis or production of hypersensitiveness by which we explain the immediate reaction in persons previously treated with serum.

To recapitulate briefly: the toxic erythemas, urticarias, and purpuras may be regarded as inflammatory reactions to the action of poisons, which act particularly upon the vessel walls and upon the tissues around. Possibly these poisons are toxins or products of living cells, either introduced as such or manufactured by the damage of the living cells by chemical or physical agents—*i.e.*, they are foreign proteids. These foreign proteids act as do the toxins of microbes. They give rise not only to the local

reactions (seen in the erythematous rashes) but to general reactions of defence. Hence they tend to produce a condition of hypersensitiveness, which is really the result of an effort of the body to rid itself of alien proteids, a stage towards the production of immunity.

The Toxic Origin of Eruptions other than Erythemas, Urticarias, and the Like.

I now turn to the consideration of those eruptions which I mentioned at the beginning of this lecture as being possibly of toxic origin. The list is a long one, and includes eczema, psoriasis, lichen planus, pemphigus, dermatitis exfoliativa, alopecia areata and many others.

Our first thought must be that there is little in common between these eruptions and the toxic erythemas, and that we cannot in the same way suppose them to represent reactions to harmful agents. But on further consideration this idea seems more reasonable. As I have already said, each of these affections has been at some time regarded as of nervous origin; but they are so distinct and so different from one another that it is difficult to realize how they could all be produced by this one cause. That they may be the result of the action of toxins seems more probable, for although each eruption has something in its clinical appearance and in its pathological anatomy which distinguishes it from the others, yet there are certain features common to them all which can be more easily explained by a toxic origin. Their differences might well be due to variations in the kind of toxin, in the same way that distinct types of reaction result from the toxins of different micro-organisms or of different varieties of the same micro-organism.

To take a few examples. We have in lichen planus, alopecia areata, scleroderma, macula atrophy, and xanthoma, five affections which seem to be quite distinct. Yet if we examine the histology of these eruptions we find that they have certain features in common. They each show evidence of destruction or of proliferation of some cellular element; and there is in each some sign of inflammation in the form of a cell proliferation round the blood-vessels. And these conditions—damaged cells and reactive proliferation—are, as we know, the usual effects of hurtful agents. So that from what we know of the action of poisons or toxins upon the tissues generally, it does not seem improbable that many of these eruptions are produced by poisons which have stimulating or destructive effects upon the cells of particular tissues, and that it depends upon the kind of poison and the tissue attacked whether there is or not marked inflammatory reaction. If, for example, the poison picks out a highly differentiated tissue like the elastic tissue, there may be destruction of this tissue without much inflammation.

It is known that the toxins of tetanus or of diphtheria may do damage to the highly differentiated nerve tissue without producing inflammation. We also know of cell poisons or cytotoxins which may give rise to profound changes in particular cells without producing inflammatory reaction. Dr. Charles Bolton has demonstrated, for example, that the blood serum of the rabbit immunized with the stomach cells of a guinea-pig is cytotoxic for the gastric cells of a guinea-pig, producing in these cells profound changes of which there is not even histological evidence, but which are said to be present by the fact that they are now readily digested by the gastric juices.

Then, among the drug poisons we may recall some which have an action upon particular cells. Arsenic may give rise to proliferation of the horny cells of the epidermis in the form of hyperkeratosis of the palms and soles. Acetate of thallium may cause baldness by its action on the hair papillæ.

So that there is nothing in the pathological anatomy of any of these eruptions which could not be explained by the action of toxins.

But, it may be asked, supposing these affections to be of toxic origin, what are the toxins or poisons which might be likely to give rise to them? To this we may reply that such poisons might be derived from some hidden or distant focus of bacterial infection; that they might be absorbed from the alimentary canal as the result of defective digestive processes, or that they might be produced in the body itself, as a result of defective metabolism or of altered gland secretion.

Toxins of Bacterial Origin absorbed from some distant Focus of Infection.

As regards the absorption of bacterial toxins from some focus of infection, the most important example is in the group of so-called *toxi-tuberculides*. I have already referred to the introduction of the idea of toxi-tuberculides by French observers in 1890. The affections now often grouped under this term had been long since described under names which suggested that they had some association with tuberculosis—namely, *lichen scrofulosorum*, *acne scrofulosorum* and *erythema induratum scrofulosorum* (*Bazin's disease*). The idea of Hallopeau and other French authors was that these affections were

due, not to the actual presence of the tubercle bacillus in the lesions, as was lupus vulgaris, but to the effect of toxins carried from some internal focus of tuberculous infection.

A feature common to all these eruptions is that they form indolent papules or nodules of various sizes, small in lichen scrofulosorum, larger in acne scrofulosorum, and largest in Bazin's disease, and that these papules and nodules tend to break down to form ulcers and punched out scars, which have no tendency to local spread, as they might be expected to have if they were due to the actual presence of the tubercle bacillus, as, in fact, has lupus vulgaris. Histologically all these eruptions show a cell infiltration primarily, and particularly marked around the blood-vessels (as would be expected from a toxin arriving by the blood stream), but also a proliferation of connective tissue with giant cells like true lupus. That these eruptions are tuberculous no one has any doubt, but it is still a disputed point as to whether they are due to toxins or to the actual presence of tubercle bacilli. Of recent years the tendency is to believe that they are the result of dead or attenuated bacilli, which is really not far removed from an admission that they are due to the toxins rather than to the actual growth and activity of the bacilli.

There are also other eruptions, for example, *lupus erythematosus*, *pityriasis rubra pilaris*, and *pityriasis rubra* of Hebra, which are believed by some observers also to be toxi-tuberculides, and although the evidence is scanty it indicates the tendency of modern ideas.

Another affection, only described in recent years, which is probably of toxic origin, is *gonorrhœal hyperkeratosis* of the palms and soles, which is associated with

chronic gonorrhœa and gonorrhœal arthritis, and which is perhaps an example of a proliferation of the horny cells from irritation by a bacterial toxin.

Pemphigus, again, has sometimes been thought to be due to the absorption of toxins from some internal focus of streptococci, but the only case that I know of which gives any support to this view is one published by Dr. J. H. Sequeira of a bullous eruption associated with appendix abscess in a child aged 3—although there was no examination of the pus, and we do not know that the abscess was streptococcal. Pyorrhœa alveolaris is often mentioned as a possible source of absorption of bacterial toxins, but there is no evidence that any skin eruptions owe their origin to this source.

Auto-intoxication in Skin Diseases.

It will be seen, then, that there is at present not any very conclusive evidence that there are, apart from toxic erythemas and, possibly, the toxi-tuberculides, eruptions which owe their origin to the toxins from a distant microbic infection. And for the majority of these affections—if we are going to suppose them to be of toxic origin—we are obliged to fall back upon the theory of auto-intoxication. By this we mean that they may be due to poisons absorbed from the alimentary canal as the result of defective digestion or to products of defective metabolism or of altered gland secretion.

Among the poisonous substances which may result from defective intestinal digestion, there are phenol, cresol, indol, skatol, indican, acetic, butyric and valerianic acids, sulphuric acid, and ammonia. But we have no evidence that absorption of these bodies ever gives rise

to any eruption of the skin. Attempts have been made to estimate the amounts of ethereal sulphates and aromatic bodies in the urine as a possible indication of absorption of toxic bodies from the intestine in cases of eruptions of supposed toxic origin, as in *lichen planus*, *psoriasis*, *eczema*, and *dermatitis herpetiformis*, but without any uniform result. So that Van Noorden, in his work on "Metabolism," says that the hope of finding in the ethereal sulphates a reliable proof of the intestinal origin of any dermatosis may therefore be almost abandoned.

Constipation and dilatation of the stomach are stated as causes of auto-intoxication and are regarded by some as the chief factors in the production of *acne* and of *lichen urticatus* or the nettle-rash of infants and children, but the majority of observers will probably agree that there is not always even clinical evidence of this association.

As regards the causation of skin eruptions by means of the products of *defective metabolism*, we know, of course, of *xanthoma* in diabetic subjects, though this eruption is comparatively rare, even in diabetics, and we are ignorant of its exact relationship with the metabolic disturbance. The association of xanthoma with hepatic disorders also points perhaps to some metabolic poison, and the histology of xanthoma shows a cell proliferation most marked around the blood-vessels with degenerative changes occurring in the proliferated cells, conditions which might be explained by the action of a toxin—but our present knowledge carries us no further than this. Gout, so often accused of giving rise to skin eruptions, and to eczema especially, has been long since, to a great extent, discredited by dermatologists. It is certain that one may see hundreds of cases of *eczema* without ever

meeting with a case of gout. In fact, a gouty patient is practically unknown in a skin clinic, although many patients who have skin complaints—even scabies or eczematoid ringworm of the groins and toes—consider these complaints manifestations of gout.

Of eruptions due to poisons which might be supposed to result from excessive or altered secretion of the *internal glands*, our knowledge is also very limited. It is known that in some cases of exopthalmic goitre there may occur alopecia, hyperidrosis, and pigmentations or leucoderma, and it has been thought that scleroderma seemed in some cases to be dependent upon changes in the thyroid gland; while many eruptions are influenced by thyroid gland administration—*ichthyosis*, *pityriasis rubra*, and *psoriasis*, for example. But this is about as far as our actual knowledge extends.

Indeed, although there is much that is attractive in the idea that certain skin eruptions are due to toxins resulting from defective metabolism, yet there is at present little, if any, direct evidence that this occurs. And it must be admitted that the toxic origin of these eruptions is thought to be probable, either because a microbic or nervous origin seems unlikely, or because the clinical features and histology are more easily explained by a toxic origin, or because we know of similar affections due to drug or other definite poisons, or that there are associated symptoms which also suggest a toxæmia.

Observations on various Diseases.

So far I have taken only a general view of this subject; to sift thoroughly what is known and suggested in regard to the toxic origin of these affections the evidence for

each disease ought to be examined separately. This I do not propose to do, but I shall merely give a few instances of special investigations or ideas.

First of all, there are certain eruptions which do appear to bear some relationship to the toxic erythemas which we have been discussing.

Lupus erythematosus is an affection which has been long thought to be of toxic origin, the only point of debate being whether it is due to the toxins of tubercle or to other unknown causes. Its histology suggests a toxic origin. So does the symmetrical arrangement of the eruption in vascular areas. As Liveing pointed out many years ago, and as Galloway and MacLeod have more recently demonstrated, it presents in some of its features a close resemblance to one of the so-called toxic erythemas—erythema multiforme; and the occurrence of albuminuria in acute extensive cases, as noted by Sequeira, perhaps also points to some acute toxæmic condition.

General exfoliative dermatitis is another skin disease which has of late years come to be regarded as probably of toxic origin, this view being based upon the clinical resemblance to exfoliative dermatitis of certain generalized erythemas with subsequent desquamation, which may follow the administration of certain drugs—of mercury especially, but also of quinine, chloral, opium, and others; and also upon the suggestion, supported by a certain amount of clinical evidence, that the more chronic forms of this disease—those of the type called pityriasis rubra of Hebra—are toxi-tuberculides.

In *scleroderma* we have an example of a skin disease regarding which the views as to causation have changed during recent years. Formerly considered to be a manifestation of rheumatism, scleroderma was afterwards

regarded as a trophoneurosis, and now is by many thought to be of toxic origin. The inflammatory nature of the early stages, and the occasional association of urticaria or erythema, or of joint pains and exudation with scleroderma, all help to suggest a toxæmic condition.

Alopecia areata, about the cause of which opinions were formerly divided between a parasitic and a nervous origin, is also now suspected to be due to some toxic agent. For it is realized that the fall of hair is due, not to a disease attacking the hair itself, but to something which does damage to the hair papilla. The suddenness with which the hair sometimes falls, the spontaneous recovery with relapses, and the fact that the whole body is often affected are very suggestive of some poison brought by the vascular system and acting on the hair papillæ. And this idea is supported by comparison with alopecias occurring after illnesses, and from the internal administration of acetate of thallium which, given for night sweating in phthisis, has sometimes led to falling of the hair. Alopecia areata is often a family disease, and it is possible that in certain persons the hair papillæ are particularly sensitive to local influences, so that various toxins, those of tubercle and of syphilis, perhaps, occasionally, among others, may lead to the production of alopecia areata.

Leucoderma is another affection which, for long regarded as of neurotic origin, is now, in the opinion of some observers, believed to be probably due to a toxæmia. Ehrmann has recorded cases in which "factitious erythema or dermographism" was well marked, and it is thought that the presence of a small round-celled infiltration around the vessels of the affected parts suggests a toxic agent. Leucoderma and scleroderma

are not infrequently associated. The occurrence of leucoderma syphilitica on areas previously occupied by the macular rash points to a toxic origin of this form of leucoderma and, by analogy, of other forms.

Macular atrophy—a somewhat rare condition in which there occur over the trunk rounded or oval areas of atrophied skin—is an example of a skin affection formerly called idiopathic, and now known to be preceded by erythema and thought to be possibly of toxic origin. The atrophy is due to destruction of the elastic fibres of the corium, and it is thought that this must be the result of some poison, the preceding erythema giving support to this view. Sometimes these macules occur in syphilitic and in tuberculous subjects, and I recently exhibited a case of macular atrophy in a tuberculous subject in whom some of the atrophic macules were actually developing upon the same area as that occupied by groups of lichen scrofulosorum, suggesting that the toxins of tubercle may have destroyed the elastic tissue, as has been supposed in similar cases by Heuss, Thibierge, Wechselmann, and others. In other cases the atrophic macules have occupied the former site of syphilitic macules or papules, suggesting that the toxins of syphilis have led to the destruction of the elastic fibres.

Then we have in the *bullous eruptions* a large group which was at one time regarded as being of nervous origin, but some members of which have been proved to be due to microbic infections, and the remainder of which are now thought to be probably of toxic origin. In respect to *pemphigus vulgaris*, the theory of nervous origin rests solely upon the fact that in a very few cases nerve changes have been found after death, though as a rule there is no evidence of any such changes, nor are

there any symptoms pointing to nervous disturbance. Against the views of a bacterial origin of pemphigus vulgaris are the facts that the earliest bullæ are sterile and that the affection is not contagious. In many cases it can be demonstrated that there is in reality a disturbance of the whole epidermis, and it is only by accident that the bullæ appear in certain parts, for by firm pressure with the finger in apparently normal areas there is found to be a loosening of the horny cell layer of the epidermis which easily slides off (Nikolsky's sign). This fact has suggested that there is some toxin in the blood which is cytolytic for the superficial horny cells. This, however, is only theory, and we have no direct evidence of toxæmia beyond the fact that there is usually a marked increase of eosinophiles in the blood—a condition which we generally understand to indicate a toxæmia.

In *herpes gestationis*, an affection perhaps allied to pemphigus, it has been suggested by Wechselmann and others that there is an intoxication by the products of disassimilation of the fœtus and placenta. Others have thought that it might be due to some infection of pregnancy. That the fœtus may die in some cases seems strong evidence of a toxæmia. Dr. Herbert French, in his Goulstonian lectures in 1908, said he thought it possible that no abnormal substance was produced, but that certain persons were unusually susceptible to some compound which is a normal metabolic product of the pregnant state. Meyer and Linser, believing this supposed susceptibility to result from the absence of natural antitoxins from the patient's serum, injected a patient who had herpes gestationis with the serum of a normal pregnant woman, with the result

that the fever ceased and the eruptive lesions disappeared. One may question, however, whether this might not have happened after ordinary horse serum injections.

There is just one other eruption of the bullous type to which I feel compelled to refer because of some interesting observations which have been made in connection with it. I mean the eruption called *hydroa æstivalis*. This is a somewhat rare vesicular and bullous eruption which appears on uncovered parts on exposure to bright sunlight. It has been shown experimentally that these eruptions are due to the action on the skin of the violet rays of the spectrum. It has also been observed that some of the persons who are liable to these "light" eruptions have hæmatoporphyrin in the urine. The interesting experiments to which I refer are those which have demonstrated the connection between this hæmatoporphyrinuria and the action of the sun's light upon the skin. Hausmann has shown that hæmatoporphyrin will kill infusoria in the light but not in the dark. He has also shown that when white mice are injected with a weak alkaline solution of hæmatoporphyrin they take no harm so long as they are kept in the dark, but they die when exposed to strong sunlight, which, alone, does not hurt them. With a less intense heat they show skin changes, redness of the ears, nose, extremities and joints, with swelling of the whole body. From these experiments Hausmann was led to believe that hæmatoporphyrin acts in a toxic manner on the cells of the skin—the endothelium of the vessels or perhaps the epidermal cells—thus rendering them more sensitive to light, so that they are readily damaged, and inflammatory reaction results. Other observers have

elaborated Hausmann's experiments by rendering rabbits hæmatoporphyrinuric by dosing them with sulphonal (which is known to produce that condition), and by finding that their skins were then easily blistered by exposure to ultra-violet light.

These observations may help perhaps to throw some light upon the ætiology of other skin eruptions, suggesting that there may often be two factors in their production—a poison damaging the epidermic cells and rendering them sensitive to the action of some local physical agent. It seems possible that one of the most common of skin diseases, eczema, may owe its origin to two such causes.

A suggestion was made a few years ago by Dr. Leslie Roberts, that *eczema* might be due to the effects of a locally produced toxin. Dr. Roberts thought that eczema might be regarded as an inflammatory reaction, as an effort to get rid of some local irritant, that local irritant being produced by metabolic changes in the epithelial cells as the result of various mechanical or other physical stimulants. Such a view accords with what we know to happen clinically. A person, apparently in good health, gradually acquires a high degree of hypersensitiveness of the skin, first to some local irritant, and then to all forms of local irritants ; and this hypersensitiveness is manifested in the form of the inflammatory reaction which we know as eczema. The correctness of this view is also supported by the results of treatment ; for we know that the only really effectual treatment for eczema is to protect the affected parts, not only from the irritant which began the mischief, but from all local irritants until the patient has lost this hypersensitiveness, and that when we have reached this stage

the eczema does not return. And yet even if we suppose the toxin which gives rise to the inflammation to be produced locally, as the result of the action of a physical agent on the epithelial cells, it is difficult to resist the idea that there is in eczematous subjects some predisposing cause which renders the epidermal cells sensitive to slight physical injuries. As to what this predisposing cause may be we have at present no idea, but that there may be such a double cause has been shown by the observations made in regard to hydroa æstivalis.

In conclusion, it may be said that, although a toxic origin seems probable for a vast number of skin eruptions, no pretence can be made that this idea yet supplies a complete solution of the question of the causation of these affections. For it must be obvious that, even supposing this view to be a correct one, dermatology has still a long way to advance before it can be possible to discover the specific toxins for these many distinct eruptions. It is probable that they are present only in the minutest quantities, and that they require methods for their detection such as we do not now possess. Some day this unknown territory may be explored by the aid of the physiological chemist, and the study of the causation of these eruptions may perhaps lead to discoveries which will clear up some of the problems of the pathology of disease in general; but at present not even the road which leads to this field of research is clearly marked out.

LECTURE III.

Delivered on March 19.

In the two previous lectures I showed that many skin eruptions are coming to be regarded as reactions to physical, microbic, or toxic agents which do damage to the tissues. It cannot be said, however, that all skin affections are to be interpreted in this way, and there still remain some which it is convenient to group under the headings of congenital eruptions, new growths, and eruptions of nervous origin.

Eruptions of Nervous Origin.

We have seen already that the part played by the nervous system in the production of skin eruptions is probably less important than was formerly supposed, and that even such eruptions as the erythemas and urticarias, to which the theory of vaso-motor nerve disturbance seemed especially applicable, are now believed to be of inflammatory nature and due to the direct action of toxins on the blood-vessels and tissues. It is true that Wolff-Eisner and other leading authorities on the problems of immunity maintain that the phenomena of hypersensitiveness are the result of irritation of the central nervous system, and explain the rashes of serum disease, urticarias from food and drug poisoning, urticaria and pruritus of pregnancy, as also hay fever and asthma and the skin eruptions of pellagra, by the action of heterogeneous albumins upon the vaso-motor centres, but I shall not

here attempt to discuss the relative merits of these two views, for I have already shown in my last lecture that modern dermatology tends to support that which regards them as inflammatory reactions.

An argument which has been used in favour of the nervous origin of certain eruptions — urticaria, lichen planus, dermatitis herpetiformis, for example—is that they are accompanied by itching, which is obviously due to a nerve disturbance. But itching can often be accounted for just as readily by supposing a local irritation of the sensory nerve terminals in the skin by mechanical or by toxic agents, as by believing it to be due to a central nerve disturbance, and it is reasonable to suppose that the toxic agent which gives rise to the eruption by its action on the vessels and other tissues also irritates the nerve-endings and causes itching.

It is perhaps true that eczematous and pruriginous eruptions are of more frequent occurrence in persons of a neurotic temperament, but it must be remembered that such persons are liable to exaggerate their sufferings and also to aggravate the eruptions by rubbing or scratching. So that while some observers maintain that these eruptions are directly dependent upon nerve disturbance, others regard them as due to a toxæmia which may also be responsible for the nervous symptoms—for the itching itself among others.

Indeed, when we come to make a list of skin affections in which we have clear evidence of nerve origin we find it to be a very small one. There is, of course, herpes zoster; and there are examples of hyperidrosis limited to the areas of distribution of particular nerves; there are a few recorded cases of alopecia following division of a nerve; there is the glossy skin of parts deprived of nerve

influence; and Raynaud's disease and some allied affections. The so-called trophic bullæ and ulcers are probably the result of injuries and infections of insensitive parts, and not true nervous lesions. It is possible that we may also include in this list certain vaso-motor disturbances, for although vaso-motor disturbance probably never alone gives rise to skin eruptions, it cannot be denied that it may have some influence on the course and character of inflammatory eruptions, and that it may also be a factor in determining the seat and distribution of others. I shall presently refer to the possible influence of the nervous system in determining the incidence and distribution of eruptions.

Congenital Skin Affections—New Growths.

In regard to the significance of congenital skin affections my remarks will also be brief, for although this subject is one of very great interest, little is known as to the true nature of these complaints. There is, indeed, a growing tendency to attribute many of these congenital affections to the results of injury or disease during fœtal life, or to the results of infections or of intoxications in the parents such as syphilis or tuberculosis, and lead-poisoning or alcohol. This would bring these affections into line with other skin eruptions resulting from injury, infection, or toxæmia. But it must be admitted that such evidence is often scanty, and that many congenital defects occurring as family traits, passing from generation to generation, would be difficult to explain in this way.

Of new growths or tumours it may be said that many eruptions which were formerly classed as tumours or new growths are now put among the infective disorders, such as warts and molluscum contagiosum, actinomycosis,

keloid ; while others, like scleroderma and xanthoma, are possibly of toxic origin. Some new growths belong probably to the group of congenital developmental defects—such as multiple benign epithelioma and adenoma sebaceum. Even rodent ulcer may perhaps be put into this group, bearing as it does a close relationship to multiple benign epithelioma. There remain squamous epithelioma and melanotic epithelioma as examples of true malignant new growths or cancers. The nature of cancer is not a subject to be discussed now, but I may perhaps be permitted to say that the invariable occurrence of precancerous conditions in the form of scars from various causes, and the histological details of these growths as they affect the skin, tend to support the view that malignant epithelioma is not of microbic origin, but that it has to do with a disturbance of the normal balance between the relationship of the epithelium and the connective tissue, so that the epithelial cells grow out of their normal course and invade the connective tissue, becoming, in fact, noxious infecting agents comparable to pathogenic micro-organisms.

The Significance of the Patterns and Distributions of Skin Eruptions.

I now come to another side of the question of the significance of skin eruptions—namely, to that which concerns their various patterns and their different manners of distribution, and I shall endeavour to show how our present knowledge of microbic infections and of toxæmias helps to make clear the reasons for some of these patterns and distributions and also how we are able to learn something of the nature and origin of eruptions by the study of their manner of distribution.

The Influence of Local Physical Agents.

An almost obvious reason for the particular distribution of many eruptions is that they are either produced or that their production is assisted by local physical causes. A familiar example is the incidence of *trade eczemas* upon the hands and fingers. This is possibly also the reason for the peculiar mask-like distribution of *eczema* in infants

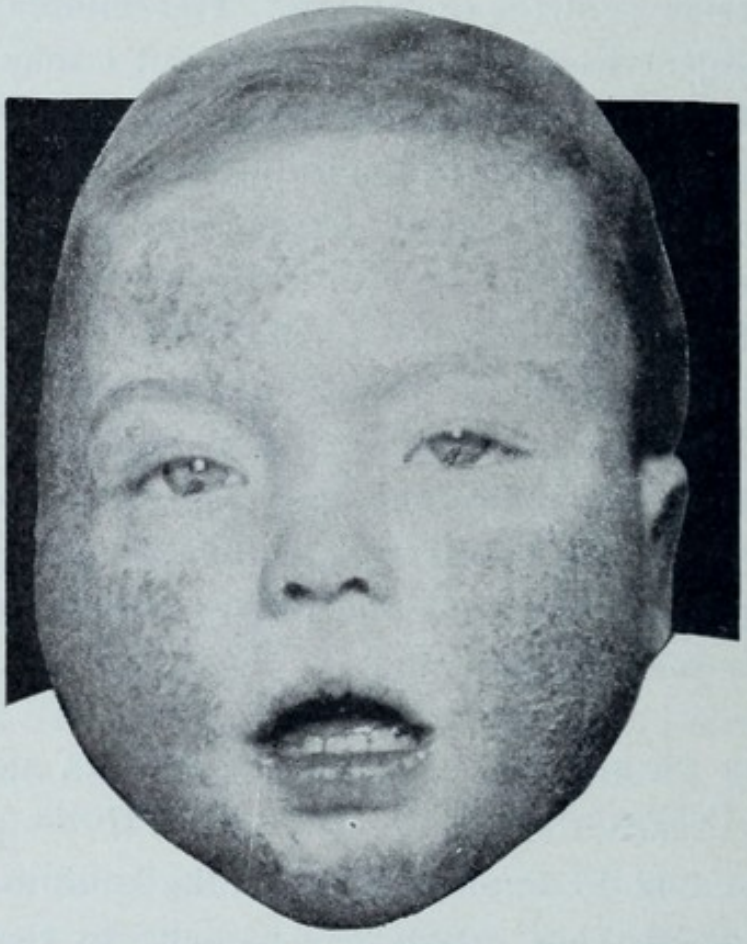

Fig. 17.—Infantile eczema, showing typical mask-like distribution.

upon an exposed part, the face, and on the convex surfaces of this exposed part—namely, the forehead and cheeks—as seen in the photograph (fig. 17). The freedom of the nose is probably accounted for by the fact that the skin here is thicker and more freely lubricated with sebaceous secretion. This peculiar mask-like dis-

tribution of eczema in babies often helps to distinguish it from impetigo, which does not respect the parts about the mouth and orbits.

A good example of the distribution of an eruption being determined by friction on prominent parts is that of *erythema of the napkin region* in infants. In this affection

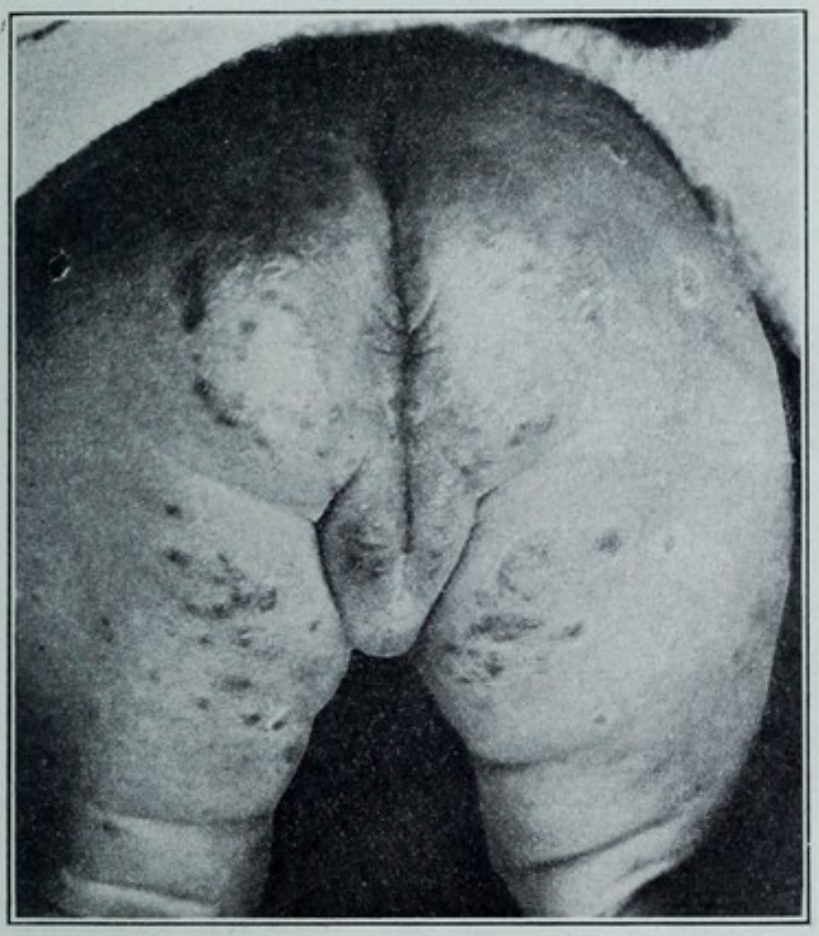

FIG. 18.—Napkin-rash, showing eruption on prominent parts and the folds and flexures free.

the child often has a general tendency to nettle-rash of infants (lichen urticatus), and the rash is brought out especially on those parts where the napkin rubs—namely, on the convex surfaces of the buttocks, genitals, thighs, and the calves and heels, the protected flexures and folds being free. This is well seen in the photograph (fig. 18).

The recognition of this simple fact is really of considerable importance, because the grave error is often made of mistaking these erythemas of the napkin-region in infants for the eruption of *congenital syphilis*, especially as the erythematous patches may develop into flat papules which become ulcerated, leading to punched-out ulcers

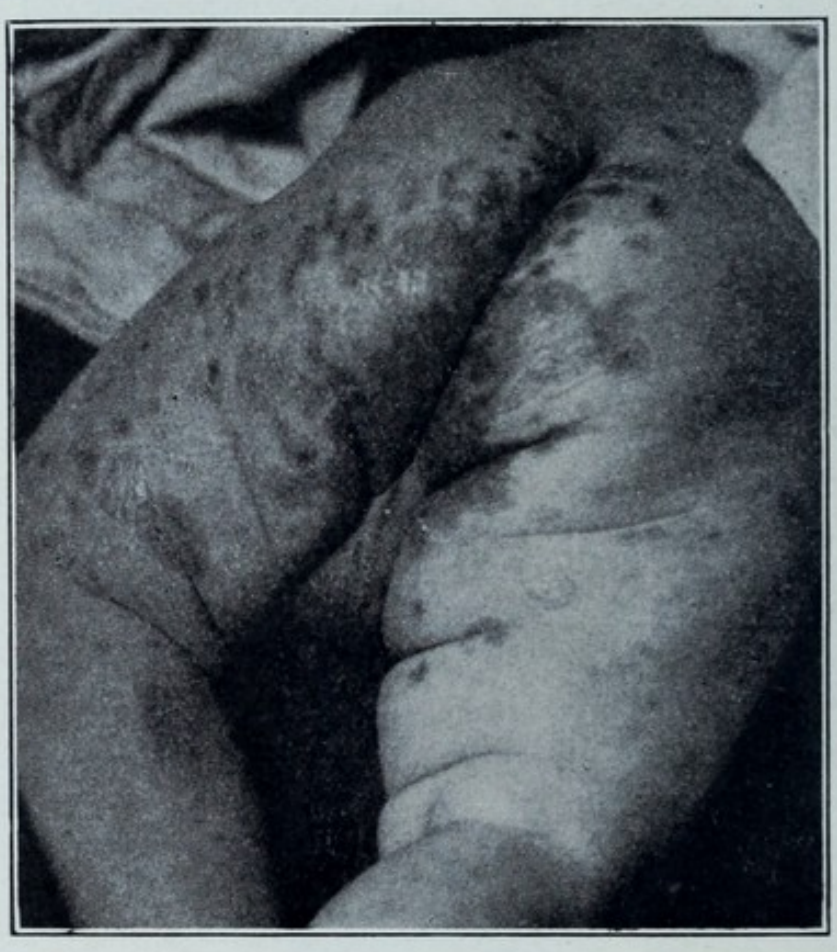

FIG. 19.—Eruption of congenital syphilis involving both convex surfaces and flexures.

which so nearly suggest ulcerated papules of syphilis that even a great physician, Trousseau, mistook them for syphilitic ulcers. The photograph of an eruption of congenital syphilis (fig. 19) shows that, in contrast to the napkin rashes, the flexures are not here respected.

In *lichen simplex chronicus*, or lichenification, we have

an eruption the distribution and shape of which, and probably the eruption itself, depend upon rubbing and scratching by the patient (fig. 20). It occurs in persons of a neurotic type, and it consists of one or more large, oval, intensely itchy, infiltrated patches on the sides of

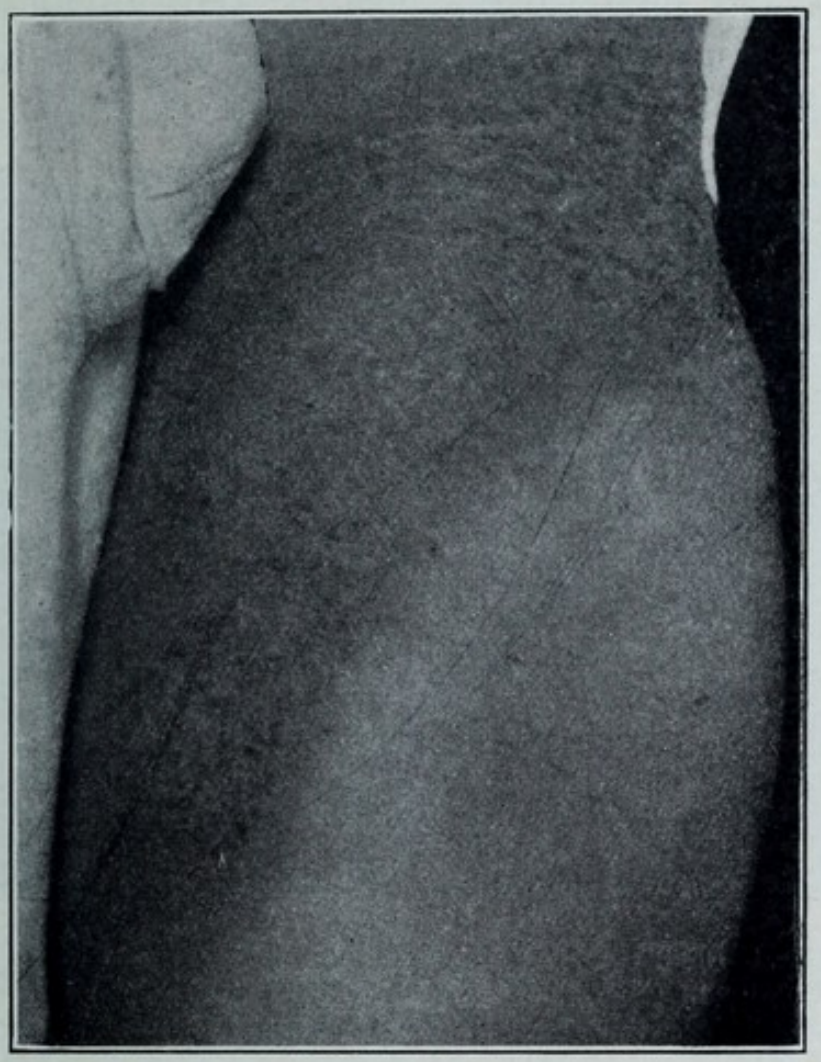

FIG. 20.—Lichenification on the inner side of the thigh.

the neck, on the forearm or shins, on the inner sides of the thighs, or on the perineum (in association with pruritus ani). These patches have their origin often in some pruritic affection, such as a nettle-rash from food poisoning, or even in the irritation from gnat-bites, and the patient being of a neurotic temperament cannot

refrain from scratching. In course of time the rubbing and scratching lead to inflammation and induration of the skin—*i.e.*, to lichenification. The oval shape of the patch and its position, with its long axis in the direction of easiest scratching, bear testimony to its mode of production, and such patches may be kept up for years, unless measures are taken to prevent the continual rubbing.

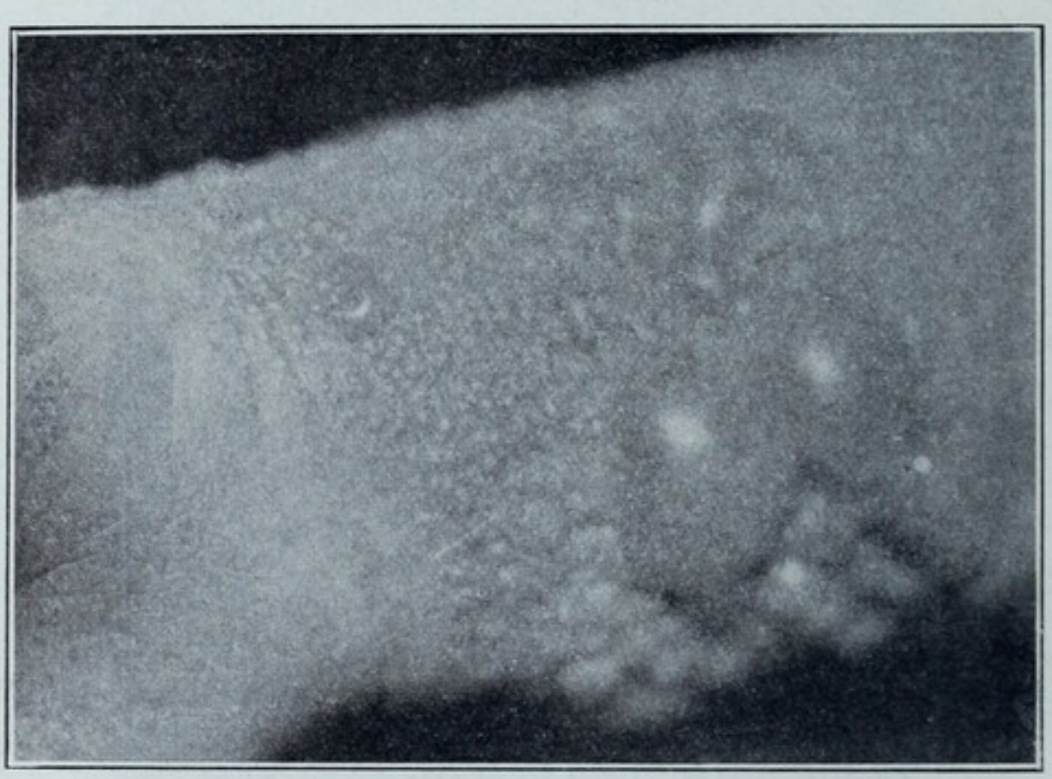

FIG. 21.—Dermatitis artefacta, the result of the application of a local irritant applied on a rectangular piece of rag.

Very striking examples of the conformation of pattern or shape of the eruption to the areas affected by mechanical agents are those of *dermatitis artefacta*, either where the eruptions are accidentally produced or intentionally by hysterical patients or malingerers. It is not uncommon for a vesicular or bullous eruption to be produced by the continuous application of a strong liniment or an ointment which was intended for embroca-

tion or inunction. The eruption then takes the shape of the cloth upon which the liniment or ointment is applied, and its square or rectangular shape gives the clue to a correct diagnosis of its origin. The photograph (fig. 21) is an example of such an eruption in which the rectangular shape is well seen.

Much more puzzling eruptions to those not familiar with them are those produced intentionally in some cases of hysteria. These eruptions are manufactured by the patient in various ways—sometimes by the painting on of a caustic or blistering fluid or by the application of a cup

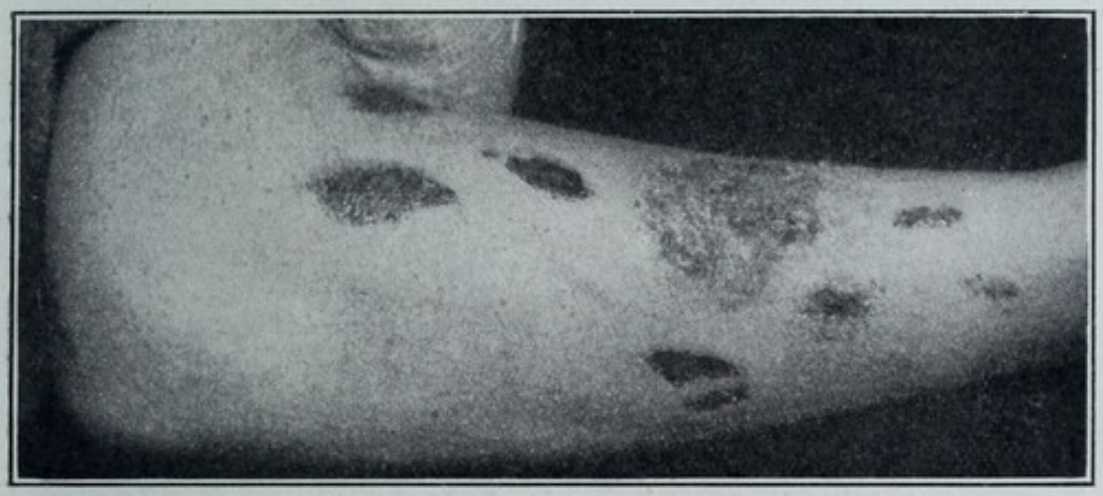

FIG. 22.—Neurotic excoriations produced by friction with the finger.

or other vessel dipped in some such fluid, or by sticking on squares of blistering paper, the lesions in these cases corresponding to the shape of the instrument used. When the excoriations are produced by painting on some acid or irritant fluid one sometimes sees at one part of the excoriated patch a long dependent streak indicating that the fluid has run down as it was painted on. In other cases the eruption is produced by friction with the finger-tip, so that long oval excoriations result. This photograph (fig. 22) is a good example of these so-called

neurotic excoriations produced by rubbing with the finger. Here, again, the odd shapes of these artificial eruptions give the clue to their correct diagnosis.

In certain eruptions we see the influence of another locally acting physical agent—namely, light, or rather the ultra-violet rays of the spectrum. I have already spoken of *hydroa æstivalis* in my last lecture as an eruption of bullæ and vesicles occurring only on parts exposed to the light.

FIG. 23.—Small-pox. The ring of pustules below the knee was caused by the pressure of the garter. (From "The Diagnosis of Smallpox," T. F. Ricketts and J. B. Byles; by kind permission of the authors.)

In *small-pox*, too, we have a striking example of the influence of light and other physical agents on a skin eruption. Ricketts and Byles, in their work on "The Diagnosis of Small-pox," lay particular stress upon this, the effect of local irritation on the distribution of the

eruption, showing that the eruption has "a characteristic tendency to shun the most sheltered parts of the cutaneous surface. These are the great flexures of the body." It is also more marked upon the uncovered parts, the face and the hands. They also show how it may be brought out by any local irritation, such as friction by a garter or of a plaster (figs. 23, 24). It is said that the rash of small-pox is much less severe if the patient be kept in red

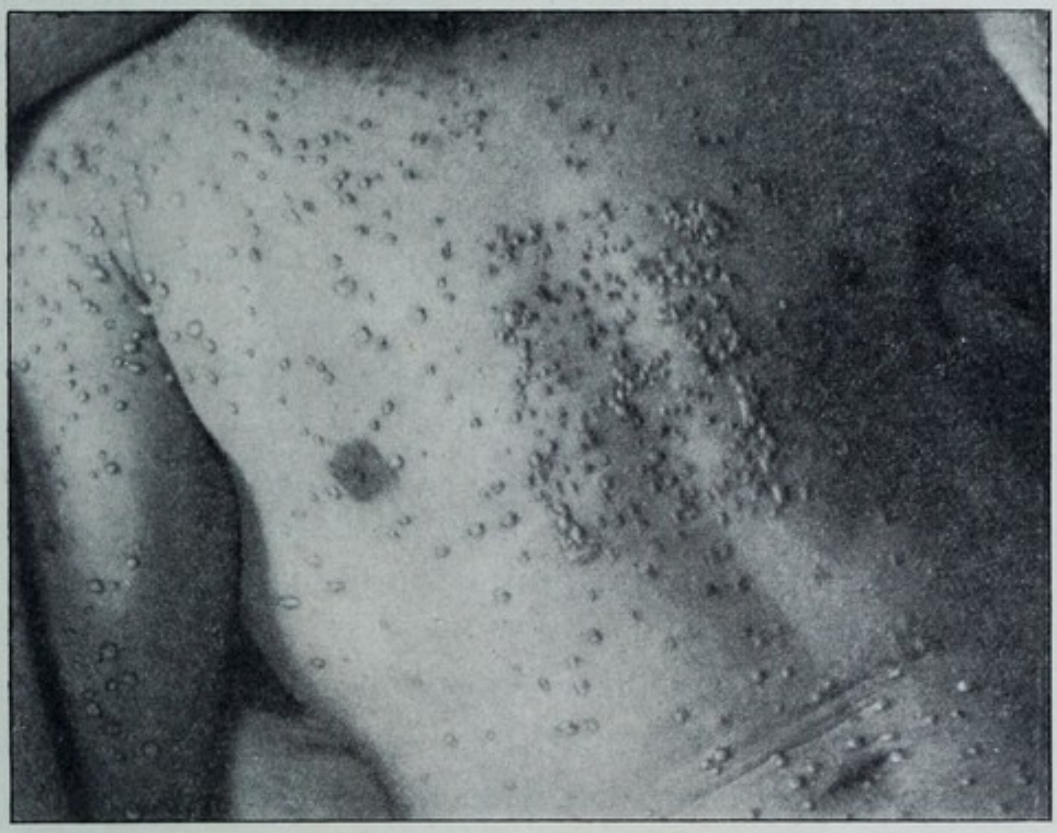

FIG. 24.—Small-pox. A mustard-leaf was applied to the chest at the onset of the illness to relieve the epigastric pain which was one of the symptoms. (Ricketts and Byles.)

light, and it is, perhaps, exposure to light which makes the eruption most abundant and severe upon the face and hands.

Further examples of the influence of physical agents on the determination of the distribution of skin eruptions might be given, but those I have mentioned will suffice as

illustrations of this particular side. I shall now turn to the consideration of some of the ways by which different distributions are brought about in eruptions due to microbic invasion.

Factors which Determine the Distribution of Eruptions of Microbic Origin.

In the first place it is clear that the site of the eruption may often depend upon the facility with which infection takes place in certain positions. Thus, the *primary sore* in syphilis is usually upon the genitals because it is a venereal infection, but it may also occur on other parts from other contacts, as on the lip or cheek, or on the finger of a medical man. *Lupus vulgaris* is common upon the cheek (and commonly occurs in children), probably from kissing by consumptive persons; but it may also occur upon the nose, by extension from the mucous membrane infected by the finger or handkerchief; and it is not uncommon on the knees or buttocks of children from infection while crawling upon the floor.

Many parasites or microbes have favourite sites according as the soil and other conditions are favourable for their growth. It is remarkable how particular are these parasites in their choice of residence, so that even different varieties of the same species flourish only upon their own favourite soil. A familiar example is that of the head-louse, the body-louse, and the pubic louse; each of which occupies only its chosen region. One sees the same thing in *ringworm*. The small-spored ringworm of children will not invade the beard region of a man, nor will it attack the scalp of an adult. Then, again, the groin ringworm grows only in the flexures between the toes or fingers, in the groins and in the axillæ, but

nowhere else ; and it never, like other ringworms, invades the hairs. Then there is the *acne bacillus*, which is found only in the mouths of the pilo-sebaceous follicles upon the scalp, face, and back, and which does not appear until puberty. When the small-spored ringworm no longer grows on the scalp, the acne bacillus flourishes there. There is possibly some alteration in the sebaceous secretion at puberty which suits the acne bacillus, but not the ringworm fungus.

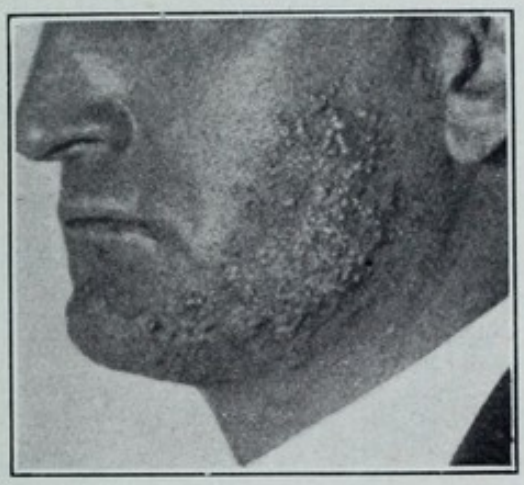

FIG. 25.—Sycosis—a staphylococcic infection of a hairy region.

The *coccic infections*, streptococcal impetigo and staphylococcal impetigo, also have their favourite sites. That of impetigo contagiosum (figs. 11 and 12, Lecture I.) is the face and hands, which are parts exposed to infection, and also the flexures of all parts of the body (fig. 10, Lecture I.), while the region of staphylococcic infection is regulated by the position of hairy parts, being common upon the beard region, as in sycosis (fig. 25).

One may note also that certain shapes and patterns are often produced by the local spread of infections. Sometimes the individual lesions widen out to form rings, as in tinea circinata and in impetigo circinata. Often fresh

infections takes place round the original patch or circle to form groups of daughter patches round the mother patch, like satellites round a sun, as seen in ringworm of the scalp and in impetigo of the face.

The Distribution of Eruptions determined by the Course of the Lymphatics.

Since the lymphatic circulation passes from the periphery to the centre it can never be responsible for the wide distribution of eruptions. But in some local infections of the skin the invading organism is able to pass the barrier of defence set up by the local tissue

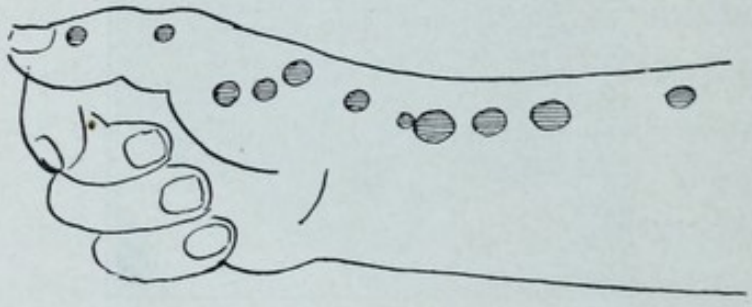

Fig. 26.—Diagram of lesions in a case of sporotrichosis. The shaded circles indicate position of the nodules and small abscesses, the original lesion being on the thumb.

reaction, and enters the lymphatics; the result of this is seen in the enlarged glands and sometimes inflamed lymphatic trunks of the region draining the site of a streptococcic or staphylococcic infection, of a primary syphilitic sore, of a scrofuloderma, or of a sporotrichial infection. The skin may then become again infected from the glands or lymphatics. The diagram here shown (fig. 26) illustrates the invasion of the lymphatics in a case of *sporotrichosis*. The infection took place on the thumb, and this was followed by a string of inflamed lymphatics and a chain of fresh nodules along the arm

Influence of the Blood-vessel Distribution in determining the Distribution of Eruptions.

When the micro-organism gains entrance into the blood-vessels, general eruptions may arise, as a result of the micro-organisms being carried to all parts of the skin.

A good example of this dissemination of micro-organisms by the blood-vessels is seen in the eruptions of secondary syphilis, in the rose rash of enteric fever, and in some infective erythemas and purpuras. It is not unusual to meet with cases of *multiple lupus* in children, due to entrance into the blood-stream of tubercle bacilli from some internal focus, often possibly a tuberculous gland. These cases nearly always occur after measles, an exanthem which we know often gives rise to dissemination of tuberculosis, and in these cases of multiple lupus the skin is involved rather than the deeper organs.

Probably in many instances widespread eruptions are due to the carrying, not of microbes, but of toxins to all parts of the skin by means of the blood-stream; and there are certain facts in regard to the distribution of the vessels of the skin which have a special interest as affording some explanation of the various patterns of the eruptions due to blood-carried microbes and toxins.

Vascular Network of Renaut.

Some years ago Renaut,[1] a French physician, demonstrated by means of injections of a watery suspension of Prussian blue that the vessels of the skin are arranged in a system of separate territories. Each territory is composed of a vascular cone, fed by a small and deep-seated

[1] Article, Dermatoses: "Dictionnaire Encyclopédique des Sciences Médicales," vol. 28, MDCCCLXXXIII., pp. 158 and 180.

central artery. The bases of the cones are towards the epidermis, so that viewed from the surface of the skin they form a number of rounded areas. These rounded

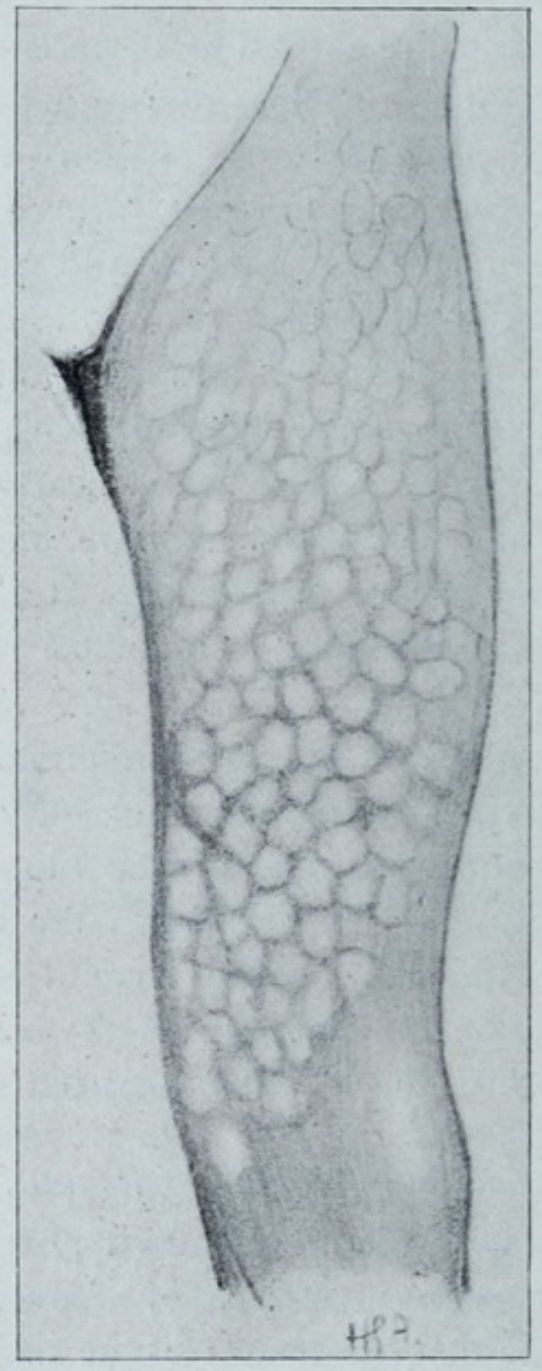

FIG. 27.—Livedo annularis—an exaggeration of the normal vascular network.

areas Renaut called *areas of maximum circulation*, and he said that they were related to the adjacent areas by a less easily permeable system of anastomoses. This

region of reduced circulation may be regarded as forming a network, of which the areas of maximum circulation represent the meshes.

This network of sluggish circulation can be sometimes very well seen in the living subject in the purplish marbling or mottling known as *livedo annularis*, which occurs in many children with poor circulations, and sometimes in normal persons on exposure of the skin to cold—livedo frigore (fig. 27).

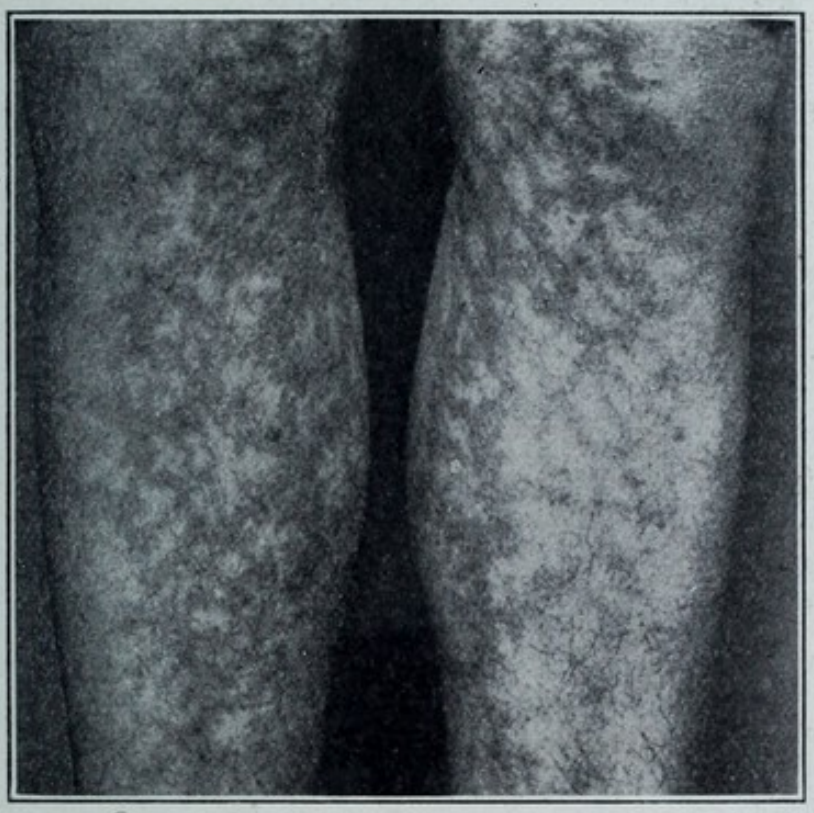

FIG. 28.—Pigmentation associated with erythema ab igne, mapping out the vascular network.

The pattern of the vascular network may sometimes be mapped out by pigmentation as a result of long exposure to heat, the constant dilatation of the blood-vessels, and the action of the heat on the tissues leading to the deposit of pigment in the areas of "reduced circulation." This photograph (fig. 28) is a striking

example of this so-called *reticular melanoderma* on the legs of a lad whose work necessitated his standing close to a fierce fire. A similar example of reticular melanoderma, as the result of arsenical poisoning, has recently been reported by Bosellini.

Dr. T. Colcott Fox and Dr. J. M. H. MacLeod have drawn attention to the correspondence of the network of

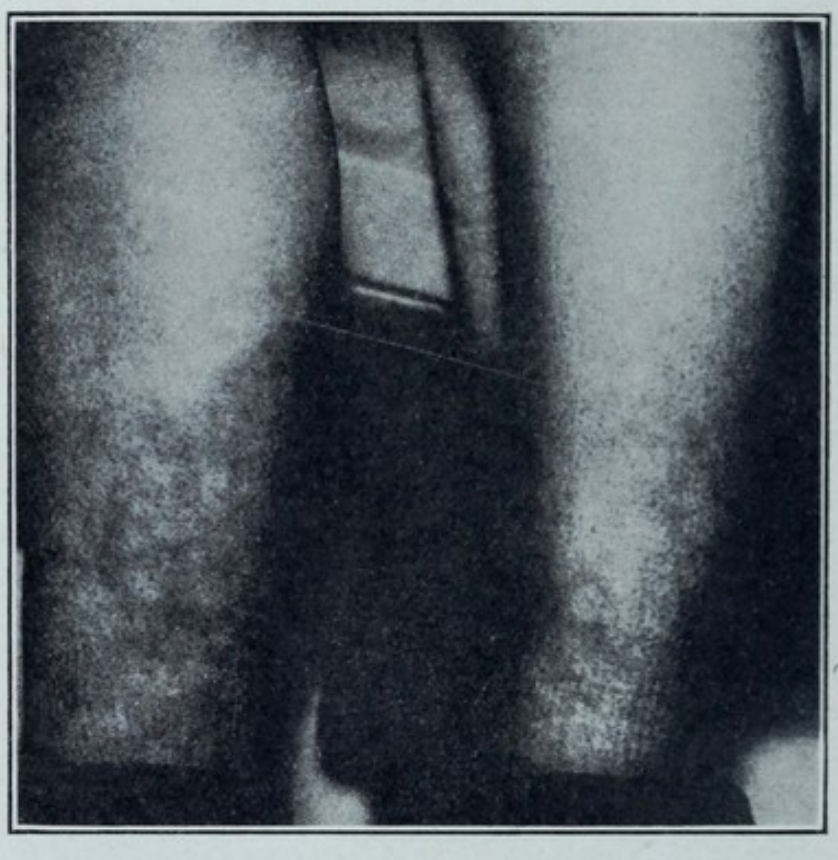

FIG. 29.—Bazin's disease involving the vascular network.

yellowish-red mottling enclosing paler areas which occurs in *parakeratitis variegata*, with the retiform distribution of the venous plexus in the skin as seen in livedo annularis.

Sometimes this same mapping out of the vascular network may be seen in cases of *erythema scrofulosorum* or Bazin's disease. Bazin's disease is one of the affections now known as tuberculides. It occurs on the legs in young girls who stand much at their work, and generally

takes the form of indolent nodules which tend to necrose and break down, leaving punched-out ulcers and scars. Histologically it has been shown that the cell-infiltration commences round the veins—probably from the lodgment there either of dead or attenuated tubercle bacilli, or from the stasis there of the toxins of tubercle. Sometimes these nodules extend along the veins and mark out the venous plexus in an imperfect network, as is seen in the photograph here shown (fig. 29).

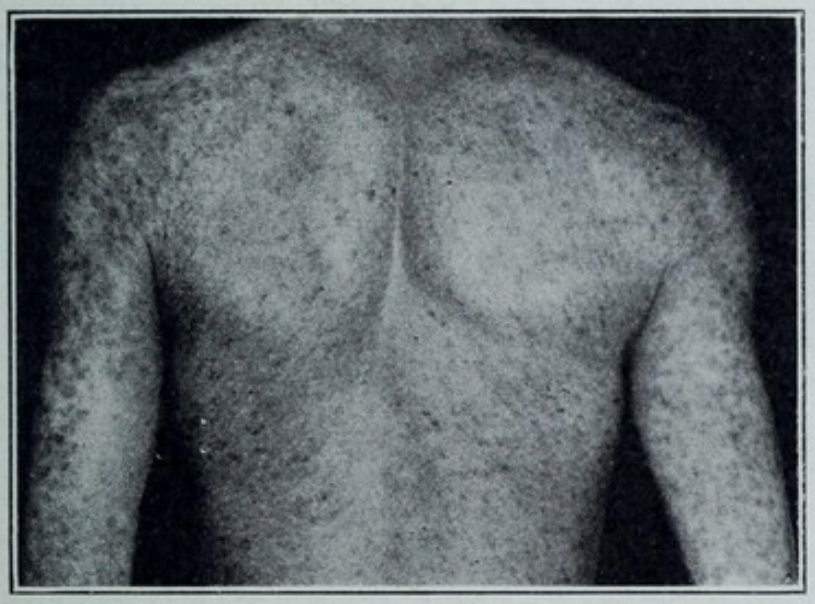

FIG. 30.—Roseola of syphilis, showing macules corresponding to meshes of vascular network (best seen on arms).

Pattern of Erythemas determined by the Vascular Network.

The relationship of the pattern of various erythemas in regard to the blood-vessel arrangement is also interesting. It has been suggested by Bonnet and others that the red macules of a *syphilitic roseola*, for example, correspond to the central arterial part of this blood-vessel system, and, as Finger has graphically put it, the arterial roseola and the venous livedo annularis are like the negative and the positive of a photograph. Here is a photograph (fig. 30)

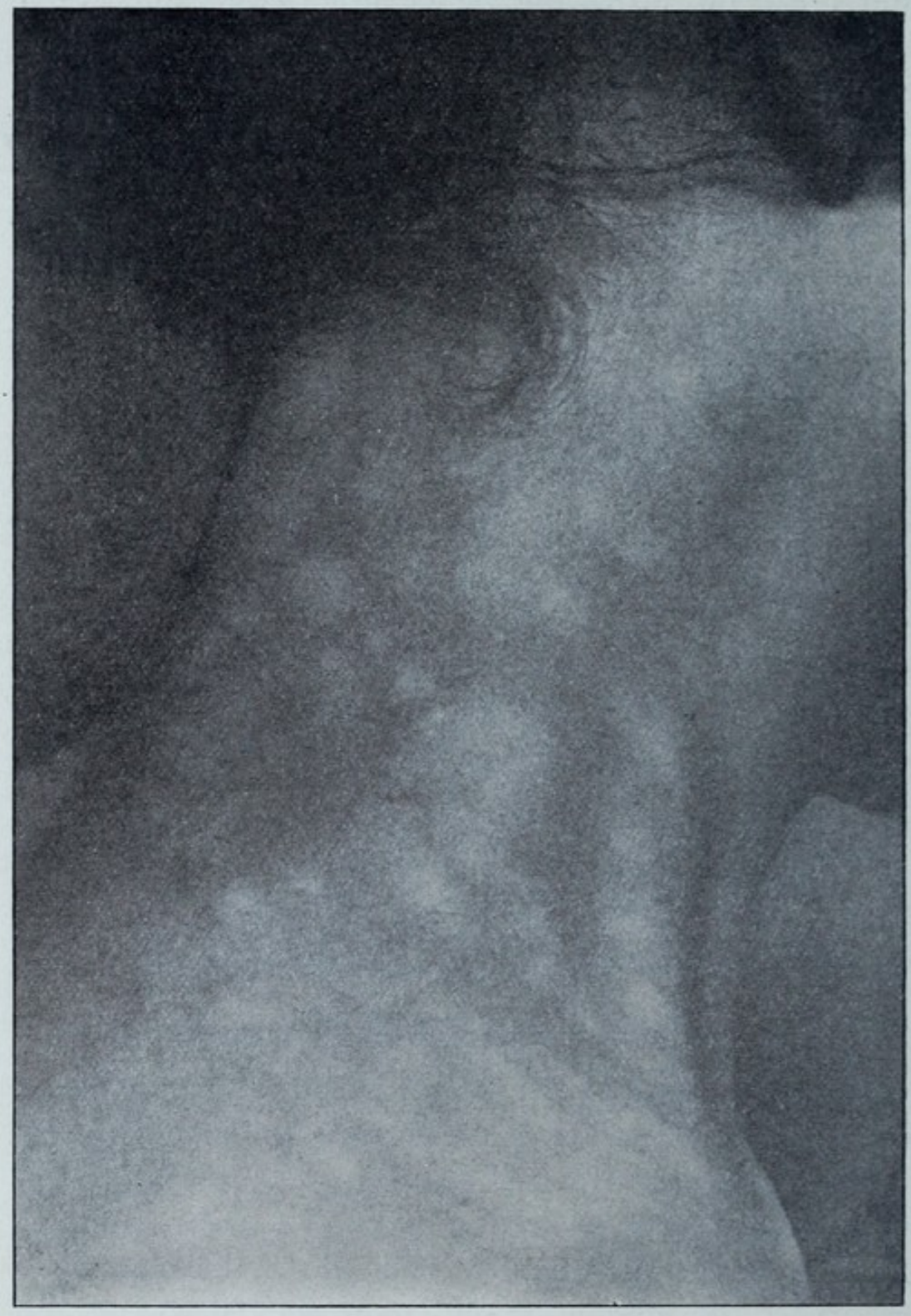

FIG. 13.—Leucoderma syphiliticum ; showing the pale areas left by the fading macules.

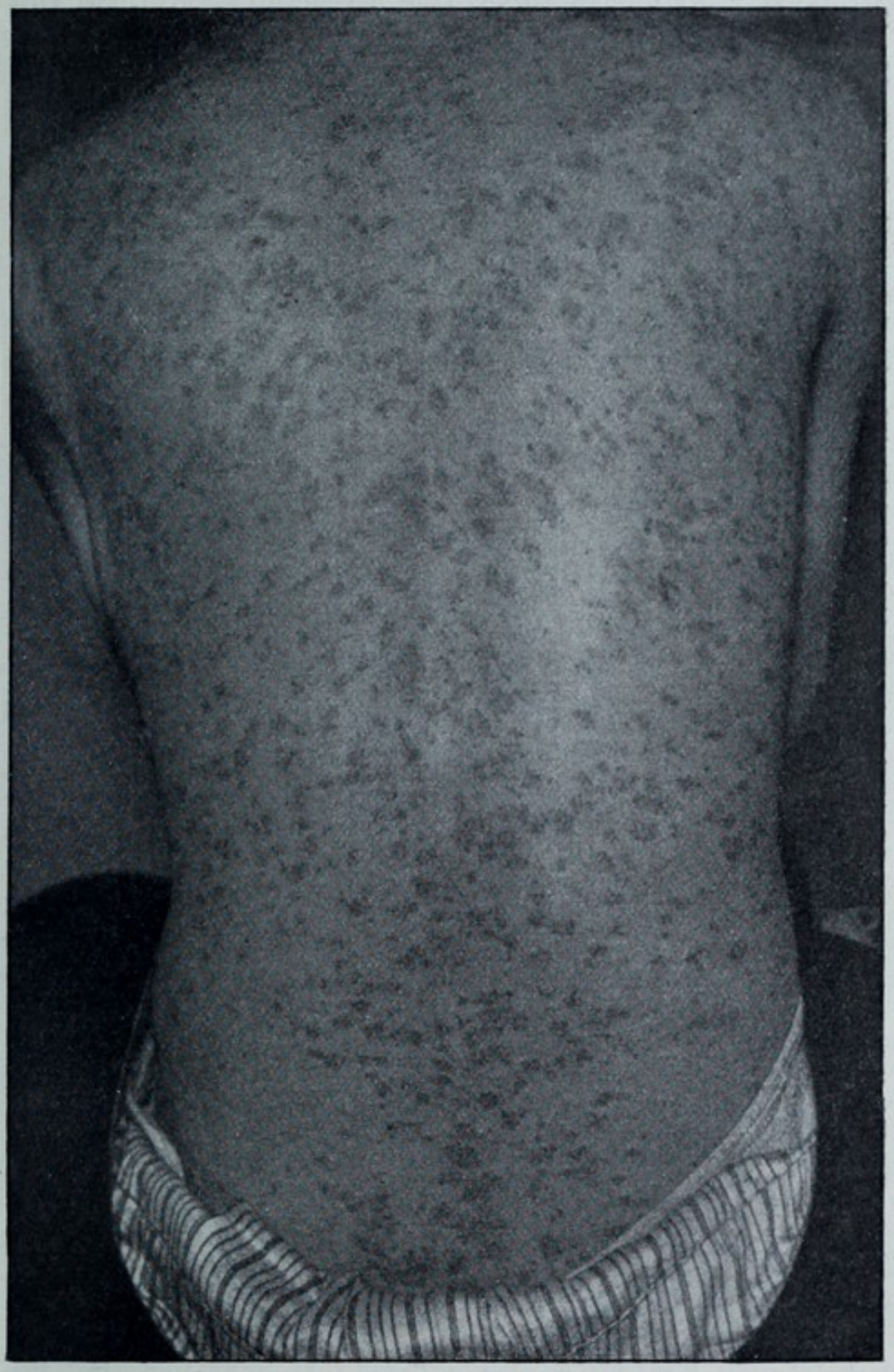

FIG. 32.—Small follicular syphilide. Groups of papules corresponding to macules of roseola.

which seems to show this. It is a roseola syphilitica, and shows very well the regularly spaced and almost uniformly sized macules which might well correspond to the meshes of the network—to the bases of the vacular cones of Renaut.

This same idea would also explain the white areas on a dark background which are characteristic of *leucoderma syphiliticum*, for it is well known that the leucodermic areas are left behind by the fading of the macules of a syphilitic roseola when it occurs on the pigmented skin of the neck, thus leaving a pigmented network with pale meshes (fig. 31).

The peculiar grouping of small follicular papules in the small follicular syphilide or *lichen syphiliticus* is to be accounted for in the same way. In a syphilitic roseola there can be seen generally some macules, the follicles included in which are red and prominent, and from these one can often trace the development of the grouped papules of a follicular syphilide (fig. 32). The photograph shows the grouping of follicular papules into areas which would correspond with the macules of a previous roseola.

I have said that it has been suggested that roseola syphilitica corresponds to the mesh of the vascular system, and this I have long believed to be the case, but from further observation I am inclined to think that it really begins in the network or area of reduced circulation. That is to say that the spirochætæ settle where there is stasis rather than in the area of active circulation (fig. 33). This agrees with the fact that the mottling of a roseola syphilitica becomes more marked on exposure to cold, or on tying a ligature round a limb. It does not alter the

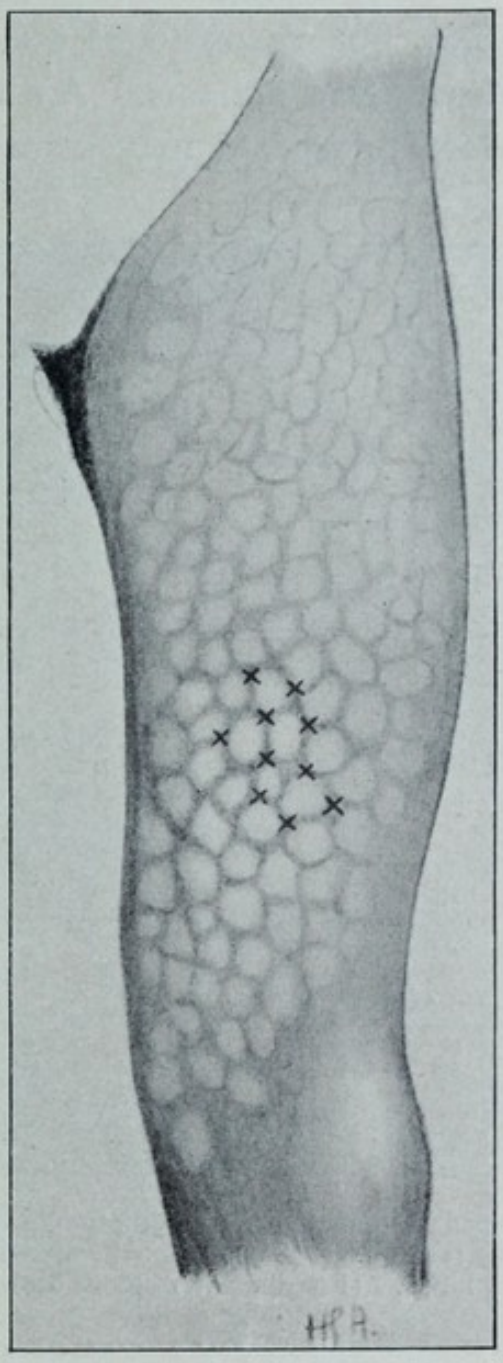

FIG. 33.—Livedo annularis. Although it has been suggested that the macules of a syphilitic roseola correspond to the pale meshes of this network, further observation seems to point to their origin in the "venous" network, as indicated by the crosses in the diagram.

explanation of the grouping of the follicular papules by their origin on an erythematous base.

We see the same grouping of follicular papules in *lichen scrofulosorum*, but the patches are usually large, covering several vascular systems. An imitation of a patch of lichen scrofulosorum may sometimes be pro-

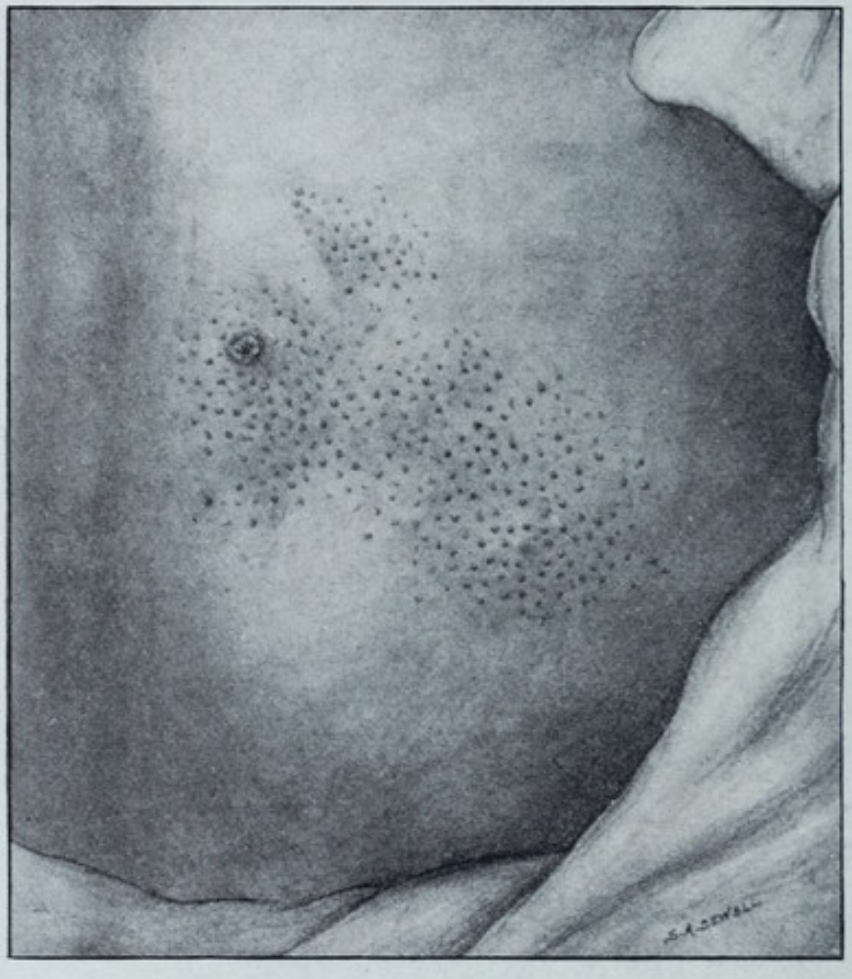

FIG. 34.—A grouped follicular-papular eruption corresponding to an erythematous area, the result of a cuti-reaction to an injection of old tuberculin in a patient with lupus. (From a water-colour drawing.)

duced by the injection of old tuberculin into the skin in a tuberculous patient. There results a cuti-reaction in the form of a large erythematous patch, over which there may develop follicular papules, as in lichen scrofulosorum or in lichen syphiliticus (fig. 34).

It is probable, too, that the distribution and pattern of *macular atrophy* may be dependent upon the same circumstances, for the macules are known to be preceded by erythematous patches. In *measles* and in *copaiba rash*

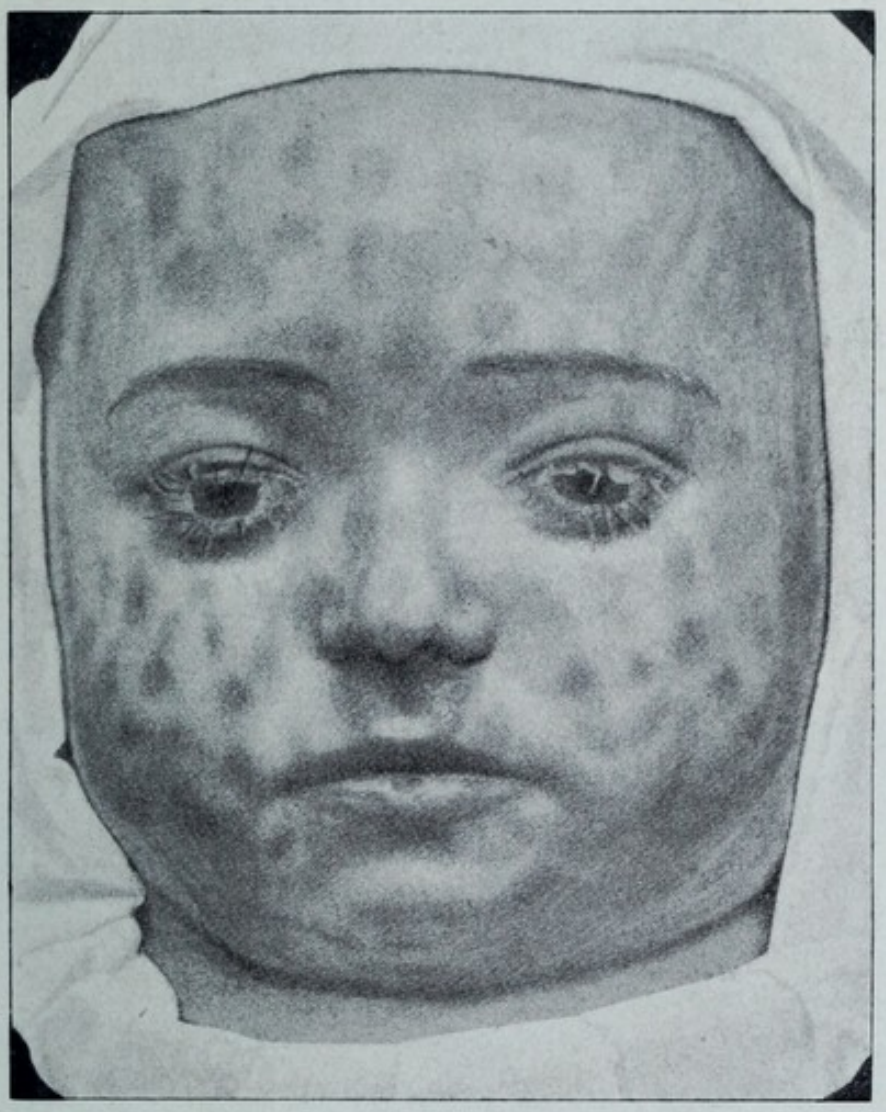

FIG. 35.—Eruption of measles, showing regular spacing of the macules. (Copied by permission from the Jacobi-Pringle Atlas.)

the same spacing of circumscribed macules may be seen as in syphilitic roseola, and good examples are to be found in the Jacobi-Pringle Atlas (figs. 35 and 36).

FIG. 36.—Copaiba rash. The regular spacing of the macules corresponding to the meshes of network (or (?) to the angles of the network of reduced circulation). A tendency to formation of grouped follicular papules is also seen. (Jacobi-Pringle Atlas.)

The Influence of the Nervous System upon the Distribution of Skin Eruptions.

Herpes zoster is, of course, the most striking example of the relationship of a skin eruption to nerve lesions. It is known that the distribution of the eruption of herpes

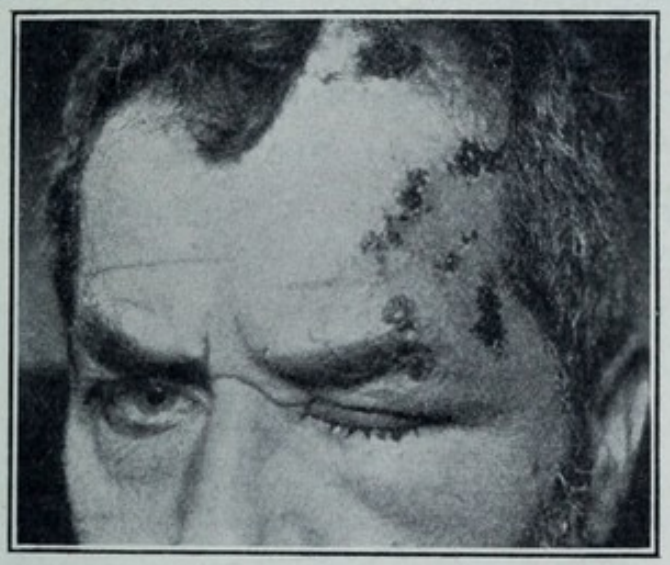

Fig. 37.—Herpes in the region of the first division of the fifth cranial nerve —herpes frontalis.

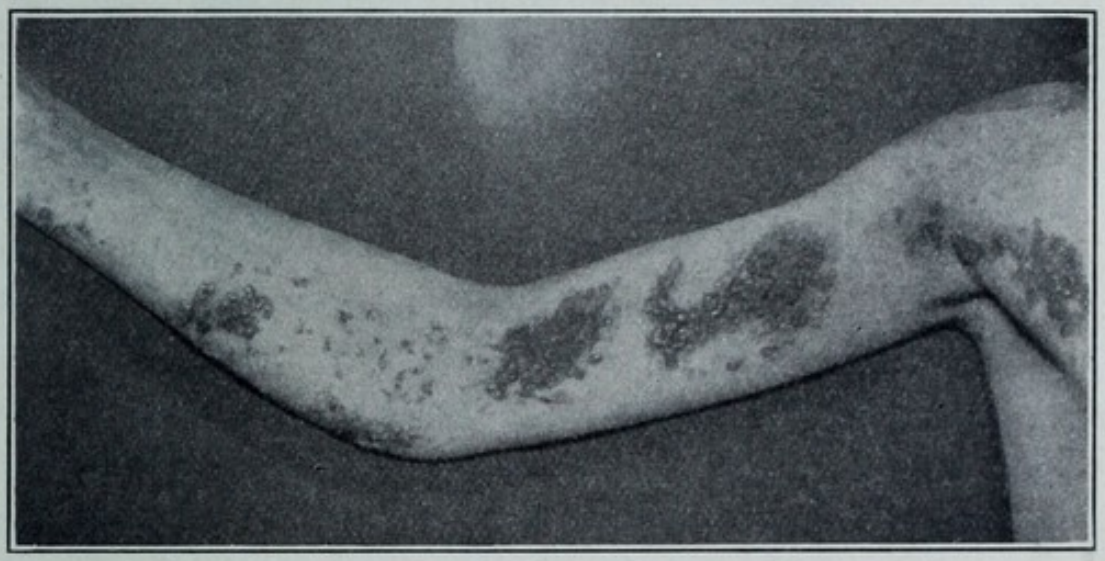

Fig. 38.—Herpes of the arm in the area supplied by the brachial plexus.

zoster corresponds to an inflammatory hæmorrhage into one or more posterior root ganglia (figs. 37 and 38), but

the manner in which the eruption is brought about and whether it actually depends on nerve influences is still unexplained.

Other examples are alopecia following section of a nerve, of which a few instances have been recorded, and hyperidrosis limited to an area corresponding to that of a particular nerve distribution, generally a division of the fifth cranial nerve. Sometimes (as in the example shown —fig. 39) scleroderma occupies the area of the supra-orbital nerve, suggesting a nervous origin. But in the

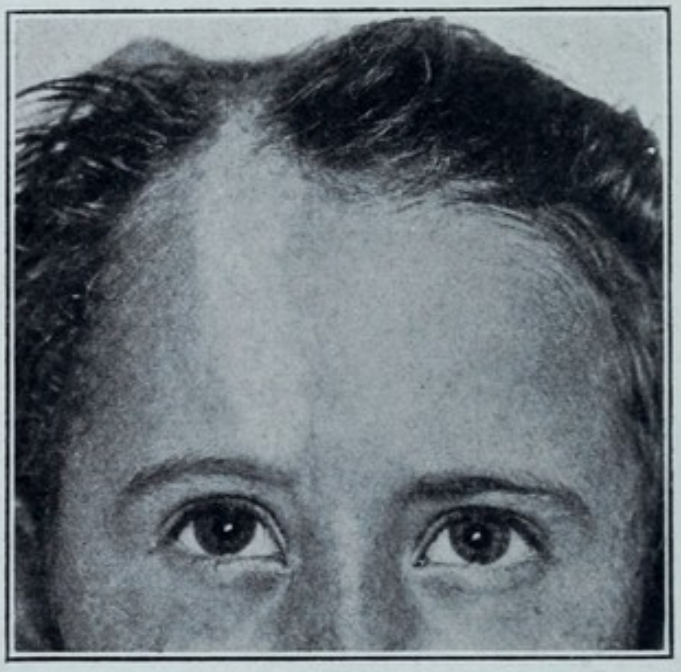

FIG. 39.—Scleroderma in region of supra-orbital nerve.

large majority of cases of scleroderma no such distribution can be made out. An interesting suggestion has recently been made by Staff-Surgeon J. P. H. Greenhalgh, R.N., that the area of distribution of the rash of typhoid fever corresponds to Head's zone for intestinal disorders, and that the eruption takes this distribution because the typhoid bacilli are apt to stagnate in the vessels here

on account of retardation of circulation by reflex vaso-dilatation.

In this connection mention must be made of the well-known views of Mr. Lenthal Cheatle. Cheatle's observations are based upon the knowledge of Head's zones. Head's zones being definite areas of cutaneous tenderness, which are associated with disease of particular viscera, and which correspond to the areas of distribution of the peripheral nerves in the skin. Mr. Cheatle, from the observation of the seat of origin of a large number of *rodent ulcers* and of *epitheliomata*, came to the conclusion that the point of origin or incidence of these diseases corresponds to the maximum points of Head's areas, or, in other words, to the points at which the peripheral nerves become cutaneous ; and he also believes that the spread of these diseases bears a causal relationship to Head's zones—that is, to the areas of distribution and influence to the cutaneous nerves. If I understand him rightly he supposes that peripheral irritation over a long period produces profound changes in the corresponding nerve centres, and that the area of skin supplied by these centres is then influenced by the altered nerve impulses, and since the maximum point would receive and convey most impulses it is natural that the incidence of the disease should be at this maximum point.

More recently Mr. Cheatle has extended his idea to embrace leucoderma and scleroderma, and latterly also some inflammatory eruptions, such as lupus and syphilis, believing that he sees in the distribution of these eruptions evidence of origin at the maximum points of Head and of limitation of spread to Head's zones, and suggesting that neurotrophic and neurovascular influences determine this point of incidence and this area of spread.

Mr. Cheatie's numerous photographs and drawings seem to lend some support to this ingenious idea, but they are not to my mind a convincing argument, firstly because the diseased areas depicted do not always correspond closely to the areas of nerve distribution, and, secondly, because if one takes a sufficiently large number of examples of any eruption it is possible to make some of them fit more or less closely into these nerve distribution areas, while, on the other hand, it is still more easy to find numerous examples in which the eruptions do not in any way correspond to such areas. Indeed, I think that with the exception of the two or three well-known examples that I have mentioned, there is little evidence that the distribution of eruptions is influenced by the nerve supply.

Influence of the Vaso-motor Apparatus upon the Distribution of Eruptions.

We are ignorant of the exact manner of distribution of the vaso-motor nerves, but we know that certain regions are more liable to vaso-motor disturbance than others. The flush patches of the cheeks and the reddening of the ears seen in blushing; the flushing of the nose in dyspepsia; the susceptibility of the nose, ears, and extremities to changes of temperature, seem to mark out these parts as regions in which the vaso-motor function is easily disturbed.

There is no evidence that vaso-motor disturbances can alone give rise to inflammation, but it is known that they may modify the intensity and the course of this process; and in this way it is easy to comprehend how vaso-motor disturbances may act as a determining cause for the particular distribution of some eruptions. In *acne*

rosacea we have an affection which is characterized by flushings of the central parts of the face which appear to be of a vaso-motor reflex nature, and it is possible that the inflammatory conditions which often develop are the result of secondary infection by the micro-organisms of the skin in tissues of lowered vitality.

Lupus erythematosus and *erythema multiforme* are eruptions which affect particularly those parts where vaso-

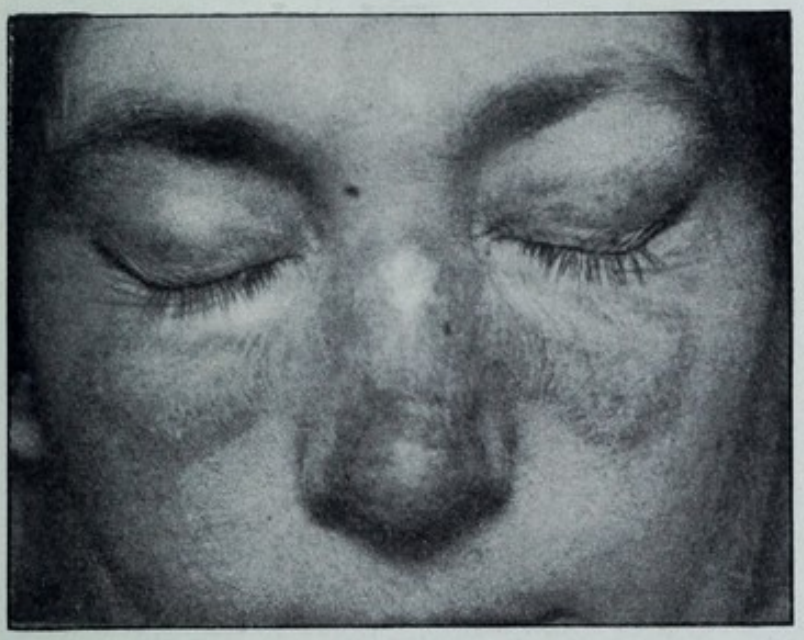

FIG. 40.—Lupus erythematosus : characteristic distribution upon the nose and the " flush patch " areas of the cheeks.

motor disturbance most readily occurs, and it seems certain that the vaso-motor apparatus must have some influence in determining this distribution. The characteristic distribution of lupus erythematosus upon the flush patches of the cheeks and the nose is well known (fig. 40). This distribution on the flush patch areas is sometimes likened to the triangular patches on the face of a clown, and the clown's patches are said to take

their origin from an attempt to exaggerate the flush of health which the actress tries to reproduce (fig. 41).

The common distribution of *erythema multiforme* is seen in the next photograph (fig. 42), in which there are

FIG. 41.—The pantomime clown. The "flush patches" of the cheeks are painted in imitation of the actress. The circus clown paints the nose and not the cheeks, perhaps in imitation of the flushed nose of alcohol.

erythematous patches on the sides of the face and on the forearms. In many eruptions supposed to be of toxic origin, notably in lupus erythematosus, in erythema multiforme, and in the toxi-tuberculides, there is what is

known as a "chilblain circulation"—that is, a coldness and blueness of the hands and feet. It is not known whether this is due to a vaso-motor nerve disturbance or to direct action of a toxin upon the vessel walls, but it

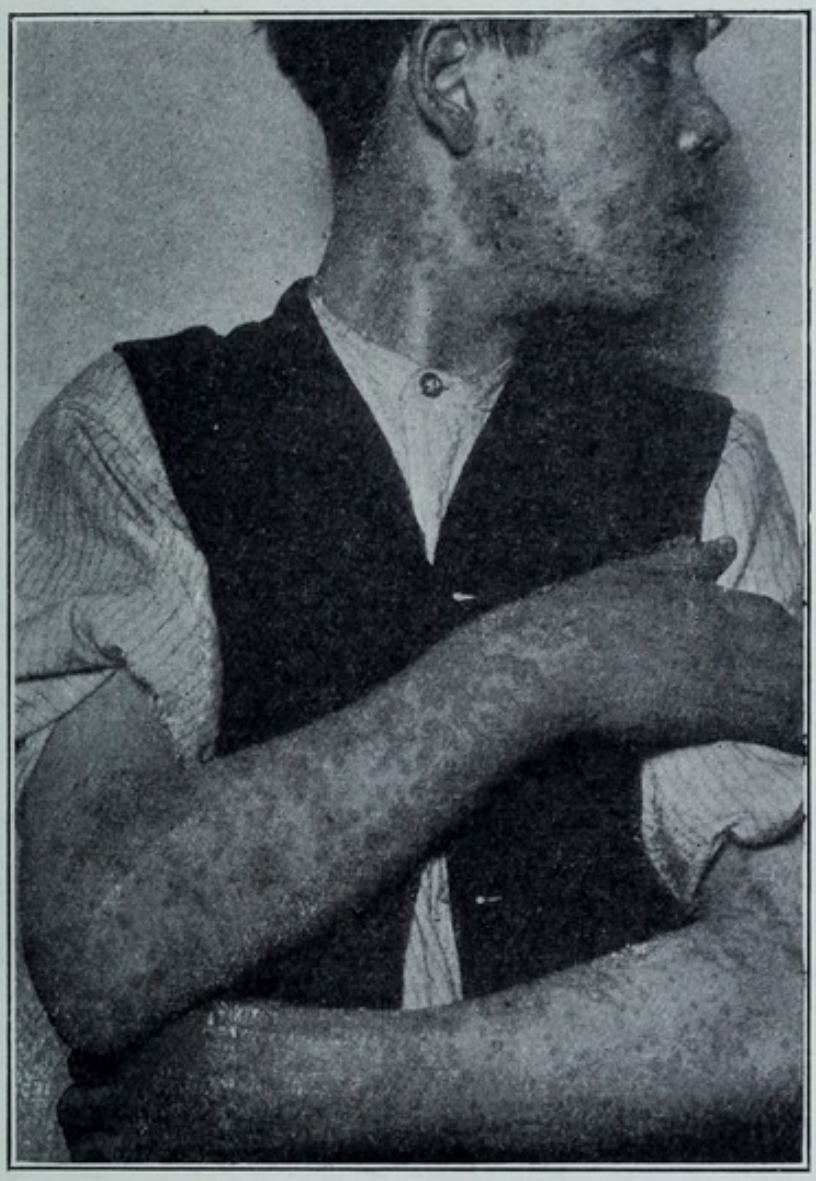

FIG. 42.—Erythema multiforme, showing typical distribution on face and forearms and backs of hands.

seems likely that this vaso-dilatation of chilblain circulation may help to determine the position of these eruptions on the face and extremities.

Although the modern tendency is to discount the vaso-motor factor in the production of erythemas and urticarias, there are a few affections which it seems almost impossible to regard otherwise than as being of vaso-motor nerve origin. Such are *Raynaud's disease* and some allied minor affections. A feature of Raynaud's disease, and of similar but less severe conditions which occur sometimes on the fingers in middle-aged women, is that vaso-dilatation is preceded by contraction, so that the parts are first white and then dusky red. But these phenomena, which are certainly vaso-motor disturbances, cannot, strictly speaking, be called eruptions comparable with the inflammatory erythemas and urticarias which I discussed in my last lecture.

The Distribution of some Congenital Skin Affections.

There is just one other question concerning the distribution of skin eruptions of which I wish to say something—namely, that which concerns the unilateral, linear or systematized nævi. These nævi are commonly due to an irregular overgrowth of the horny epidermis which produces a warty prominence generally of a linear form—*verrucose linear nævus*. But these nævi may also be made up of one of the other elements of the skin—sebaceous glands, hair-follicles, sweat-glands, pigment, or blood-vessels—and they may occupy whole territories on one side of the body instead of being merely in streaks or lines. The photograph here shown (fig. 43) is an example of such a nævus made up of pigmented patches scattered over a limited area on one side of the

body. It will be noticed that this case also shows a supernumerary nipple on the right side.

Because these nævi have some appearance of occupying areas of nerve distribution like herpes, a theory has

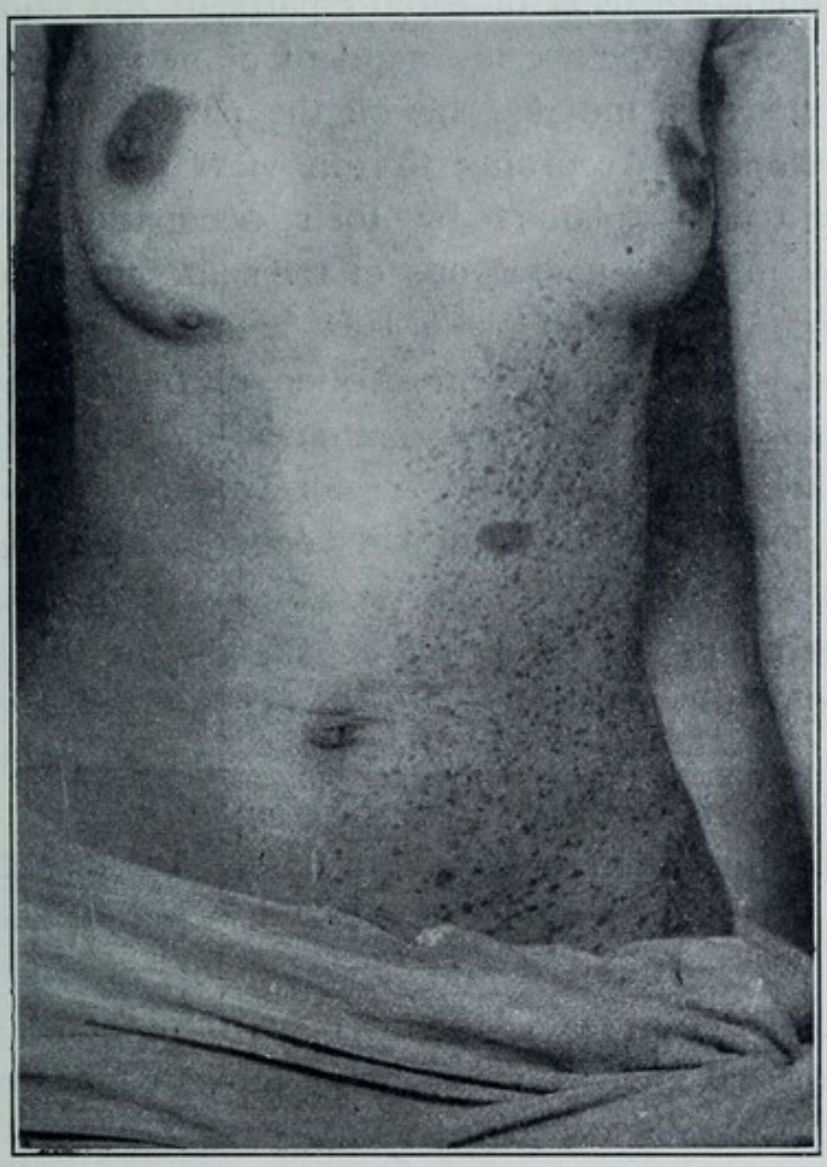

FIG. 43. — Unilateral pigmentary nævus and supernumerary nipple on opposite side.

been propounded that they are due to some injury to the spinal cord during fœtal life owing to mild infections or toxæmias in the mother. But a closer study of the

distribution of these nævi has shown that they seldom, if ever, correspond accurately with areas of nerve distribution.

Another hypothesis has been suggested by Blaschko and by Brinaud—namely, that these nævi result from developmental defects of certain parts of the skin, and that they are altogether independent of nerve influence, in that they are initiated before the nerves themselves are developed. According to this view the shapes of the nævi are explained by their occupation of the primitive metameric divisions of the skin, which do not necessarily correspond with later areas of nerve distribution. They are seen most often on the frontiers of two metameric segments or dermatomes—*i.e.*, upon Voigt's lines; and most frequently of all where two dermatomes, originally widely separated, become joined together during the growth of the embryo, as upon the limbs.

But although this theory might account for the linear forms, it could hardly be said to explain those which occupy large broad areas or sections, and in reality the reason not only of the peculiar distribution of these nævi but also of their nature remains obscure. Perhaps it may be said that the presence of other deformities, such as supernumerary nipples and absence of or excessive number of digits, seems to put them into the class of developmental defects rather than into that of lesions resulting from toxic or inflammatory causes.

This, Mr. President and Gentlemen, concludes my lectures. It has been my endeavour to place before you some of the modern ideas in regard to the significance of skin eruptions. I hope that I have at least succeeded in showing that dermatology presents many problems of interest. It is true that skin affections seem often to bear

little relation to diseases of internal organs; but this is explained by the circumstance that hurtful agencies which give rise to disease often confine their attacks to one organ, and that when the skin is that organ there is generally no disturbance of a vital function, so that general symptoms are not produced. It is, in fact, not so much by its clinical side as by the common bond of pathology that dermatology is united to general medicine.

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