The secondary organisms were *Streptococcus longus*, *Micrococcus catarrhalis*, *M. flavus*.

The antigen was made in the following strengths 1 (million *Str. longus*) + 1 (million *M. catarrhalis*) + 1 (million *M. flavus*) 2+2+2 and so on, doubling the dose on each successive occasion, unless a reaction occurred, i.e., rise in temperature, malaise, &c., when the following dose was reduced, leaving two clear days interval after all signs of reaction had settled down.

The tuberculin dose was given alternately with that of the antigen, taking the same precaution regarding reaction.

No. 2 plate was taken after six months treatment. It shows the cavity very much reduced in size with much clearer perenchyma.

No. 3 plate was taken finally showing the cavity completely healed. At this time the sputum was completely gone. The patient had put on about 2 stone in weight and was carrying out her usual occupation.

The last report in February, 1933, showed patient maintaining improvement without any sign, clinically, of the condition whatever.

X-ray photographs by Dr. Peter Kerley.

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ALLERGIC SKIN AFFECTIONS RELATED TO FUNGUS INFECTION.

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SINCE Jadassohn demonstrated the first case of a lichenoid trichophytide, over twenty years ago, many other forms have been described and very considerable advances have been made in the study of the pathogenesis of allergic skin affections associated with fungus infection.

Until then it was thought that only the more deeply seated chronic infections, such as tuberculosis, were capable of producing allergic skin diseases, but now it is generally recognized that not only the deep-seated trichophyton infections but also the more superficial ones due to the epidermophyton and monilia group of organisms may produce the so-called "ide" eruptions.

The term "trichophytide" that Jadassohn introduced to describe his case of a papulo-lichenoid eruption that followed a deep-seated trichophyton infection was certainly well chosen, but it is rather unfortunate that it has remained to cover, according to the usage of some authors, conditions which can be attributed to primary sensitisation to the microsporon, favus and epidermophyton fungus too. As the late Prof. Bruno Bloch suggested, it would be more accurate to describe all these affections as mycides, and it is my intention to adopt this word in this paper as a general term for the trichophytide, microsporide, favide or epidermophytide.

In considering the evolution of the mycide we can subdivide the process into four stages. To begin with we have the primary lesion, then the development of a specific sensitivity of the integument generally, to be followed by the transference of the antigen to the allergic skin, resulting finally into the various forms of mycides.

Let us deal first with the primary lesion.

In general one can say that the commonest cause of the primary infection is a virulent fungus, capable of giving rise to a hypertrophic granulomatous lesion; and it is therefore with the kerion-producing animal ectothrix that one encounters the greater number of mycides. It is for this reason that, on the Continent, a high percentage of the patients suffering from mycides are to be found among land-workers and their families where infection with animal ringworm, particularly with the *Trichophyton ectothrix gypseum* of cattle, is sometimes rife. It is no wonder, too, that when statistics are taken of the ages at which mycides are most prevalent, we find that about 90 per cent. of cases occur in young children between the ages of 3 and 14. Of these approximately 75 per cent. are boys, which can be attributed to the fact that kerion of the scalp is predominantly a condition affecting young boys.

The human endothrix and ecto-endothrix trichophyton are known to produce mycides as also are the human microspora and epidermophyta, though usually the eruptions are neither as severe nor as widespread as those of animal origin. It should be mentioned however that, when a fungus of human type is held responsible for the primary affection, it is usually found that there is a greater degree of tissue reaction than normal, probably due to a greater virulence of the strain, or some factor producing a lowered degree of skin resistance. In addition I must add that stimulation of the primary lesion by local irritating fungicides, or through X-ray therapy, not infrequently provoke the eruption of a mycide from what might otherwise have been a non-virulent fungus infection.

I remember seeing such a case with Dr. Roxburgh about three years ago in a young child with simple, non-inflammatory tinea of the scalp due to a human microsporon. After X-ray treatment he developed a slightly raised kerion, and twelve days later a typical, wide-spread, grouped lichenoid mycide appeared on the trunk. Such cases are probably not uncommon, but are overlooked, as the condition is usually symptomless, not very obvious and frequently of short duration.

It is now known that, at least in severe cases of ectothrix ringworm, the infection may pass over from a localized to a generalized one, giving rise to a condition known as trichophytosis, during which time the patient may be severely ill. Bloch recognized trichophytosis in experimental animals long before trichophytides were described, for he noticed that when guinea-pigs were injected with an emulsion of ringworm cultures, they became ill, developed splenic enlargement, lost weight and occasionally died of cachexia.

Trichophytosis in man usually begins with symptoms of headache, vomiting, loss of appetite, slight rise of temperature and sometimes with rigors.

The regional lymph glands are always enlarged and may be very painful to the touch. From time to time observers have reported enlargement of the spleen to percussion. Blood examinations at this stage shows a definite leucocytosis with relative polymorphonucleocytosis which reaches its highest point when the symptoms are most pronounced. Sutter found experimentally in man that after a first injection of achorion

quinckeanum, an early lymphocytosis was followed by polymorphonucleocytosis and that a re-inoculation could result in a leucocytosis of as much as 15,000 c.mm. Eosinophilia, though it may occasionally reach high percentages of 10—25 per cent, is rare. Arthritis and bronchitis have been recorded in very few cases.

During this phase, the skin is developing an allergic state, the degree of allergy as ascertained by the trichophytin test becoming stronger until the mycide appears.

We now pass to the third stage when the antigen reaches the now allergic skin to produce the mycide. Three theories have been put forward to explain the mode of transport of the antigen—the ectogenic, the lymphatic and the vascular.

Let us discuss the ectogenic theory first. Here one assumes that the skin condition is produced by the external contact of the fungus. This view might hold for those cases where the mycide is localized to the near vicinity of the primary lesion, but it is difficult to believe that it could account for such widespread eruptions as the disseminated scarlatiniform or lichenoid types to be described later. Ballagi, in support of this view, put forward the suggestion that the fungus lies dormant in the hair follicles until the degree of allergy reached is sufficient for the production of the mycide. This, of course, is very unlikely, for if it were so one would expect to find a correspondingly wide distribution of fungal elements during the interval between the primary and secondary eruptions; but this is not the case. Again, it would be difficult to account for the enanthemata that are sometimes encountered in severe cases.

The method of lymphatic spread, too, does not fit in with the clinical picture, as it would be difficult by this means to account for the production of a bilaterally symmetrical eruption.

Lastly, we come to the vascular theory which, in all probability, is the correct one, as it appears to have most support from clinical findings, pathological investigations and animal experiments.

In the first place, as would be expected from a blood-borne infection, the rash is widespread and may affect the mucous membranes, appears rapidly and is almost always symmetrical. The blood shows definite leucocytic changes and splenic enlargement has been noted. All these facts point to spread of the antigen via the bloodstream. Granted this, we have now to try to determine whether the antigen so disseminated takes the form of actual fungus elements or of their soluble toxins.

Let us first see what experimental pathology teaches us.

At one time it was thought that fungus diseases of the skin were always brought about by external infection, but Bloch showed that, at least in the guinea-pig, this condition could also be arrived at after intracardiac or intravenous injections of fungus cultures.

Saeves and Kogoj, carrying these investigations further, found that a second inoculation resulted in fewer and less pronounced fungus infected lesions which appeared earlier and disappeared more rapidly. This was the first piece of evidence which seemed to point to the development of an allergic state resulting from the primary inoculation.

In order to keep the animal experiments more in line with the clinical conditions in man, Jadassohn, junr., and Sulzberger injected guinea-pigs *subcutaneously* with emulsions of achorion quinckeanum. They found that spores were already present in the bloodstream within one to two hours, and that they then immigrated to the skin to produce lesions there. The presence of the spores in the blood could well be responsible for the leucocytosis.

Corroborative evidence in man of the dissemination of fungal elements via the lymphatic and blood channels is found in the investigations of Sutter, Jessner and others.

The former, in a case of kerion due to trichophyton granulosum, with an acute scarlatiniform mycide which later developed a lichenoid character, recovered the fungus from a draining lymph gland and demonstrated its presence in histological preparations.

He also made cultures from the mycide itself with the following interesting result :

On the first day he obtained rich cultures of the fungus—the second day produced fewer colonies, and similar attempts made at later periods produced no growths whatsoever. These findings suggest that the spores are transported to the skin where, probably owing to the enhanced power of the skin to combat the fungus, they are rapidly killed. This phenomenon corresponds closely with the findings of an animal experiment described earlier in this paper, where a second intravenous injection of spores always resulted in a less pronounced trichophyton infection of the skin.

Jessner made blood-cultures (by diluting the blood tenfold in Sabouraud's fluid medium) from a severe case of a lichenoid mycide a day after its appearance and succeeded in growing one colony of the causative fungus. In a second case of a kerion Celsi and a lichenoid mycide, similar blood-cultures on two successive days were sterile, but twenty-four hours after X-ray treatment, and six hours after inoculation with trichophytin, the author succeeded in cultivating a colony of *T. gypseum*. In this case the factor that determined the entrance of the spores into the blood-stream was either the activation of the primary lesion as a result of X-radiation, or of the trichophytin injection. Ambrosoli reports a case where cultures were positive a few days after the appearance of the mycide, but this must be the exception, as in most cases the fungus is found to have disappeared from the blood-stream by the second day.

Arzt and Fuhs record a very interesting case of a young boy with typical non-inflammatory tinea tonsurans due to *Microsporon audouini* with a negative trichophytin test who was treated with X-rays. Fourteen days later, with the beginning of the defluvium, the scalp lesions became inflamed and developed pustules and crusts. A fortnight later the inflammation increased and the regional lymph glands enlarged, but at this time there was no evidence of any mycide. The next day the authors made blood-cultures from which they were able to obtain growths of *M. audouini*. Three days later a typical lichenoid eruption appeared and at this stage the intradermal trichophytin test became strongly positive.

The interesting feature of this case lies in the fact that the causative fungus was grown from the blood three days before the appearance of the mycide.

Another interesting case is one described by Peck, as in his patient a less virulent organism, the epidermophyton, was the primary cause. Here he was dealing with a vesiculo-pustular mycotic affection of the feet of a young girl who later developed a dysidrosiform eruption of both hands and wrists ; no fungus could be found in microscopical examination of the lesions on the hands and cultural examination too proved negative. The trichophytin reaction was, however, strongly positive, and a few hours after this test blood-cultures were made. This resulted in the growth of the epidermophyton of Kaufmann-Wolf which corresponded with that found on the feet.

All these findings therefore suggest that, at an early stage in the development of the

granulomatous reaction to the fungus, fungal elements enter the blood-stream and sensitize the general integument. At some later period, at a time when the primary reaction reaches its climax, or immediately after, there is a further shower of spores into the blood-stream. On reaching the allergic skin, these spores meet with considerable opposition which results in their death within the course of a day or two. The mycide, which then makes its appearance, is the manifestation of the exaggerated response of the skin.

Further, this view appears to have confirmation from an observation made by Sulzberger. He injected ach. quinckeanum subcutaneously into a series of guinea-pigs, and examined numerous specimens of blood culturally at various intervals after inoculation. It was found that the positive cultures occurred at two phases—an early one within a period of one to forty-eight hours after injection—and a later one ten to thirteen days afterwards, with an intermediate negative phase. This second shower of spores, he notes, occurs when the reaction of the primary lesion is at its highest and corresponds with a state of maximum allergy of the skin.

These results suggest that it is the fungus itself and not merely the toxins which pass into the blood-stream to act as the antigen. But it may be asked why, if such large numbers of spores enter the blood, is it so rare that one succeeds in obtaining cultures from this source. Jessner and Hoffman found that antibodies are developed in the serum, which hinders the growth and reduces the virulence of the fungus, and it was for this reason that they recommend a tenfold dilution of the blood in fluid medium, for in so doing one can minimize the effect of the anti-growth element of the serum.

We now come to the toxin theory, which suggests that a soluble product of the fungus, and not its formed elements, is transported to the skin to produce the mycide. Here we cannot approach the problem under investigation as easily as we could the previous case as we have no means of isolating any toxin which may be present in the blood-stream. Basch, in attempting to illustrate the presence of trichophytin in the blood from a suitable case, injected some of the serum, so obtained, intradermally, but this was followed with a negative reaction.

Nevertheless, there are a few plausible arguments that could be used in favour of the toxin theory. We know that an intradermal injection of trichophytin in a sensitized patient frequently gives rise to a lichenoid reaction identical to the naked eye and also histologically to the spontaneously produced mycide.

Again, it has occasionally been observed that the reaction following an intradermal trichophytin test may give rise to a lesion corresponding in type to that already existing in the mycide—for example, an erythematous-squamous reaction in a scarlatiniform mycide and a lichenoid in a lichenoid eruption.

Bloch conducted two rather daring, but in this respect valuable, experiments on two patients suffering from deep-seated trichophytin infection, one with a lichenoid, the other with a maculo-pustular mycide. He treated them until all evidence of primary infection had disappeared and there was no trace of the allergic eruption. He then injected them intravenously with large doses of trichophytin. Now such doses give rise to no symptoms whatsoever in normal individuals, but in these cases they were followed by fever and symptoms of trichophytosis. Eventually the patients developed lichenoid and maculo-pustular eruptions respectively, but not necessarily with the original distribution. Here we have, therefore, an example where a mycide appears to be caused by the toxin in the absence of any fungal elements.

Taking all these facts into consideration, one feels inclined to accept the view that both fungus and toxin are carried into the blood-stream, for it would be difficult otherwise to imagine that fungal elements could act on the epidermal or dermal tissue without the medium of some serum soluble substance.

Having dealt with the primary lesion and the probable method of transport of the antigen to the sensitized skin, we can now pass on to the description of the various forms of allergic mycoid eruptions.

The commonest type that is encountered was that first described by Jadassohn and Guth, the lichen trichophyticus, but since then the microsporon favus and epidermophyton have been shown to be capable of producing lichenoid mycoides too.

The clinical appearances are those of a symmetrical, widespread, pink or red eruption, the individual patches consisting of groups of minute conical follicular papules. Occasionally these may be flattened and shiny, being not unlike true small lichen planus papules.

The rash usually appears very suddenly, but may increase in intensity over a period of a few days. It is localized chiefly to the trunk, with a relatively greater density around the umbilicus, in the presternal and interscapular regions, and also on the buttocks. The eruption may spread to the neck, face and limbs, but the palms and soles appear to escape. It is frequently observed that the region surrounding the primary affection shows a more pronounced development of the rash. The papules may undergo changes resulting in the formation of scaly caps, vesicles and even pustules. Subjective symptoms are usually absent but in a small percentage of cases irritation is severe. In cases where much absorption of toxin obtains, fever, malaise, headache and the other signs of trichophytosis previously mentioned may be present.

The rash is usually short-lived and disappears within about five days, but may in some severe cases persist for several weeks. During this time the papules diminish in size, become scaly and finally disappear without leaving any trace. Rarely there is a residual pigmentation or even leucoderma.

The lichenoid variety may sometimes pass over into a lichen mycoticus spinulosus, with long, horny filamentous processes 2-3 mm. in length. A case of Martinotti's was so extensive and well-developed that it resembled rather closely the picture of pityriasis rubra pilaris.

Variations in the grouping of the individual lesions have also been noted and corymbiform and annular varieties have been described. Varieties such as these are probably dependent on the particular predisposition of the patient, and it is interesting to read, in this respect, of a case of lichenoid trichophytide with an annular arrangement reported by Goehl, where the trichophytin test injection resulted in a similar type of reaction.

A typical lichenoid eruption may take on various other forms and become eczematoid or psoriasiform.

Lichenoid mycoides may also appear after an injection of trichophytin. I have had such a case recently where a child with simple, human microsporon infection of the scalp developed a typical lichenoid eruption on the abdomen after injections of the toxin.

Another interesting, and not uncommon, variety is the dysidrosiform eruption which usually appears on both hands spontaneously, and is to be distinguished from primary

mycotic infection where one hand is almost always affected before and not to the same degree as the other.

We now come to the scarlatiniform mycide. Here we are frequently confronted with a very widespread erythematous rash, and when this is associated with injection of the fauces, fever and vomiting the diagnosis from scarlet fever, if one overlooks the presence of the primary lesion, might be difficult. Observation of the case during the next twenty-four to forty-eight hours will usually help to confirm the diagnosis, for, during this time, owing to the disposition of the epidermis to produce follicular hyperkeratosis as a result of the presence of the fungus toxin, the rash usually becomes converted into the lichenoid or spinulosus form.

Closely allied to the scarlatiniform mycide is one which resembles post-scarlatinal desquamation of the palms first described by Peck in Bloch's clinic. He quotes a case of a boy who was removed from school by the doctor who diagnosed post-scarlatinal desquamation because the patient had scaling of both hands, particularly at the metacarpophalangeal and phalangeal joints. On examination it was found that he was suffering from a vesiculo-pustular mycotic infection of both feet, from the lesions of which the fungus was found and grown. The trichophytin reaction was strongly positive and resulted in a rise of body temperature and regional adenitis. Like all mycides, the condition cleared up when the feet were completely healed.

A third group of mycides which has long been recognized is the maculo-papular reaction, into which group we may also include the urticarial and erythema multiforme-like varieties.

The maculo-papular mycide is frequently the forerunner of the lichenoid eruption, but may pass over into one resembling measles rather closely. Rarely the macules may become urticarial and develop the clinical appearances of erythema multiforme exsudativum.

An experiment made by Bloch is of some interest at this stage. He inoculated ach. quinckeianum into the forearm of a patient who had no history of past fungus infection, and then treated him until all evidence of the condition had disappeared. He then injected 0.1 c.c. of concentrated trichophytin into the dermis in the neighbourhood of the original lesion. This resulted in a very severe local reaction together with the appearance of a symmetrically distributed typical erythema multiforme exsudativum on the hands and face.

In my own experience I have encountered the typical erythema multiforme mycide only once, in that case the patient had a very severe epidermophyton infection of both feet with what appeared to be a developing dysidrosiform mycide of the hands. I gave him an intradermal injection of trichophytin, which Professor Bloch kindly gave me, but administered it in a far less heroic concentration—1/1,000. Within thirty-six hours the patient noticed that his foot condition became temporarily aggravated, that the dysidrosiform mycide appeared with marked intensity and, in addition, he developed typical erythema multiforme on the upper and lower extremities.

It may be argued that the appearance of the erythema multiforme was merely a coincidence, as the patient might have been subject to such attacks previously. Goldsmith in a very instructive paper published in the *British Journal of Dermatology* two years ago, described a case where such a possibility could quite justifiably be ruled out. His patient developed an acute inflammatory condition around the nail fold of one finger.

The condition became pustular and further pustules developed along the finger. Direct examination of the vesicle caps revealed the presence of mycelium, and cultures which were made eventually showed the characteristics of trichophyton interdigitale of Priestley. Twelve days after the first appearance of the infection a typical erythema multiforme was seen on the hands, elbows and feet. A blood-culture made four days after the outbreak of the rash proved sterile, but this was to be expected as, from experience, we now know that all fungal elements disappear from the blood-stream within forty-eight hours of the appearance of the rash. The trichophytin test with an 0.1 per cent. solution was strongly positive but intradermal tests with *B. coli* and streptococci derived from the urine were completely negative. Goldsmith noted that she had never had a previous attack of erythema multiforme nor had one since.

Lastly, we must deal with quite a different type of mycide, one that corresponds closely to erythema nodosum. Here we have a condition brought about by the inter-action of antigen and sensitized tissue, the latter in this case being the deeper layers of the cutis and sub-cutis, resulting in deep-seated painful, nodular lesions affecting chiefly the lower limbs but occasionally the upper arms too. This type of mycide like the maculo-papular and the scarlatiniform rashes is usually accompanied by the presence of lichenoid eruptions too.

An important link in the chain of evidence of the allergic nature of these mycides is furnished by an important experiment conducted by Peck. An epidermophyton infection of the feet was produced in a patient who had never had any previous fungus disease and who was completely trichophytin negative. Thirteen days after the beginning of the experiments the trichophytin test became positive and twenty-four hours later the patient developed a slight dysidrotic mycide, from which no fungus could be recovered, on both hands. A reinfection of the feet of the same patient with fungus grown from the previous infection was followed, fourteen days later, by a severe and more typical dysidrotic eruption.

Before concluding, I should like to say a few words about the specific sensitization tests. The trichophytin that I employ is made by Bloch by crushing a three to four-month old culture of ach. quinceanun with CO₂ and kieselgur. This is filtered, the filtrate dried, dissolved in water and precipitated with methyl alcohol several times. The end result is a dried compound which is water soluble.

The trichophytin tests can be employed in the following ways: Scarification (v. Pirquet), the intradermal, the subcutaneous and the rubbing in to the skin of a 50 per cent. trichophytin in lanoline (Moro's test), but more reliable results are to be obtained with the intra-dermal tests. To prevent excessive reaction I usually employ a 1 in 500 or 1 in 1,000 aqueous solution of the soluble product. If the skin is specifically allergic a local inflammatory reaction appears between twelve and twenty-four hours, which usually reaches its maximum in about seventy-two hours, after which time it begins to fade, to disappear completely in about five to seven days. In cases of severe primary inflammation the reaction is usually very well marked and extensive, and frequently taking on a papular or lichenoid character after the second or third day. Some authors report that the form of reaction occasionally corresponds to the type of mycide already existing, but this has not been my own experience.

To conclude, we learn therefore that, like the secondary manifestations of syphilis or tuberculosis or the toxic conditions associated with Salvarsan, we may encounter a

similar series of rashes varying from the scarlatiniform, morbilliform, lichenoid and urticarial rashes to eruptions resembling erythema multiforme and erythema nodosum.

That the individual mycides are in no way related to any particular group of fungi is generally recognized, and the literature now contains innumerable examples of almost every type of fungus, whether of animal or human origin, trichophyton or epidermophyton producing any variety of mycide. All that one can say is that the greater the inflammatory disturbance in the primary infection the more pronounced and widespread will be the allergic eruption.

CASE OF PRIMARY CARCINOMA OF THE LUNG.

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History.—Male, aged 41, labourer. Quite well until four months before admission, when he developed a cough and shortness of breath on exertion. The dyspnoea became progressively worse until, a fortnight ago, he had to give up work. Lately he has complained of some pain in his upper right chest, and has observed increasing weakness and loss of weight. There has been a slight spitting up of blood on two or three occasions in the last month. His voice has been getting increasingly husky.

Examination.—Patient shows signs of recent wasting. He breathes with some effort and his voice is weak and husky. The head, neck and upper limbs are markedly cyanosed and congested, with slight oedematous swelling. There is striking evidence of obstruction of the superior vena cava; all the veins of the neck, head, upper limbs and upper trunk are dilated and stand out, forming a very complete pattern of the venous tree.

A hard and fixed mass can be seen and felt in the right supraclavicular region. This has all the characters of carcinomatous lymph-glands. Laryngoscopy shows a right-sided abductor palsy. Both pupils are normal and react to light.

Examination of the chest reveals advanced changes in the upper lobe of the right lung. It is completely dull on percussion, the air entry is very poor and breath-sounds can hardly be heard.

Discussion.—This is clearly a case of carcinoma involving the upper lobe of the right lung. It may have started in the lung tissue, or it may be primarily a carcinoma of the bronchus. Radiography shows a definite opacity corresponding to the area of clinical involvement.

The striking and suggestive clinical features are: (a) The short history; (b) the cough and increasing dyspnoea; (c) the marked venous engorgement pointing to compression of the superior vena cava; (d) the mass of malignant glands in the right supraclavicular region; (e) the laryngeal abductor palsy, pointing to involvement of the right recurrent laryngeal nerve (probably by the glandular metastasis); (f) the very definite physical signs in the chest.