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A CUTANEOUS REACTION IN SYPHILIS.*

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PLATES 50-52.

Active or passive immunity, the state of allergy, and numerous other phenomena, which have been so commonly observed and profitably studied in certain infectious diseases since the successful pure cultivation of their respective causative agents, are rather imperfectly understood in syphilis. Soon after obtaining pure cultures of *Treponema pallidum*, I commenced to study these questions experimentally. While the results of my experiments on the effects of repeated injections of living and killed pallida on experimental syphilis in animals will be presented later, I wish to make a brief report here on one of the phases of study that seems to me to be of interest not only to those who are engaged in experimental work but also to clinicians at large; namely, on a cutaneous reaction in experimental and human syphilis, to the possible existence of which my attention was directed by Professor Welch.

Stimulated by von Pirquet's discovery of a specific cutaneous reaction for tuberculosis, several investigators (Meirowsky, Wolff-Eisner, Tedeschi, Nobl, Ciuffo, Nicolas, Favre and Gauthier, Neisser and Bruck, and Jadassohn) attempted to obtain a specific reaction for syphilis by applying extracts of syphilitic tissues, prepared from syphilitic fetal liver or chancre, to the skin of syphilitic patients. Their results were, on the whole and in spite of some encouraging effects, contradictory. Neisser and Bruck, however, found that a reaction similar to that produced with syphilitic extract can be obtained also with a concentrated extract of normal liver. This peculiarity of the skin of syphilitics is ascribed by Neisser to what he calls the state of "Umstimmung" in the later stages of

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syphilis. Neisser, nevertheless, expresses the hope that the reaction may possibly be improved by employing an extract of the pallidum free from tissue constituents. This had not been accomplished before. Pure cultures of *Treponema pallidum* obviously offer many advantages, since in them we possess not only pallida of different ages, but also their metabolism products, which doubtless are important factors in establishing an allergic state in syphilitic subjects.

THE PREPARATION OF CULTURES FOR THE CUTANEOUS REACTION.

Two strains of the pallidum were used for the present series of experiments. Pure cultures were allowed to grow for periods of six, twelve, twenty-four, and fifty days at 37° C. under anaerobic conditions. One was cultivated in ascitic fluid containing a piece of sterile placenta, and the other in ascitic fluid agar also containing placenta. The lower portion of each solid culture in which a dense growth had occurred was cut out and the tissue removed. The agar columns which contained innumerable spirochætæ were then carefully ground in a sterile mortar. The resulting thick paste was gradually diluted by adding, little by little, the fluid culture which also contained an enormous mass of the pure organisms. The dilution was continued until the emulsion became perfectly liquid. The preparation was next heated to 60° C. for sixty minutes in a water bath, and then 0.5 per cent. carbolic acid was added. When examined under the dark-field microscope, 40 to 100 dead pallida per field could be seen. Cultures made from this suspension remained sterile, and with them no infection could be produced in the testicles of rabbits. The suspension was kept in a refrigerator when not in use. I propose to speak of this preparation under the name of *luetin*.

In order to ascertain whether the reaction produced with this suspension might not be due to the introduction of the carbolized culture medium alone, it was necessary to prepare a similar emulsion with uninoculated media to be used for control purposes.

METHOD OF APPLICATION.

For rabbits, the hair on the lower side of the back is shaved off and one or two injections of the luetin and one injection of the

control suspension are made in different spots. The injections are made intradermically with a very fine needle, the amount injected being in each case 0.05 of a cubic centimeter. For human subjects, the skin of the upper arm was selected as the site for the intradermic injection of the luetin and the control suspension. In the earlier experiments, different spots on the same upper arm were used for both, but later, one arm was used for luetin and the other for the control. The amount injected in each instance was 0.05 of a cubic centimeter, and the skin was always sterilized with alcoholic sublimate solution before the injection.

THE CUTANEOUS REACTION IN RABBITS.

Before the skin test was applied to human subjects, several series of experiments were performed on rabbits. The tests may be divided into five groups according to the treatment previous to the cutaneous tests. The first group comprised four rabbits which received within five months twelve intravenous injections of emulsions prepared from syphilitic orchitis or rabbits rich in pallida, the last injection being given two months before the date of application of the skin reaction. Ten different strains of pallidum were represented in this series. The second group was composed of four rabbits which had been injected with similar emulsions, the difference being that the pallidum had been killed by heating the emulsions to 60° C. for thirty minutes before injection. The third group included twelve rabbits which were showing, four to six weeks after inoculation, syphilitic orchitis experimentally produced with several different pallidum strains. The fourth group consisted of four rabbits in which experimental syphilitic orchitis had been cured about four months previously by the intravenous administration of salvarsan. The fifth group consisted of eight normal male rabbits. The intradermic injections of the luetin and control emulsions were made on the same day to all the rabbits.

RESULTS OF THE TESTS.

In the control group, a very slight erythematous condition appeared at the injection sites twenty-four hours after inoculation, which disappeared within forty-eight hours, the skin resuming its

normal appearance. The first and second groups of treated rabbits gave different reactions. The sites of injection of the control emulsion became normal within forty-eight hours, while the sites of injection of the luetin became distinctly red and indurated after forty-eight hours. The point of redness gradually spread and became raised to the size of a pea. This condition persisted for four to six days, when the reaction commenced to recede. The redness and induration disappeared in most animals within ten days. In one instance, a round sterile pustule developed on the fifth day on the site of each of the two inoculations of the luetin (figure 1). These pustules resembled variolous pustules in general appearance and healed with crust formation. The third group gave only slight reactions, which possibly were somewhat greater than in the control rabbits. But, as a whole, they were not, except in a few instances, distinct enough to be considered positive. The fourth group behaved like the control. No constitutional effects were observed even among the animals with positive cutaneous reactions.

THE CUTANEOUS REACTION IN MAN.

Through the courtesy and collaboration of Dr. Martin Cohen (Harlem Hospital, Randall's Island Asylum, New York Ophthalmic and Aural Institute), Dr. Henderson (State Hospital, Ward's Island, New York), Dr. Lapowski (Good Samaritan Dispensary), Dr. McDonald (King's County Hospital), Dr. Orleman-Robinson (North-Western Clinic, New York Polyclinic), Dr. Pollitzer (German Hospital), Dr. Rosanoff (King's Park State Hospital), Dr. Satenstein (City Hospital, Blackwell's Island, New York), Dr. Schmitter (Captain United States Army, at Fort Slocum), Dr. Schradieck (King's County Hospital), Dr. Charles Schwartz (California), Dr. Smith (Long Island State Hospital), Dr. Strong (Manhattan Eye, Ear, and Throat Hospital), Dr. Swinburn (Good Samaritan Dispensary), Dr. Windfield (King's County Hospital), Dr. Wiseman (King's Park State Hospital), and the Hospital of the Rockefeller Institute for Medical Research, I was enabled to apply the skin reaction to a number of human cases.

The total number of cases studied was 400; of these 177 were of syphilitic nature, 77 of parasyphilitic nature, while 146 represented various controls.

The emulsions were always injected intradermally, that is, in the skin as superficially as possible. When the injection is successfully carried out, the epidermic layer is raised up sharply from the cutis, the pale swelling thus produced going down in from ten to fifteen minutes.

DESCRIPTION OF THE REACTIONS.

Normal or Negative Reactions.—After applying the emulsions, both luetin and control, to about fifty normal individuals, I was able to determine the variations and limitations of the reactions that follow intradermic administration in the normal skin of man. In the majority of normal persons, there appears, after twenty-four hours, a very small erythematous area at and around the point of injection. No pain or itching sensation is experienced. This reaction gradually recedes within forty-eight hours and leaves no induration. In certain individuals, the reaction may reach a stage of small papule formation after twenty-four to forty-eight hours, after which and within seventy-two hours it commences to subside. No induration is left behind, although occasionally slight yellowish pigmentation may result from mild ecchymosis.

Positive Reactions.—According to the manner and intensity with which the skin of syphilitics responds to the introduction of the luetin, one may distinguish the following varieties of effects:

(A) *Papular Form.*—A large, raised, reddish, indurated papule, usually five to ten millimeters in diameter, makes its appearance in twenty-four to forty-eight hours. The papule may be surrounded by a diffuse zone of redness and show marked telangiectasis. The dimensions and the degree of induration slowly increase during the following three or four days, after which the inflammatory processes begin to recede. The color of the papule gradually becomes dark bluish red. The induration disappears within one week, except in certain instances in which a trace of the reaction may persist for a longer period. This latter effect is usually met with among cases of secondary syphilis under regular mercurial treatment in which there are no manifest lesions at the time of making the skin test. Cases of congenital syphilis also show this reaction.

(B) *Pustular Form.*—The beginning and course of this reaction resemble the papular form until about the fourth or fifth day, when

the inflammatory processes commence to progress. The surface of the indurated, round papule becomes mildly edematous, and multiple miliary vesicles occasionally form (figure 2). At the same time, a beginning central softening of the papule can be seen. Within the next twenty-four hours, the papule changes into a vesicle filled at first with a semi-opaque serum that later becomes definitely purulent (figures 3 and 4). Soon after this, the pustule ruptures spontaneously or after slight friction or pressure. The margin of the broken pustule remains indurated, while the defect caused by the escape of the pustular content becomes quickly covered by a crust that falls off within a few days. About this time the induration usually disappears, leaving almost no scar after healing. There is a wide range of variation in the degree of intensity of the reaction described in different cases, as some show rather small pustules, while in others the pustule is much larger. This reaction was found almost constantly in cases of tertiary syphilis, as well as in cases of secondary or hereditary syphilis which had been treated with salvarsan.

(C) *Torpid Form.*—In rare instances, the injection sites fade away to almost invisible points within three or four days, so that they may be passed over as negative reactions. But sometimes these spots suddenly light up again after ten days or even longer and progress to small pustular formation. The course of this pustule is similar to that described for the preceding form.

This form of reaction has been observed in a case of primary syphilis, in one of hereditary syphilis, and in two cases of secondary syphilis, all being under mercurial treatment.

Neither in syphilitics nor in parasyphilitics did a marked constitutional effect follow the intradermic inoculation of the luetin. In most positive cases, a slight rise in temperature took place lasting for one day. In three tertiary cases and in one hereditary case, however, general malaise, loss of appetite, and diarrhea were noted.

THE PECULIARITY OF THE SKIN OF SYPHILITICS.

The skin of certain individuals suffering from tertiary syphilis is noted for its susceptibility to traumatic irritations. This tendency has been much discussed by dermatologists. To account for this

phenomenon, Finger advanced the theory of superinfection, which presupposes that a trauma creates a spot of weakened resistance in the skin and that the syphilitic virus wanders thither from a hidden focus in the interior to set up the lesion. On the other hand, Neisser maintains that it is not the spirochæta that produces a syphilitic lesion after a slight trauma, because he failed to prove the presence of any spirochæta or infectious agent in the lesions; but he believes that it is due to a pathological condition of the skin itself, which he calls "Umstimmung." Among 177 cases of syphilis, I observed nine cases (one secondary, six tertiary, and two hereditary) in which the sites of the control emulsion reacted quite intensely. But these reactions were always less intense than those produced by the luetin in the same persons. Furthermore, in these cases the induration remained much longer at the sites of luetin injection than at the control sites. In view of these results and of the additional fact that the majority of cases giving the positive skin reactions did not react to the control emulsion, I am of the belief that the reactions set up by the intradermic inoculation of luetin are due not to Neisser's so-called state of "Umstimmung," but to a purely allergic condition. It is, of course, possible that both conditions may be coexistent in the same patient, although the occurrence of "Umstimmung" appears, from my experience, to be far less frequent than that of allergy. In carrying out the cutaneous reaction for syphilis (as for any other infectious disease), it is highly important to provide adequate control observations to determine whether the state of "Umstimmung" exists only in syphilis, or whether it may not also occur in other diseases.

THE RESULTS OF THE CUTANEOUS REACTION IN MAN.

In all, 400 cases, comprising 177 syphilitics, 77 parasyphilitics, and 146 controls, have been studied. The results obtained in syphilitics are summarized in table I. The table shows that in cases of primary and secondary syphilis, which have had either insufficient treatment or none at all, no skin reaction occurred, except in a few instances. The reaction in the positive cases was always of the indurated papular variety. In one primary case, in which the skin test was applied before regular mercurial treatment was begun, a

torpid reaction followed the administration of mercury. On the other hand, most of the secondary cases which had been mercurialized before the administration of salvarsan, and which remained

TABLE I.

| | Primary syphilis. | | Secondary syphilis. | | | | Tertiary syphilis. | | | | Cerebro-spinal syphilis. | | Hereditary syphilis. | | Latent syphilis. | | Controls. | | | | |
|--|-------------------|---|---------------------|----|------------------|----|--------------------|----|------------------|---|--------------------------|---|----------------------|---|------------------|---|---------------------|----|-------------------|-----|-----|
| | Symptoms present. | | Symptoms present. | | Symptoms absent. | | Symptoms present. | | Symptoms absent. | | Symptoms present. | | Symptoms present. | | | | Normal individuals. | | Non-luetic cases. | | |
| | + | - | + | - | + | - | + | - | + | - | + | - | + | - | + | - | + | - | + | - | |
| No antisyphilitic treatment..... | | 2 | | | | | | | | | | | | | 24 | 6 | | | 46 | | 100 |
| Slight mercurial treatment..... | 1 | 2 | 2 | 10 | | | | 12 | | | | | | | | | | | | | |
| Regular anti-syphilitic treatment..... | | | | | 4 | 3 | 15 | | 19 | 1 | 5 | 5 | 19 | 1 | | | | | | | |
| Salvarsan treatment..... | | | 1 | | 22 | 8 | | | 11 | 1 | | | 3 | | | | | | | | |
| | 1 | 4 | 3 | 10 | 26 | 11 | 27 | 0 | 30 | 2 | 5 | 5 | 22 | 1 | 24 | 6 | 0 | 46 | 0 | 100 | |
| | 5 | | 50 | | | | 59 | | | | 10 | | 23 | | 30 | | 146 | | | | |

177

+ indicates a positive, and - a negative cutaneous reaction.

without symptoms for some months after the salvarsan injections, gave striking and unmistakable reactions.

Two distinct groups that give a negative or doubtful reaction occur among the salvarsan cases. One consists of cases showing a reappearance of the Wassermann reaction, but no other symptoms, and usually gives doubtful cutaneous reactions. The other, which, however, comprised only two cases treated with salvarsan that remained without any clinical symptoms or Wassermann reaction for many months, gave no cutaneous reaction.

To this group also belong two interesting cases that have been under my observation since September, 1910. One was treated for gumma of the liver by an intramuscular injection of salvarsan by Dr. Kakels at the Lebanon Hospital. The large gumma promptly disappeared, and the patient has remained without symptoms up to the present. The Wassermann reaction in this patient disappeared slowly but completely in about ten weeks. The

blood, tested every two months, has remained negative. The skin test with luetin, made in August, 1911, was negative. The other case is one of malignant syphilis, refractory to mercurial treatment. Three intramuscular injections of salvarsan were given in September and November, 1910, and in January, 1911. The Wassermann reaction disappeared soon after the healing of the extensive and destructive lesions, and still remains negative. A luetin test made in August, 1911, was negative. Both patients are now in excellent health. I have introduced these cases to illustrate the point that the allergic state of the skin in syphilis seems not to persist beyond a certain time after the probable complete eradication of the pallidum from the body. This point has been confirmed experimentally by rabbits treated with salvarsan.

The results in tertiary and hereditary syphilis present a striking contrast to those observed in the earlier stages of the disease. The skin reacts intensely to luetin in these cases. The intensity of the reaction in the tertiary cases is probably increased by the state of "Umstimmung," but the constancy with which it appears suffices to render it a valuable clinical diagnostic aid. It is in this stage that syphilis manifests itself in its most diverse and often most obscure forms. A gumma or other tertiary lesion on the visible parts of the body offers but little diagnostic difficulty; but it is not always easy to ascertain the luetic nature of lesions of the internal organs. In tertiary cases, moreover, the Wassermann reaction is frequently absent, especially after specific treatment. Thus it is important to find that the skin reaction is more constant than the Wassermann reaction in tertiary syphilis. Two causes for a negative Wassermann reaction in the tertiary stage may be distinguished. The first, which may apply also to latent syphilis, consists of the restraining power of the body upon the propagation of the pallidum together with the neutralization of its injurious products through the formation of antibodies. The second cause, which also operates in some primary and secondary cases, arises from the inability of the body to respond to the pallidum stimulus by the formation of the substances on which the Wassermann reaction depends. The results of the luetin reaction in syphilis of the central nervous system are even less constant than is the Wassermann reaction.

Whether a better result can be obtained by improving the luetin can be determined only by future work. The cases of latent syphilis reported here consist chiefly of parents of the hereditary syphilitic cases reported in table I. Most of them became infected many years before and have remained without symptoms. Many of the mothers have, however, suffered miscarriages previous to or after the birth of their syphilitic children.

The controls include 46 normal individuals, chiefly children between the ages of two and eighteen years, and 100 individuals suffering from various diseases of non-syphilitic nature. These include tuberculosis, leprosy, pneumonia, typhoid fever, psoriasis, malaria, alcoholic psychosis, dementia præcox, gonorrhœa, chancre, brain tumor, eczema, epithelioma, carcinoma, etc. In none was a positive luetin reaction obtained.

The results thus far obtained in parasyphilitic cases are unsatisfactory and call for further study with more active preparations of the luetin. Seventy-two cases of general paralysis and five of tabes were studied. Of the seventy-two cases of general paralysis, forty-five reacted positively. In a few instances pustules were formed, but twenty-seven gave no reaction. Of five cases of tabes, three reacted positively. Among thirty-five controls of this series, consisting of fifteen cases of dementia præcox, six of alcoholic psychosis, and fourteen of other non-syphilitic psychoses, four reacted positively, and these were cases of dementia præcox. These patients were adults, and two of them gave positive Wassermann reactions. I incline, therefore, to the opinion that they had suffered either from congenital or acquired syphilis.

CONCLUSIONS.

1. I have proposed the name *luetin* for an emulsion or extract of pure cultures of *Treponema pallidum* which is designed to be employed for obtaining, in suitable cases, a specific cutaneous reaction that may become a valuable diagnostic sign in certain stages or forms of syphilitic infection.

2. The repeated inoculation of either living or killed *pallida* into the testicles of rabbits leads to a condition in which an intradermic injection of luetin is followed by a well marked inflammatory reac-

tion. A corresponding reaction has been obtained neither in rabbits suffering from active syphilitic orchitis, nor in those in which the condition had been cured by the administration of salvarsan four months previously. Normal rabbits, likewise, do not react to the luetin.

3. The luetin produces a similar cutaneous reaction in syphilitic and parasyphilitic patients that is most constant and severe in the tertiary and hereditary affections. In my series of cases, it was present constantly (100 per cent.) in the manifest tertiary affection, in 94 per cent. of latent tertiary affection, and in 96 per cent. of the hereditary affection.

4. During the primary and secondary stages, the reaction is infrequent, and when present it is of mild degree. An exception has been found in cases in which energetic treatment has been or is being carried out and in which clinical signs of syphilis are absent. Such cases may show a severe reaction. Apparently this is true especially of the cases treated with salvarsan.

5. In certain cases of old infection in which no treatment has been taken and in which no symptoms have appeared for many years, and in the course of which miscarriages have not occurred, the cutaneous reaction has failed to appear. But, despite the absence of symptoms, mothers who have young syphilitic children have usually given the reaction.

6. It remains to be determined in how far the cutaneous reaction with luetin can be used to supplement the Wassermann reaction in determining the complete and permanent suppression of a syphilitic affection.

7. It appears probable that the Wassermann reaction is more constant in the primary and secondary, and the cutaneous reaction in the tertiary and latent forms of syphilis. Moreover, it appears that the Wassermann reaction is more directly and immediately affected by antisyphilitic treatment than is the cutaneous reaction.

8. A more active preparation of luetin can certainly be produced by improved methods. This phase of the subject is being considered at the present time and will be reported upon in a later paper.

EXPLANATION OF PLATES.

PLATE 50.

FIG. 1. An actively immunized rabbit (No. 4), inoculated on June 14th, 1911, and painted on the sixth day. Both pustules are produced by the luetin. The control site disappeared.

FIG. 2. Female, aged 16 years. Hereditary syphilis, and interstitial keratitis of six months' standing. Salvarsan injected five months ago without good results. Wassermann reaction positive. Inoculated on June 17th, 1911, and painted on the fifth day. Both sites of the luetin injection show a tendency to pustulation. Marked telangiectasis.

PLATE 51.

FIG. 3. Male, aged 29 years. Chancre seven months ago, followed by secondaries. Six intramuscular injections of salvarsan, the last about three months ago. Developed exudative choroiditis six weeks ago. The right eye shows typical exudative choroiditis; the left eye is free from it. Wassermann reaction negative. Inoculated on June 23, 1911, and painted on the sixth day. Between the two large luetin pustules there is a faint trace of the injection of the control material.

PLATE 52.

FIG. 4. Female, aged 51 years. Became infected twenty years ago, and was treated moderately by Lassar in Berlin. Present symptoms: exostosis and stenosis of lacrimal canal. Wassermann reaction weakly positive. Luetin test on July 11th. The left arm shows two well marked pustules at the sites of the luetin injection, while the right arm shows a faintly visible trace on the control site. Photographed on the sixth day. (Dr. S. Pollitzer kindly took this photograph for me.)

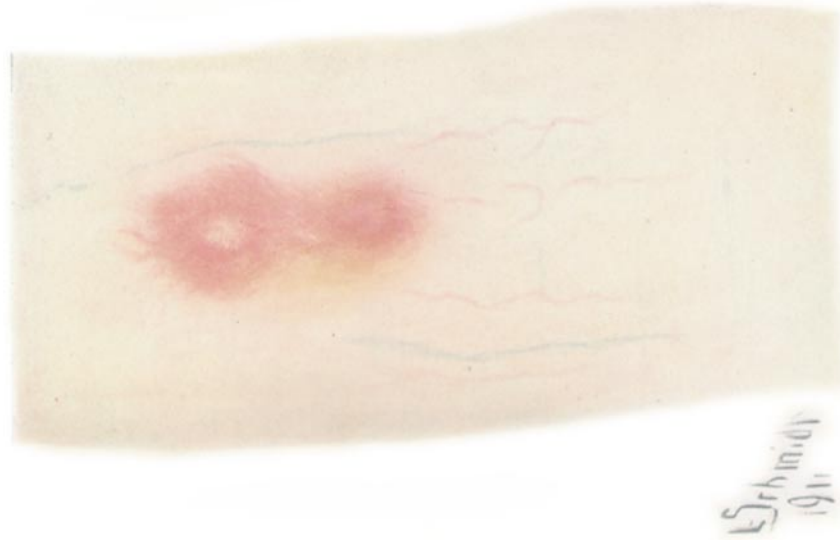


FIG. 2.



FIG. 1.



FIG. 3.



LEFT.



RIGHT.

FIG. 4.