EXPERIMENTAL SYPHILIS IN THE RABBIT.

II. Primary Infection in the Scrotum.
Part 1. Reaction to Infection.

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Plates 72 to 82.

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Primary skin lesions in the rabbit were first reported in 1908. Hoffmann, Löhe, and Mulzer (1), and Ossola (2) reported instances of scrotal infection resulting from testicular inoculation, while Levaditi and Yamanouchi (3) succeeded in producing infection by inoculation of the prepuce. With the introduction of skin inoculations, a decided advantage was gained in the study of experimental syphilis. Not only were the conditions of the inoculation more akin to the mode of infection in the human subject, but the lesions themselves were more analogous to the primary lesions of man. In addition, the infection took place in a region more accessible to observation and the reaction to inoculation could be followed directly, which in itself was a decided advantage.

Of the various skin areas in which inoculation was attempted, the scrotum proved to be best adapted and is now the only area used for purposes of routine inoculation. The methods devised for scrotal inoculation were of three types, all of which were quite simple and consisted in the implantation of bits of infected tissue beneath the skin of the scrotum, in the injection of a fluid medium containing the infecting organisms, or in scarification of a skin area and the local application of the virus. Satisfactory results have been reported from the use of all three of these methods.

EXPERIMENTAL.

In our own work upon scrotal infections of *Treponema pallidum*, the experimental conditions employed were much the same as those outlined in the case of the testicular infections (4).

Animals Used.—A great variety of animals was used, but those preferred were young albinos, grays, browns, or Dutch belts. Individual animals were chosen in which the scrotum was thin and delicate and as free from hair as possible. Old animals with thick, fibrous, or redundant scrota gave results inferior to those of younger animals with more active tissue.

Method of Inoculation.—Inoculation of the scrotum was carried out according to one of two methods. The procedure commonly employed was essentially the same as that described by Tomasczewski (5) which consists in the implantation of a small piece of infected tissue in a pouch prepared for it in the scrotum. The tissue used was either an infected testicle or a granulomatous skin nodule removed with as little contamination as possible and cut into pieces measuring from 3 to 5 mm. in diameter. The inoculation was performed either by the use of a trocar needle of 8 to 9 gauge inside diameter or by snipping the superficial layers of the scrotum with scissors and introducing the fragment of tissue by means of a pair of forceps; the latter method was in general preferred. The only precautions necessary were the observance of reasonable cleanliness and making the implants as superficial as possible.

Both of these methods proved highly satisfactory when rapid development of large skin lesions was desired. They are not adapted, however, to the study of the finer details of the reaction to infection, and for this purpose, we used an intracutaneous or subcutaneous injection of a virus emulsion prepared as for testicular inoculation except that the emulsion contained a greater number of spirochetes, averaging 5 to 10 to the microscopic field. In this operation, the scrotum was cleansed as usual and 0.1 to 0.2 cc. of the emulsion injected by inserting the needle well above the point to be inoculated and carrying it downward to the desired location.

Material Studied.—During the past 4 years, we have inoculated a large number of rabbits by these two methods. Among the earlier animals, there was an occasional one in which infection could not be established with absolute certainty, but all animals inoculated during the last 3 years have developed characteristic lesions from which *Treponema pallidum* could be recovered.

The material afforded by these rabbits was used in various ways. After well developed lesions had become established, a majority of them were used for therapeutic experiments and hence were not available for further study of the course of the local infection except where recurrent lesions developed. Some lesions were excised for histological study at various stages of their development, but a large number of rabbits was held under constant observation throughout the course of the local infection,—some of them as long as 18 months and a few for 2 years or longer.

Reaction Following Inoculation with a Virus Emulsion.

By whatever method scrotal inoculation is performed, the specific reaction which takes place is essentially the same. The early stages of the reaction can be traced more accurately, however, by the use of some methods than by others, and for this purpose, we used an emulsified virus which is but little more than a diluted tissue extract containing the *pallidum*. When inoculations are properly performed by this method, there is very little traumatism, and the slight inflammatory reaction which may develop on this account disappears completely within 24 to 48 hours. Thus, one is not only able to keep the dose of virus used comparatively uniform and to control the conditions of inoculation, but the resulting reaction is as little complicated by extraneous circumstances as is practicable upon any large scale. The chief objection to the method is that it tends to diffuse the infection over a wider area and the resulting reaction is not always so sharply circumscribed as one might wish.

Incubation Period.

The incubation period of scrotal infections produced by inoculation with a virus emulsion came within the comparatively narrow limits of 1 and 4 weeks. Under favorable circumstances, a definite reaction was usually recognized within 10 days to 2 weeks after inoculation and in many instances by the end of the 1st week. Occasionally, the specific reaction developed more slowly and characteristic lesions were not recognizable for several weeks.

The average incubation period of scrotal infections was somewhat shorter than that previously given for the development of gross or clinical alterations in the testicle but corresponded fairly well with

the time within which lesions could be demonstrated microscopically or within which multiplication of spirochetes could be determined by dark-field examination of fluid obtained from the testicles.

Form of the Initial Reaction.

The specific reaction in the scrotum appeared in one of three general forms differing somewhat according to the location of the lesion. The first and most important form of reaction began as small circumscribed swellings or diffusely spreading patches of a rose-pink color situated in the papillary and reticular layers of the skin. These lesions were soft or gelatinous in character and were frequently associated with a rich vascular network such as that shown in Fig. 1, which is probably the most significant feature of the syphilitic reaction. The second form taken by the initial lesion was that of a minute translucent nodule or plaque of induration likewise situated in the papillary layer of the skin but more superficial than the first (Fig. 5). The third type of lesion appeared as an opaque porcelain-white nodule or plaque of extreme hardness situated in the depths of the scrotum and was usually connected with the outer surface of the tunica vaginalis. The first two forms of reaction were the most common and usually the earliest to appear.

Development of the Primary Lesions, or Chancres.

The development of primary skin lesions, or chancres, from initial foci of reaction, such as those described, followed a course which may be represented in general by Figs. 1 to 4 and 5 to 8 which were from two animals of the same series. As indicated in these illustrations, the progress of the infection was marked by an extension of the reaction and the occurrence of certain transformations. The infection tended to spread diffusely through the scrotum, and as the reaction about the focus of infection increased, lesions were formed which assumed the character of circumscribed nodular elevations or of flattened, diffusely spreading patches.

In the development of the gelatinous type of lesion (Figs. 1 to 4), the swelling first subsided to a slight extent and the color changed to a more coppery tint. The lesions then became firmer, and as the

induration increased, changed to more opaque, porcelain-white masses. Purplish red spots and streaks of congestion and hemorrhage then appeared over the central portions of these lesions and with them yellowish gray or yellowish brown areas of necrosis which tended to spread and become covered with thin scales or crusts. Finally, the central area of the lesion became necrotic and sloughed away or was covered by a more or less continuous crust.

In the case of circumscribed lesions such as those in Figs. 1 to 4, these changes led to the formation of elevated masses with a necrotic or ulcerated center surrounded by a zone or collar of induration. If the lesions spread diffusely, as they not infrequently did, the resulting lesion was a thickened or indurated patch over which the areas of necrosis were more diffusely scattered; the crusts were usually imperfectly developed and loosely attached, and while ulceration was slight, weeping patches were formed here and there.

When the scrotal lesions first appeared as translucent nodules or patches of induration, development of the lesions followed a slightly different course (Figs. 5 to 8). The vascular reaction about such areas was relatively less than in the preceding case. As the lesions increased in size, the central portions became more dense and opaque, while the overlying skin became smooth and glistening. The covering epithelium was thinned out until small defects or superficial areas of necrosis appeared and were covered by thin scabs or crusts.

When these lesions assumed the form of circumscribed nodules (Figs. 5 to 8), the area of necrosis enlarged and deepened with the growth of the lesion and was covered by a thick crust or formed a depressed ulcer surrounded by a mass of indurated tissue. The more diffuse lesions of this class appeared as parchment-like thickenings in the skin which either remained intact and appeared translucent, smooth, and glistening throughout or were irregularly covered by loosely attached scales with raw or ulcerated areas here and there.[1]

The third form taken by the initial lesion in the scrotum, that of an opaque white nodule or plaque of induration in the depths of the scrotum, usually followed a still different course of development.

[1] See section below on diffuse scrotal lesions.

As in the case of the lesions just described, the vascular reaction about these lesions was of minor degree. They developed rather slowly as a rule and grew or spread in the form of extremely hard masses over which the skin was freely movable. The plaques usually remained deep seated and spread along the surface of the tunica vaginalis, but the nodular lesions gradually extended towards the surface so that the overlying skin not infrequently became involved. Necrosis and ulceration then took place with the formation of lesions much like those which have been described. However, many of these deep seated nodules did not involve the overlying tissues to a sufficient extent to bring about necrosis and ulceration but remained throughout as circumscribed nodular lesions in the deeper tissues of the scrotum.

The subsequent course of the reaction to infections produced in this way was essentially the same as that of an infection produced by other methods of inoculation and may be followed out in connection with the infection produced by implantation.

Reaction Following Inoculation by Tissue Implantation.

While inoculation by the use of tissue implants possesses certain advantages, there may be some difficulties attending its use. Due to unequal distribution of spirochetes in infected tissues as well as to inequalities in the vitality of the organisms present in different portions of a lesion, inoculations carried out by implantation may not yield results which are as uniform as from the use of methods by which the dose of virus can be kept more nearly constant. It is possible, however, to overcome these difficulties to a large extent by the observance of certain precautions: first, the use of infected tissues at a relatively early stage of the infection or only at a period when the infection is actively progressing; second, the use of only such portions of a lesion as are actively growing at the time; and third, as a means of insuring an adequate dose of organisms when any doubt exists, the use of pieces of tissue as large as can conveniently be used without causing necrosis and sloughing of the surrounding tissues. Obviously, judgment in the use of these precautions can be acquired only by experience. A second difficulty in the

use of this method is the traumatism necessarily inflicted and the chances offered for the development of secondary infections. These need not prove serious, however, since reasonable care in the performance of inoculations will remove such difficulties to a considerable extent.

For certain purposes, implantation has advantages over other methods of inoculation which more than compensate for its disadvantages. When properly safeguarded, large, actively growing skin lesions can be obtained more quickly and with greater certainty by this method than by any other method of inoculation with which we are acquainted.

Incubation Period.

The exact incubation period of infections produced by scrotal implantation is difficult to fix since a non-specific foreign body reaction frequently overshadows the specific reaction. As nearly as can be determined, however, the incubation period in our series of animals fell within much the same limits as for inoculations made with emulsions. There was usually a definite specific reaction about the implant, and spirochetes could be obtained from the surrounding tissues within 10 days to 2 weeks after inoculation and were obtained as early as the 3rd day, but it was not certain that the organisms found were more than transient invaders. In a few instances, incubation was unusually prolonged after inoculations performed by this method, and no specific reaction could be recognized for several months—in one instance 6 months and 6 days. This unusual prolongation of the incubation period probably had no connection with the method of inoculation used except as a possible instance of the inoculation of a small number of organisms or of organisms of low vitality, and is merely cited to show the time which may elapse before any definite reaction can be detected.

Early Reaction.

The reaction which takes place in the scrotum following inoculation by implantation may be regarded as partly one of wound healing, partly a foreign body reaction, and partly specific in character. During the first 24 hours, the scrotum became slightly reddened and

edematous, but this acute inflammatory reaction rarely lasted beyond the 2nd or 3rd day. Then the process of organization became established; the swelling subsided, leaving the skin about the implant slightly reddened, smooth, and glistening. This condition persisted for upwards of 7 to 9 days without producing any considerable increase in the size of the nodule. In some instances, the skin over the implant became necrotic and was covered by a crust or sloughed away leaving a depressed ulcer surrounded by a zone of granulation tissue. If no specific reaction had developed by this time, the nodule began to shrink and soften while the skin became relaxed as the process of organization or healing subsided. If the tissues about the implant retained their appearance of activity beyond the 10 day period, and especially if the reaction appeared to be increasing, it was usually found that a specific reaction had commenced.

However, the specific reaction usually became apparent after the process of organization had abated to an appreciable extent and appeared almost as a renewal of this process. The differences which could be recognized were that there was less reddening in the specific reaction, the tissues were more translucent and more definitely indurated, and the reaction resulted in a rapid growth of the lesions. In many instances, there was no break in the continuity of the two processes and it was impossible to determine exactly when the specific reaction began.

Not infrequently, multiple foci of infection resulted from inoculation by this method. Thus, lesions developed independently about the implant at the point of incision and occasionally other discrete foci were scattered along the track of the sinus.

Course of the Scrotal Reaction and Development of Typical Scrotal Chancres.

In following out the successive stages in the scrotal reaction and the development of what may be called typical scrotal chancres, it may be assumed that the specific element in the reaction is the same in all essential respects whether inoculation is carried out by the use of a virus emulsion or by tissue implantation. The mechanical conditions of the reaction in the two cases are quite different, however.

The production of an infection by the introduction of a solid mass of tissue into the scrotum undoubtedly exercises a considerable influence in itself upon the character of the lesions produced and favors the development of large circumscribed lesions, but chancres produced in this way do not always follow the same course of development, and the resulting lesions themselves may be quite different. It is well, therefore, to consider the growth of these lesions according to the general character of the reaction.

Three characteristic examples of chancre development following the use of this mode of inoculation are given in Figs. 9 to 12, 13 to 16, and 17 to 20. The first group of photographs (Figs. 9 to 12) represents stages of chancre development where optimum conditions of virus, animals, and technique were combined. The animal shown was one of a series of ten rabbits in which the results were remarkably uniform. The first photograph (Fig. 9) taken 10 days after inoculation shows a well established specific reaction. There were some edema and congestion of the scrotum, and the skin over the implants had undergone necrosis with the formation of hard dry crusts which showed a line of demarcation at their periphery. Both implants were surrounded by a distinct but narrow zone of specific granulation, more prominent on the left than on the right. These lesions developed very rapidly and by the 13th day (Fig. 10) presented all the characteristics of typical chancres with depressed ulcers surrounded by broad zones of induration.

With the growth of the lesions as illustrated in Figs. 11 and 12, taken 3 and 5 weeks respectively after inoculation, the diffuse congestion and edema of the scrotum persisted; the scrotum gradually became thickened and a few petechial hemorrhages appeared towards the lower end of the right scrotum (Fig. 11), which formed the center about which a second circumscribed lesion soon developed. Eventually, the entire scrotum of both testicles became involved in the specific reaction and the condition existing at the end of the 5th week was that shown in Fig. 12. On the right, there were two circumscribed lesions connected by areas of more diffuse infiltration, while on the left, there was a single massive chancre surrounded by tissues which were themselves markedly infiltrated and covered by diffusely spreading patches of hemorrhage and necrosis.

This is an instance of a high grade infection in the scrotum of the rabbit such as may be produced under favorable conditions and has been observed many times. It may not be out of place to point out that this case illustrates, in particular, first the extreme rapidity with which the infection may become established and typical circumscribed lesions developed, and secondly the inherent tendency of

pallidum infections to spread beyond the local confines of the initial focus of infection, together with something of the character of the reaction which occurs under such circumstances.

The second case in this group (Figs. 13 to 16) illustrates a course of chancre development which is more nearly an average than that just described. The reaction exhibited by this animal was of the same general character as that of the first, but differed in two essential respects. There was early ulceration of the lesions as in the former case, and by the 14th day, characteristic chancres with well defined collars of induration were present (Fig. 13). The growth of the lesions then ceased, the edema in the scrotum subsided, and the chancres themselves decreased in size (Fig. 14). During the 4th week, there were a slight recurrence of the edema (Fig. 15) and renewed growth of the circumscribed lesions which continued with slight remissions until large indurated lesions were formed (Fig. 16, 57 days after inoculation).

These two examples will serve to illustrate the type of reaction which takes place in most instances of active chancre development. A third form of reaction commonly seen is that illustrated in Figs. 17 to 20. This animal was one with a rather thick fibrous scrotum (note the scrotum in Figs. 17 and 18) and the implants could not be made so superficially as one would wish. The incubation period was somewhat longer, and the lesions did not begin to grow actively until about the end of the 4th week after inoculation. The photograph reproduced in Fig. 17 was taken at the end of the 5th week (34 days) when the nodules measured approximately 1 cm. in diameter. The skin about the nodules was still but little affected and for the most part retained its normal appearance. During the next 18 days, these lesions underwent a considerable transformation (Figs. 18 to 20); they increased in size and became more indurated, while the process extended to the overlying skin which became smooth, translucent, and highly refractile. Areas of necrosis then appeared upon the surface, and as these extended and contracted, the lesions flattened out into the form seen in Fig. 20. Specific reactions of this type were especially apt to occur when the lesions developed in the depths of the scrotum or when, for any reason, the reaction pursued a less active course and involvement of the skin with consequent necrosis and ulceration took place at a relatively late period in the growth of the lesions.

Multiple Chancres.—Multiple lesions of a chancre-like character developed in the scrotum under two different conditions, first as a result of simultaneous infection of several points in the scrotum, and second as a result of spread of the infection from a given focus. While lesions of both classes might be regarded as chancres, the significance of the two cases is different, and in the present connection, we shall refer only to lesions of the first class.

Inoculation of the scrotum of the rabbit by the methods described usually resulted in the production of unicentric lesions. Not infrequently, however, lesions appeared simultaneously at other points reached directly in the process of inoculation. The most common seat of the accessory chancre was the point of incision in the skin, and a typical instance of an early lesion of this kind is shown in Fig. 21, the photograph of which was taken 14 days after inoculation. Accessory lesions of this type were frequently abortive or were overgrown by the more vigorous reaction about the main focus of infection as was the case in this animal (Fig. 22, 36 days after inoculation).

A second case of a similar character is shown in Fig. 23. Originally there was an accessory focus of reaction on both sides of this animal. That in the right scrotum was abortive and had almost disappeared when this photograph was taken (29 days after inoculation), while the one on the left was growing quite actively.

In some animals the accessory chancres reach a considerable size even though they are encroached upon by the main chancre mass. Figs. 24 and 25 show a case of multiple chancres in which there were three foci of reaction in the right scrotum and two in the left (Fig. 24, 29 days after inoculation). As these lesions developed, the middle focus of infection on the right became obliterated, but the other accessory chancre grew almost as vigorously as the main lesion. On the left, the two lesions fused at their proximal borders forming a figure of eight chancre (Fig. 25, 49 days after inoculation).

In rare instances, one finds little difference in the vigor displayed by the several lesions present, and all may develop at about an equal rate as shown in Fig. 26 (47 days after inoculation). In addition to the group of multiple lesions described, all of which were situated in the skin itself or pointed upon the skin surface, there was another interesting group of multiple focal lesions in which the foci of reaction were located at different levels in the scrotum—one above the other; these lesions were situated in the skin and upon the outer surface of the tunica vaginalis. This form of localization occurred especially after subcutaneous inoculation with a virus emulsion and is of especial interest in revealing a tendency of *Treponema pallidum* to localize in these two structures.

These few examples of the reaction to infection in the scrotum and the growth of the primary lesions will serve to illustrate what may be called typical skin reactions and typical chancre development in the sense that they represent processes which are in themselves perfectly characteristic and result in the formation of lesions which are easily recognized as lesions of a specific character. In many instances, however, reactions occur and lesions develop which are not so well recognized as processes of a syphilitic nature, and we may refer briefly to a few instances of this kind.

Influence of Different Elements of the Specific Reaction upon Chancre Development.

Irregularities of Chancre Development.

The condition which gives the characteristic picture to the specific reaction in the skin and to the chancre itself is the maintenance of a certain balance among the several processes which take part in this reaction. It was found that when for any reason this balance was disturbed, the character of the reaction was altered and the lesions became modified in accordance with existing conditions. The irregularities of chancre development which were most commonly seen were associated with the occurrence of excessive edema or of congestion and edema, with conditions simulating an acute inflammatory reaction, or with irregularities in the process of granulation, the cause of which cannot be discussed.

Edema.—It was found that excessive edema with or without congestion might occur at any time during the course of the local infection. When it developed at an early stage of the infection, it not infrequently overshadowed the proliferative reaction and produced a lesion which showed chiefly a depressed ulcer with a firm margin surrounded by an edematous skin (Fig. 27). In some instances, this condition persisted for some time, while in others it was no more than an important feature of the reaction or an event in the course of the reaction. Figs. 28 and 29 illustrate an instance of this kind in which the specific reaction was proceeding rather slowly, and at the end of the 3rd week, there were ulcers surrounded by a narrow zone of induration. An acute edema then developed (Fig. 28), and with the appearance of this edema, the focal lesions began to grow at an extremely rapid rate; in 2 weeks, they had reached the condition shown in Fig. 29, the edema persisting to an appreciable extent all the while.

Late edema or edema occurring after characteristic lesions had developed was also seen occasionally and was so marked in some instances as to obscure completely the character of the lesion (Fig. 30).

Acute Inflammatory Reactions.—A small number of rabbits in the series showed an early reaction resembling an acute inflammatory process. There was the usual inflammatory reaction during the first few days following inoculation, and as this subsided, an extremely active process of granulation set in; the tissues surrounding the implant remained reddened or cyanotic and were quite firm, while the zone of induration increased rapidly. The center of the nodule became necrotic and sloughed, leaving a moist, depressed ulcer, or, if no slough occurred, the necrotic tissue softened to a creamy semifluid mass covered by a crust. As the reaction progressed, the tissues surrounding the zone of granulation or even

the entire scrotum became congested and edematous (Fig. 31). This condition usually lasted for not more than 3 to 5 weeks before regression set in. The lesions which appeared subsequently were usually of a minor character, but in some instances, typical chancres were formed as in the case illustrated (Figs. 31 and 32).

At first we were inclined to regard these acute reactions as non-specific, inflammatory processes, but investigation showed that this was not entirely correct. Spirochetes were present in considerable numbers both in the zone of granulation and in the edematous portions of the scrotum entirely removed from the region of the implant, but secondary infection could not be excluded as a factor in the reaction. However, true suppuration did not occur as it usually did where pyogenic organisms were present to any considerable extent. It was noted that these reactions were more frequent when large implants were made from testicles during an early stage of extremely active infections. It seemed possible, therefore, that these were cases of acute specific reaction influenced to a greater or less extent by bacterial infection as well as by the implant itself.[2]

Irregularities in the Process of Granulation.—In many instances, irregularities in the development of scrotal chancres were traceable to peculiarities in the process of granulation, and since this is such a noticeable feature of what we are accustomed to regard as the typical *pallidum* reaction, the peculiarities naturally took the form of a lowered intensity of reaction or of some irregularity in the process, both of which were commonly seen in scrotal infections in the rabbit.

The case illustrated in Figs. 33 to 36 furnishes an example of an abortive skin reaction with subsequent development of granulomatous nodules in the subcutaneous tissues of the scrotum. The lesions first formed were simple ulcers surrounded by a thin, parchment-like zone of induration in which spirochetes were present (Fig. 33, 35 days after inoculation). On the left, the zone of induration increased slowly and a characteristic skin chancre was produced (Fig. 34, 83 days after inoculation). Meanwhile, the skin lesion on the right had regressed, and a small nodule had developed in the subcutaneous tissues (Fig. 34). Then followed a period during which the lesion on the left extended into the subcutaneous tissues, while the induration in the skin diminished and the ulcer healed (Figs. 35 and 36, 139 and 188 days after inoculation).

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[2] In this connection, it may not be out of place to call attention to the fact that in all syphilitic infections, the presence of a toxin as an exciting factor distinct from the organisms must be kept in mind. We have avoided introducing this element into the discussions, since we are not prepared, as yet, to make any definite statement upon this point. It seems not unlikely, however, that certain features of the syphilitic reaction may find their explanation in the action of such a toxin, and this applies to reactions of the type just described.

A second case of even less characteristic chancre formation is shown in Figs. 37 to 40. The initial skin lesion in this animal was no more than a thickened patch, the surface of which was smooth and glistening with small erosions here and there; some of these were covered by scales, while others were of a weeping character. These lesions underwent many transformations (Figs. 37 to 40), but never developed beyond the point shown in Fig. 37 which represents the condition existing 36 days after inoculation. Here again, the granulomatous lesions which ultimately developed were subcutaneous in origin and were of very slow and irregular growth (Figs. 38, 39, and 40; 92, 106, and 127 days after inoculation).

Diffuse Scrotal Reactions and Transformations of Diffuse Lesions.

As we have already pointed out, there is a tendency on the part of *pallidum* infections to spread beyond the point of inoculation, and not infrequently this local extension of the infection gives rise to lesions of a more diffuse character than those which have been described. No sharp line of distinction could be drawn between these two groups of lesions; it appeared that one was but a step removed from the other, and diffuse and circumscribed processes were frequently coexistent, or one type of lesion might be transformed into the other, instances of which have already been noted.

As a connecting link between these two forms of scrotal reaction, attention may be called to the lesions shown in Figs. 41 to 44. The photograph reproduced in Fig. 41 was taken 33 days after inoculation. In this animal, there was a moderate but fairly well defined thickening in the skin about the incisions as well as about the implants, and the characteristic feature of the lesions was the spreading necrosis in the skin over the implants and the formation of loosely attached scales, or exfoliation, over all affected parts of the skin, which is shown very well in the left scrotum (Fig. 41).

The second photograph (Fig. 42) shows a later stage of a similar lesion. In this animal, there are two things to be noted, first the puckered scar-like areas on both sides, and second the peculiar appearance of the skin about these areas. The skin was in general of a parchment-like character, very smooth and translucent with grayish yellow or yellowish brown scales or crusts distributed over its surface. Needless to say, these portions of the scrotum contained spirochetes in abundance.

The other two figures on this plate (Figs. 43 and 44) illustrate a somewhat different manifestation of the syphilitic infection. In Fig. 43, there is shown a rather irregular and slightly nodular thickening in the right scrotum with a scurfy condition of the skin over portions of the lesion; on the left, there is a puckered ulcer with moderate thickening of the surrounding skin. These were the lesions as

they appeared 76 days after inoculation. Subsequently the thickening or induration in the skin became diminished, but instead of healing, the lesions spread in an irregular way, producing a peculiar serpiginous necrosis and ulceration over a considerable part of the scrotum (Fig. 44, 118 days after inoculation). There was no suggestion of an acute inflammatory process associated with these changes, and spirochetes were present in fluid drawn from about the lesions.

The next series of photographs (Figs. 45 to 48) shows successive stages in the transformation of a diffuse scrotal infection which reverses somewhat the sequence of events illustrated in the preceding series. The reaction began here as a diffuse infiltration with exfoliation of the epithelial covering of the scrotum (Fig. 45, 53 days after inoculation). After a time, the scaling, or exfoliation, ceased, and the skin became very smooth and translucent. At the same time, the skin became diffusely indurated, and circumscribed nodules appeared in the subcutaneous tissues on both sides. These nodules grew rather slowly, and on the 151st day after inoculation, the condition presented was that shown in Fig. 46. The subcutaneous nodule in the left scrotum was later excised, but the infection in the scrotum persisted in spite of the operation. The nodule on the right continued to grow, and as it developed, the infiltration in the skin diminished. There was, however, a slight recurrence of the exfoliative reaction (Figs. 47 and 48, 165 and 172 days after inoculation).

No attempt can be made to indicate the diversity of conditions to which the specific reaction in the scrotum may lead. By comparing and following the various phases and stages of the reaction, it will be seen that the elements in these reactions are the same in all cases; all show a vascular reaction, a certain amount of exudation, infiltration, and proliferation together with secondary necrosis and ulceration or exfoliation where the necrosis is superficial. The lesions we regard as but an expression of the operation of these factors in the reaction and the balance obtaining in a given case at a given time. As the response to the specific infection varies in different animals or even in the same animal from time to time, so do the lesions, and the possibilities of such variations are almost infinite. The consideration of this phase of the local infection will be taken up in the second part of this paper.

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EXPLANATION OF PLATES.

The first four illustrations are drawings made from the living animal and are based upon photographs taken at the time. The remaining illustrations are reproductions of untouched photographs. All objects are represented at their natural size. The statements of time refer in all cases to the time after inoculation unless otherwise stated.

PLATE 72.

FIGS. 1 to 4. Successive stages of the reaction to infection in the scrotum following inoculation with a virus emulsion.

FIG. 1. 2 weeks. Localized swelling in the scrotum with vascularization of the area. An unusually characteristic reaction.

FIG. 2. 23 days. Early induration with congestion and petechial hemorrhage from the vessels in the center of the lesions.

FIG. 3. 28 days. Anemic necrosis and exfoliation.

FIG. 4. 41 days. Circumscribed and indurated chancres with marked central necrosis and ulceration.

PLATE 73.

FIGS. 5 to 8. Development of scrotal chancres from focal infiltrations following inoculation with a virus emulsion.

FIG. 5. 1 week. Minute focus of induration in the right scrotum and diffuse infiltration with vascularization in the left.

FIG. 6. 19 days. Circumscribed areas of infiltration and induration. The skin over the center is becoming thin and translucent; slight congestion and hemorrhage on the right.

FIG. 7. 28 days. Surface necrosis and exfoliation.

FIG. 8. 43 days. Chancres with well developed collars of induration and marked central necrosis and ulceration.

PLATE 74.

FIGS. 9 to 12. An intense reaction to infection with the development of circumscribed indurated chancres and subsequent extension of the lesions following implantation in the scrotum.

FIG. 9. 10 days. The early syphilitic reaction following inoculation by implantation. There are diffuse edema and congestion of the scrotum and the implants are surrounded by a narrow zone of induration, while the skin over their center has been converted into hard dry crusts.

FIG. 10. 13 days. The early chancre. Note especially the well marked collars of induration and the tendency to exfoliation in the right scrotum.

FIG. 11. 22 days. The diffuse reaction has persisted and the edema has given place to infiltration and thickening of the scrotum.

FIG. 12. 36 days. Large indurated chancres. Diffuse extension of the reaction with widespread necrosis and ulceration of the scrotum.

PLATE 75.

FIGS. 13 to 16. A usual case of scrotal reaction showing cyclic changes in the development of the lesions. Scrotal implantation.

FIG. 13. 14 days. Typical circumscribed lesions with depressed ulcers; edema and congestion of the scrotum.

FIG. 14. 21 days. The lesions have decreased in size; edema and congestion have subsided.

FIG. 15. 28 days. Renewed growth of the chancres and reappearance of scrotal edema.

FIG. 16. 57 days. Large indurated chancres with well marked central necrosis and the formation of ulcers.

PLATE 76.

FIGS. 17 to 20. Deep seated scrotal infection, characterized by slow growth of the lesions and late involvement of the skin. Implantation.

FIG. 17. 34 days. An early stage of the reaction. Skin but slightly involved.

FIG. 18. 41 days. Involvement of the skin with obliteration of papillæ and beginning skin necrosis.

FIG. 19. 44 days. A very active advance of the process indicated in Fig. 18.

FIG. 20. 52 days. The reaction is still quite active. The lesions are extending laterally and the central necrosis is increasing.

PLATE 77.

FIGS. 21 to 26. Multiple foci of primary reaction. Multiple chancres Implantation.

FIG. 21. 14 days. A well marked accessory focus of reaction at the point of incision of the scrotum on the right.

FIG. 22. 36 days. Overgrowth of the accessory chancre by the main focus of reaction.

FIG. 23. 29 days. Quadruple foci of reaction. The accessory lesion on the right is already regressing.

FIG. 24. 29 days. Triple and double foci of reaction.

FIG. 25. 49 days. Subsequent development of chancres from four of the five initial foci of reaction in Fig. 24.

FIG. 26. 47 days. Quadruple chancres. An unusual case of equal reaction about all of four centers of reaction.

PLATE 78.

FIGS. 27 to 32. Variations and irregularities of the specific reaction. Edema, congestion, and acute inflammatory reactions.

FIG. 27. 16 days. Early circumscribed chancres with diffuse congestion and marked edema of the scrotum. Spirochetes recovered from the point indicated by the arrow on the right.

FIG. 28. 25 days. Focal lesions with acute edema and congestion of the scrotum.

FIG. 29. 39 days. Marked growth of the focal lesions following the exudative reaction in the scrotum.

FIG. 30. 102 days. Sudden development of edema in the scrotum which was the seat of an old indurated lesion. (Compare left.)

FIG. 31. 11 days. An intense granulomatous reaction associated with edema and marked congestion of the scrotum, the exact nature of which is uncertain (see text).

FIG. 32. 50 days. The same animal as in Fig. 31, showing the development of typical indurated chancres following partial regression of the previous lesions.

PLATE 79.

FIGS. 33 to 36. Successive stages of an atypical granulomatous reaction.

FIG. 33. 35 days. Simple ulcers of the scrotum with slight induration about their margins and base.

FIG. 34. 83 days. Slow but characteristic development of the lesion in the left scrotum. Regression of the lesion on the right with the formation of a small subcutaneous nodule underneath the original lesion.

FIG. 35. 139 days. Continued growth of the lesion on the left while that on the right has diminished in size.

FIG. 36. 188 days. Complete healing of the original skin lesions with the development of active subcutaneous nodules on both sides.

PLATE 80.

FIGS. 37 to 40. Successive stages of an irregular scrotal reaction.

FIG. 37. 36 days. Patches of superficial induration in the skin with necrosis and exfoliation.

FIG. 38. 92 days. The patch of induration on the left is still present, while that on the right has almost completely resolved. Subcutaneous nodules forming on both sides.

FIG. 39. 106 days. On the right, there is a small patch of glassy induration in the skin and beneath this a small indurated nodule surrounded by a mass of diffusely thickened tissue. On the left, the subcutaneous nodule is developing rapidly.

FIG. 40. 127 days. Active development of both nodules with extension to the skin. Note the recurrence of the indurated patch in the right scrotum.

PLATE 81.

FIGS. 41 to 44. Diffuse syphilitic processes following scrotal inoculation.

FIG. 41. 33 days. Slight granulomatous reactions about both the implants and the points of incision in the scrotum. The characteristic feature of the reaction is the spreading necrosis and exfoliation over the areas involved.

FIG. 42. 105 days. Diffuse infiltration about the site of inoculation with superficial necrosis and exfoliation. No typical chancre was ever formed in this animal.

FIG. 43. 76 days. A group of irregular and slightly nodular lesions in the right scrotum with surface necrosis and slight exfoliation. On the left, there is a diffuse infiltration of the scrotum with necrosis over the central area.

FIG. 44. 118 days. Same animal. Spreading serpiginous necrosis involving the areas of infiltration.

PLATE 82.

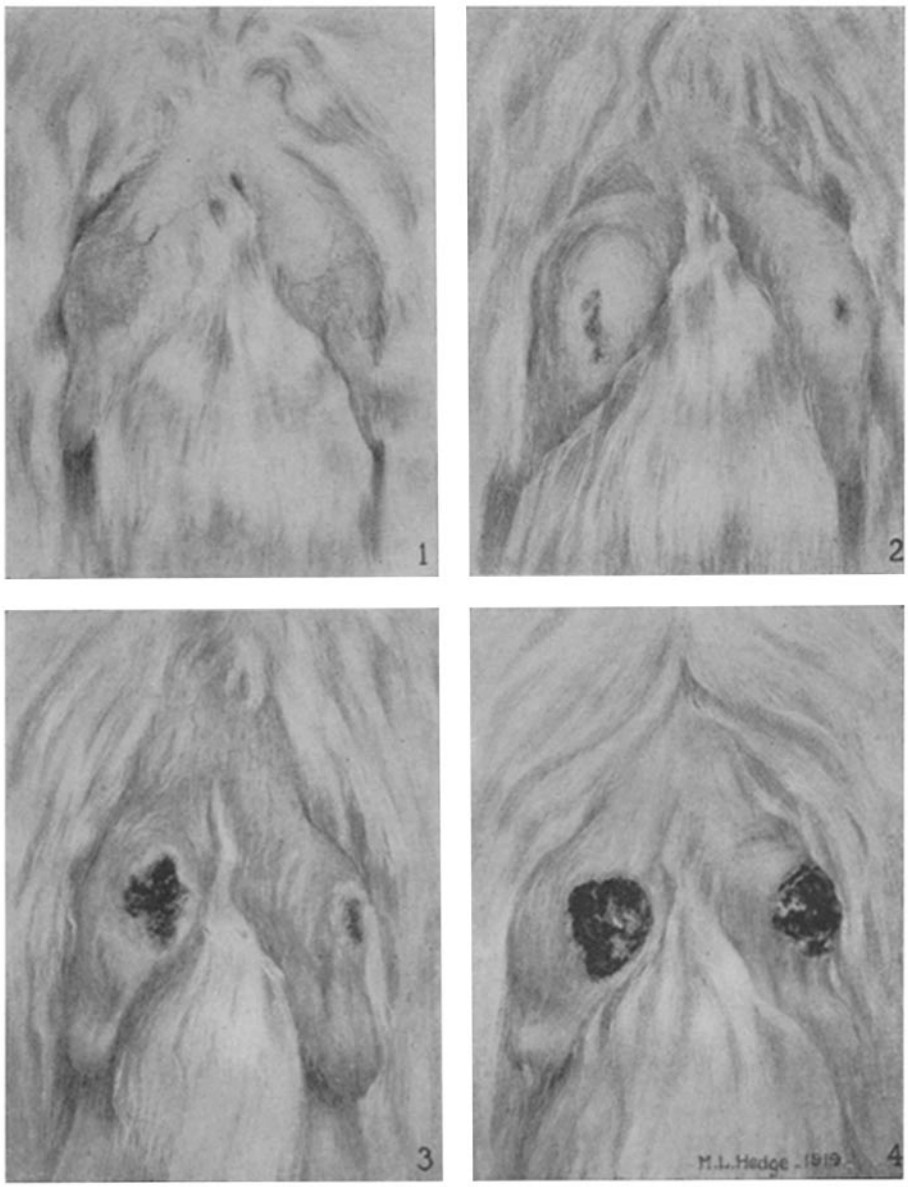
FIGS. 45 to 48. Successive stages in the transformation of diffuse scrotal lesions.

FIG. 45. 53 days. Diffuse infiltration of the scrotum, slight necrosis, and well marked exfoliation of surface epithelium—the initial lesion.

FIG. 46. 151 days. Marked diffuse infiltration of the skin with obliteration of the papillæ; large granulomatous nodules developing in the subcutaneous tissues.

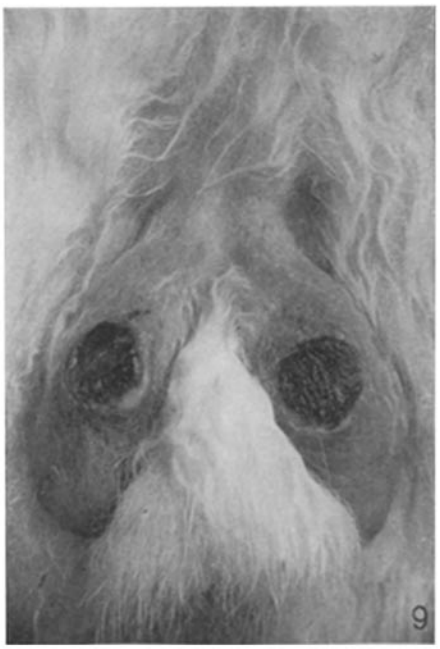
FIG. 47. 165 days. Subcutaneous nodule removed on the left; that on the right still increasing, while the infiltration of the scrotum is slightly diminished.

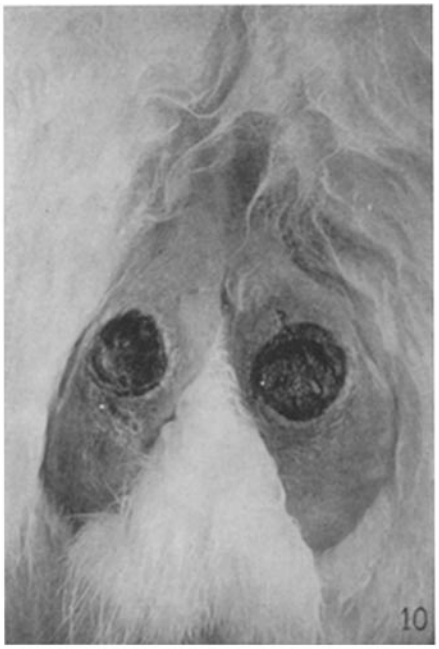
FIG. 48. 172 days. The operative wound is practically healed; active infection still persists in the skin on the left; the nodule in the subcutaneous tissues is increasing, but the infiltration of the skin has almost disappeared; there is slight desquamation of surface epithelium.



(Brown and Pearce: Experimental syphilis in the rabbit. II.)

(Brown and Pearce: Experimental syphilis in the rabbit. II.)





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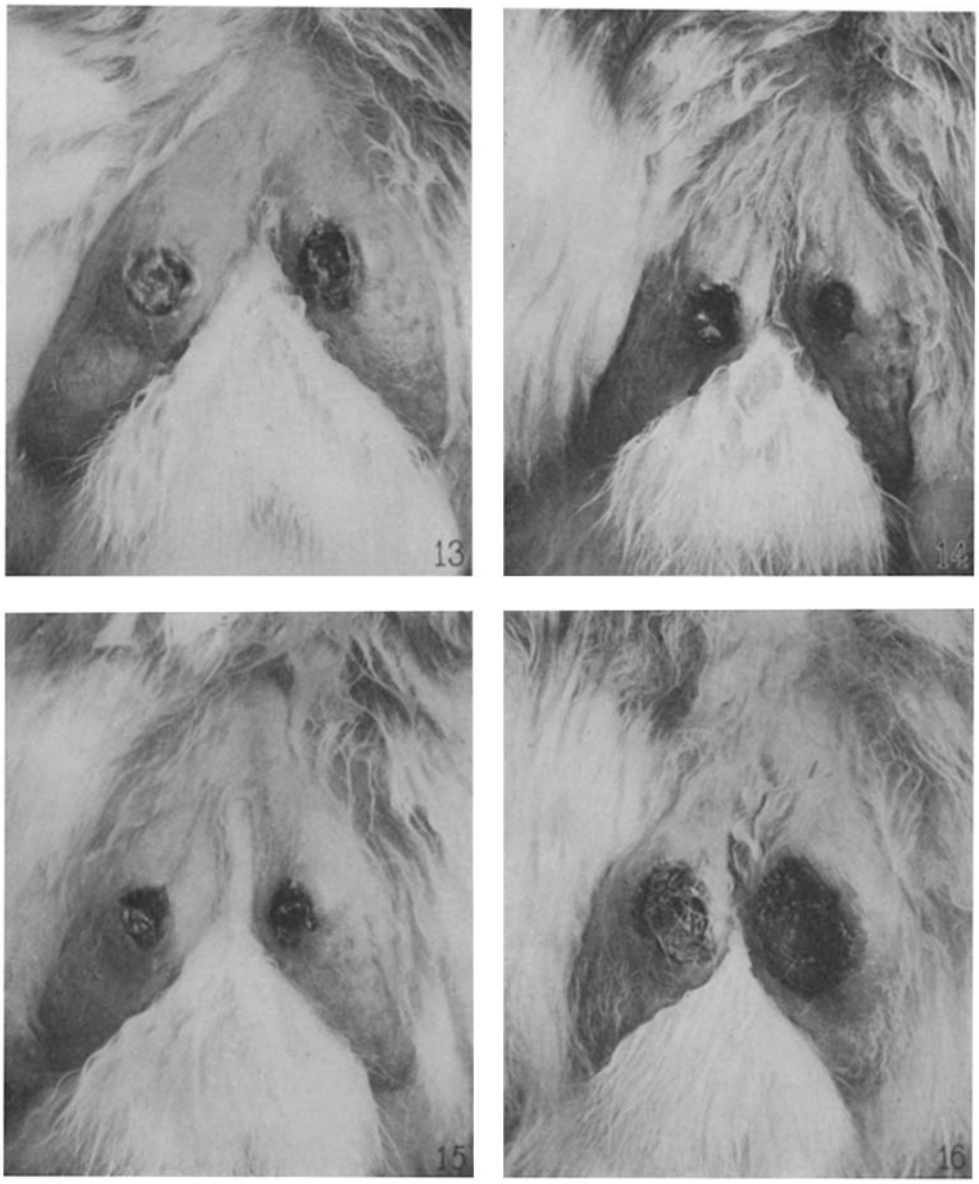

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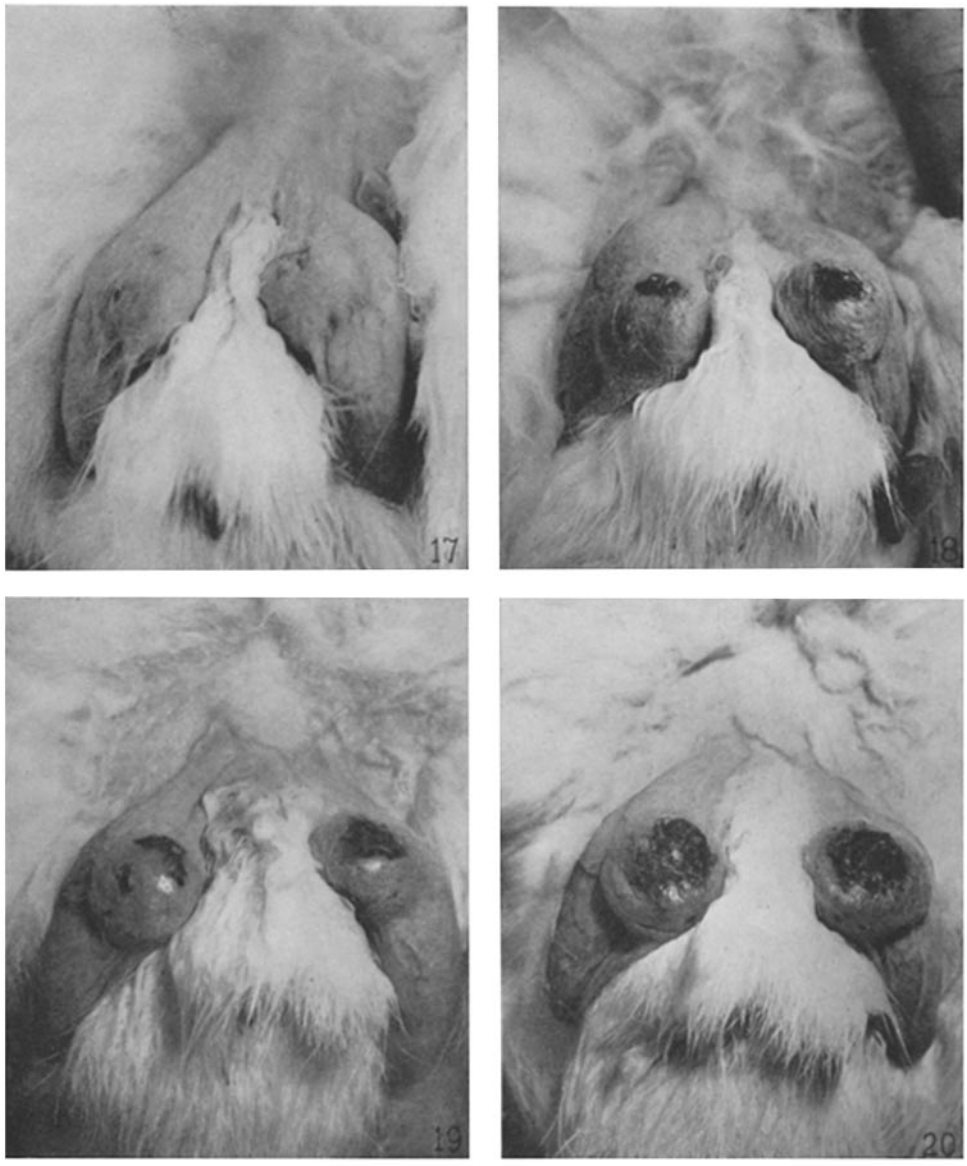

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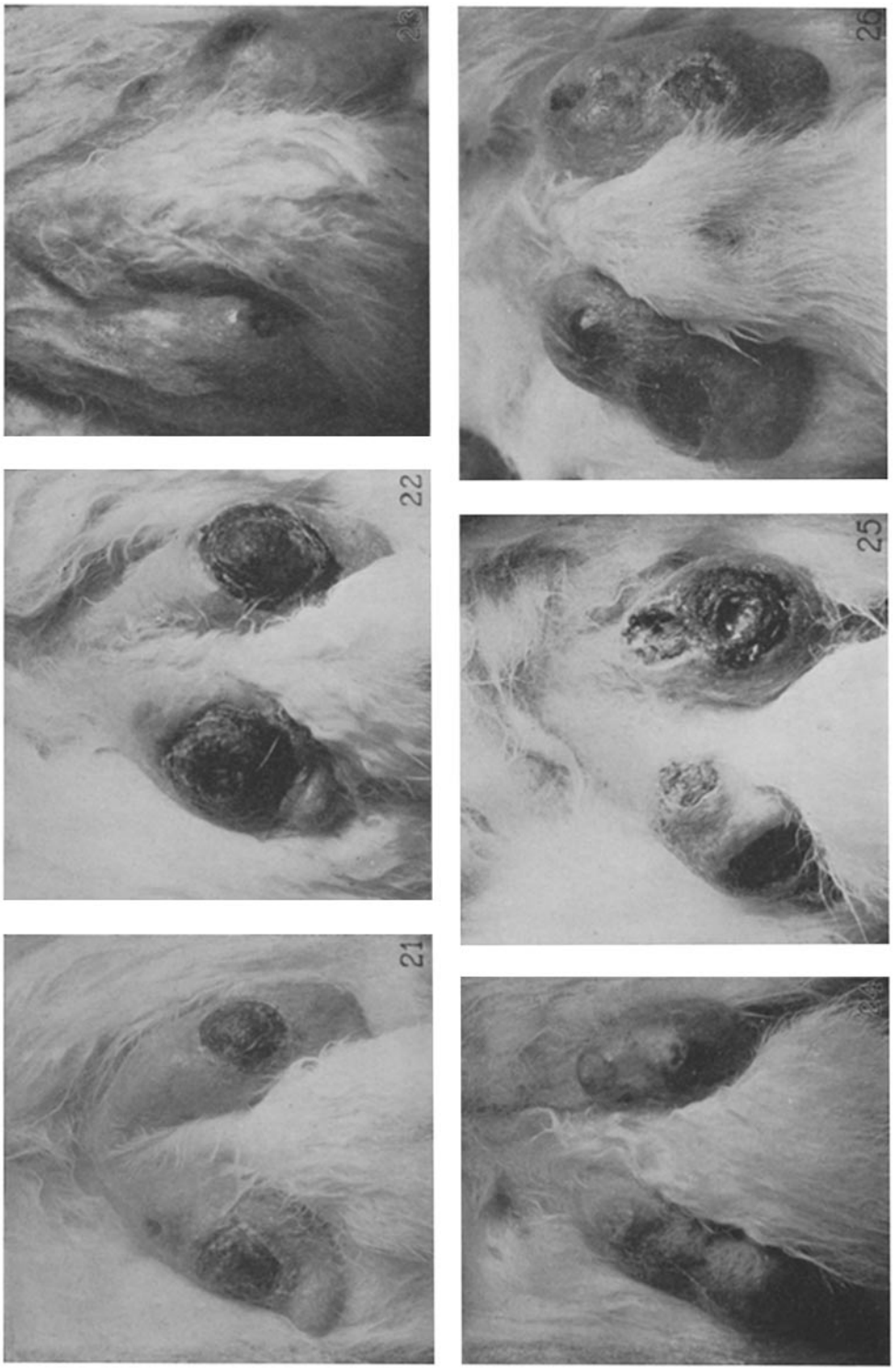

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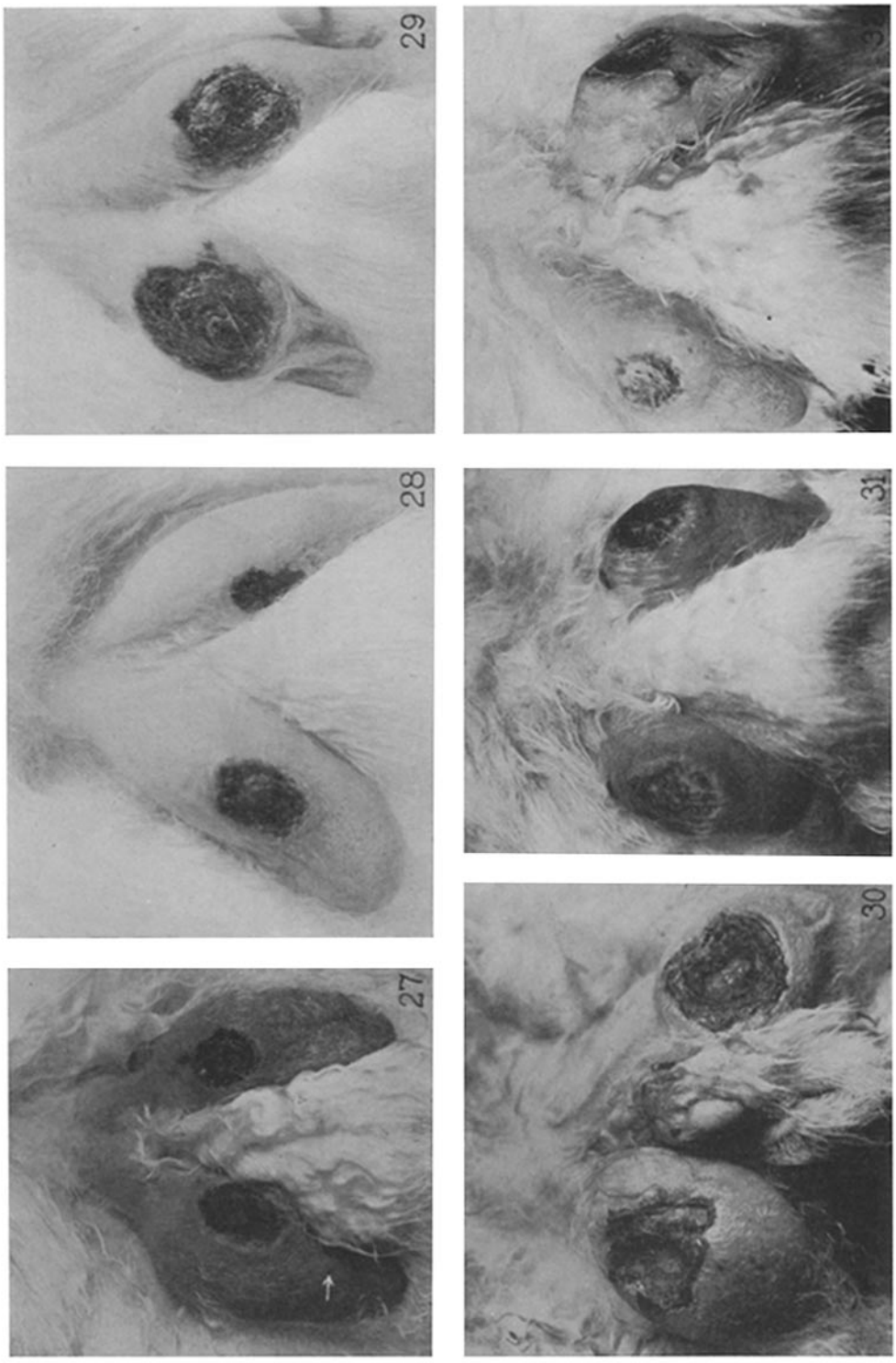

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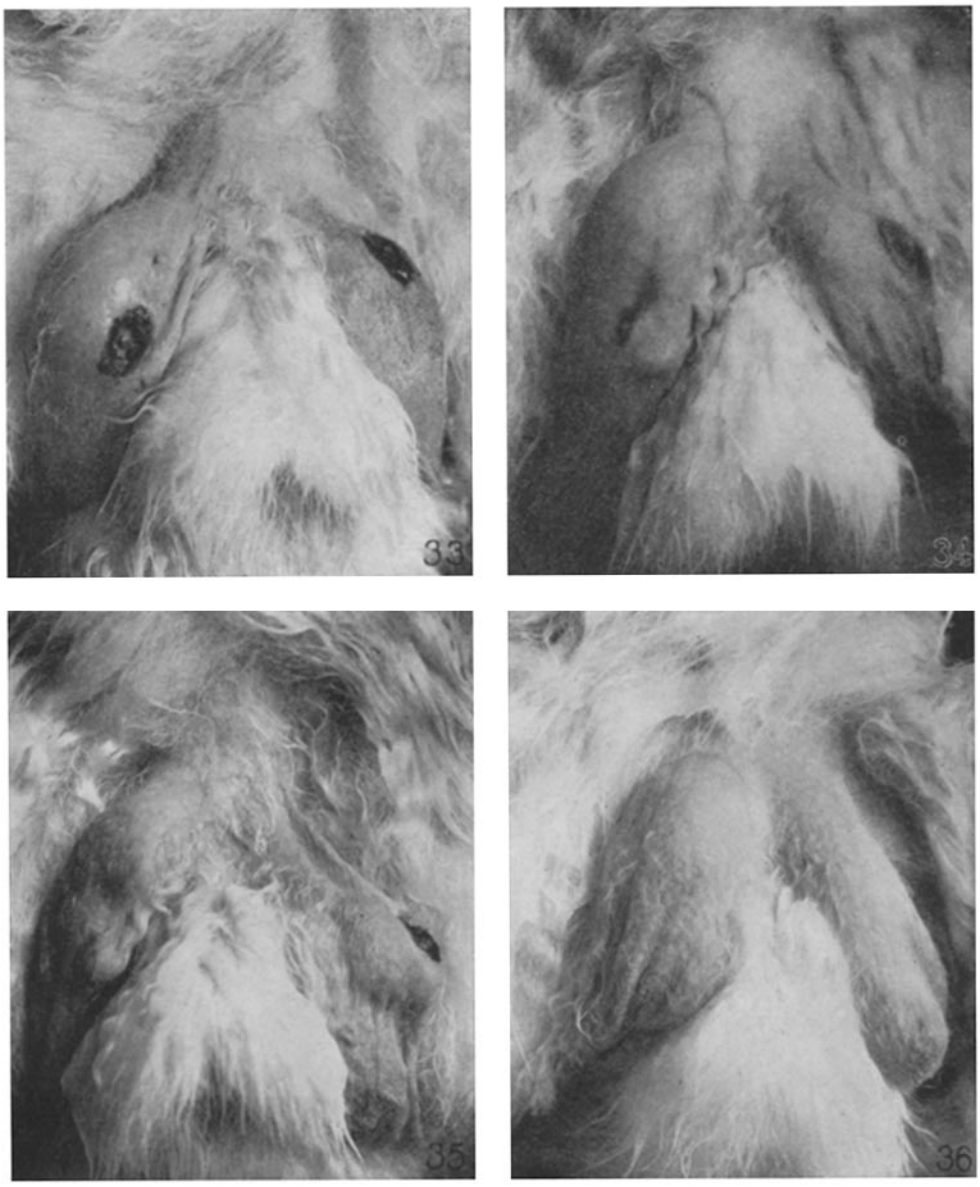

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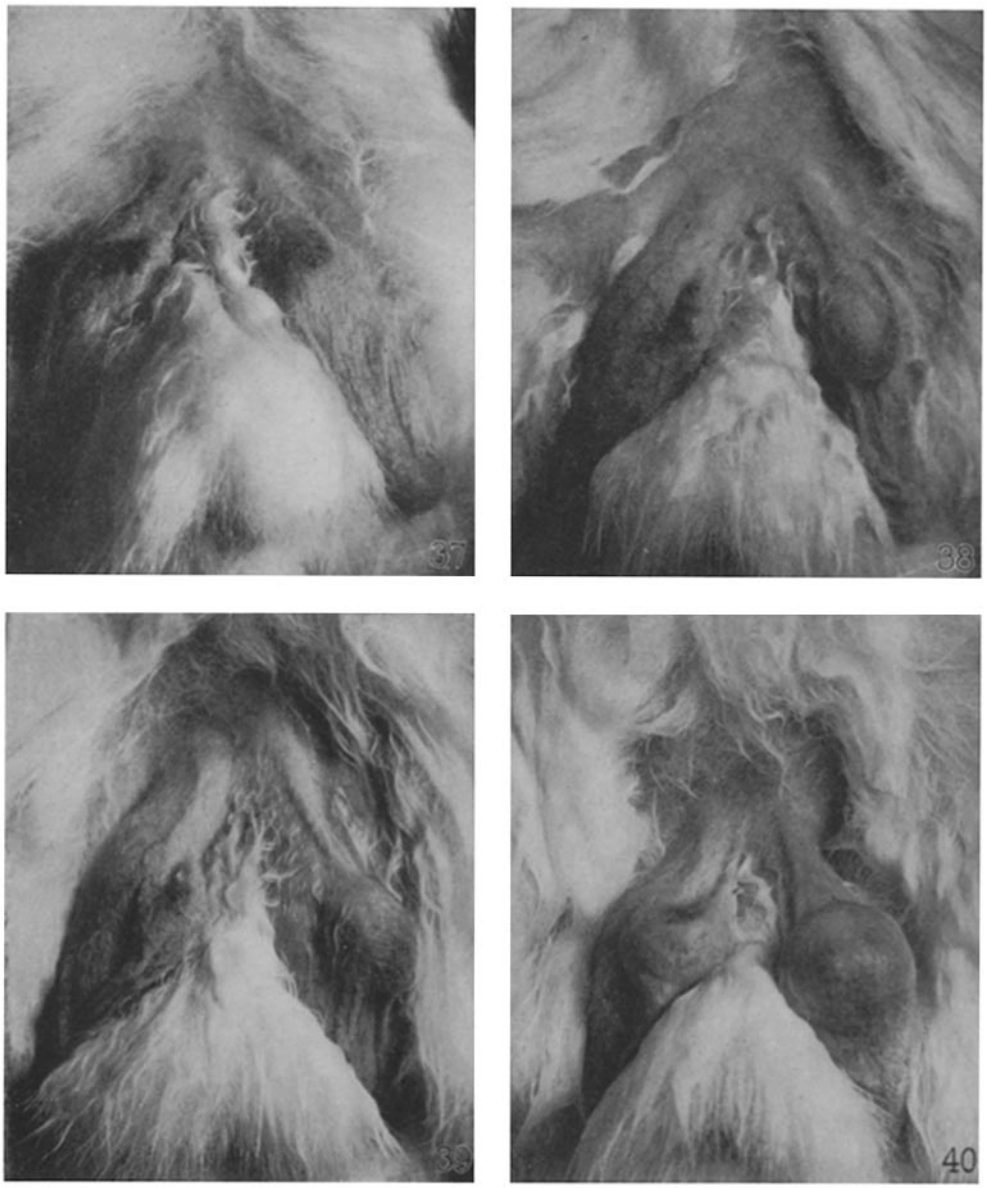

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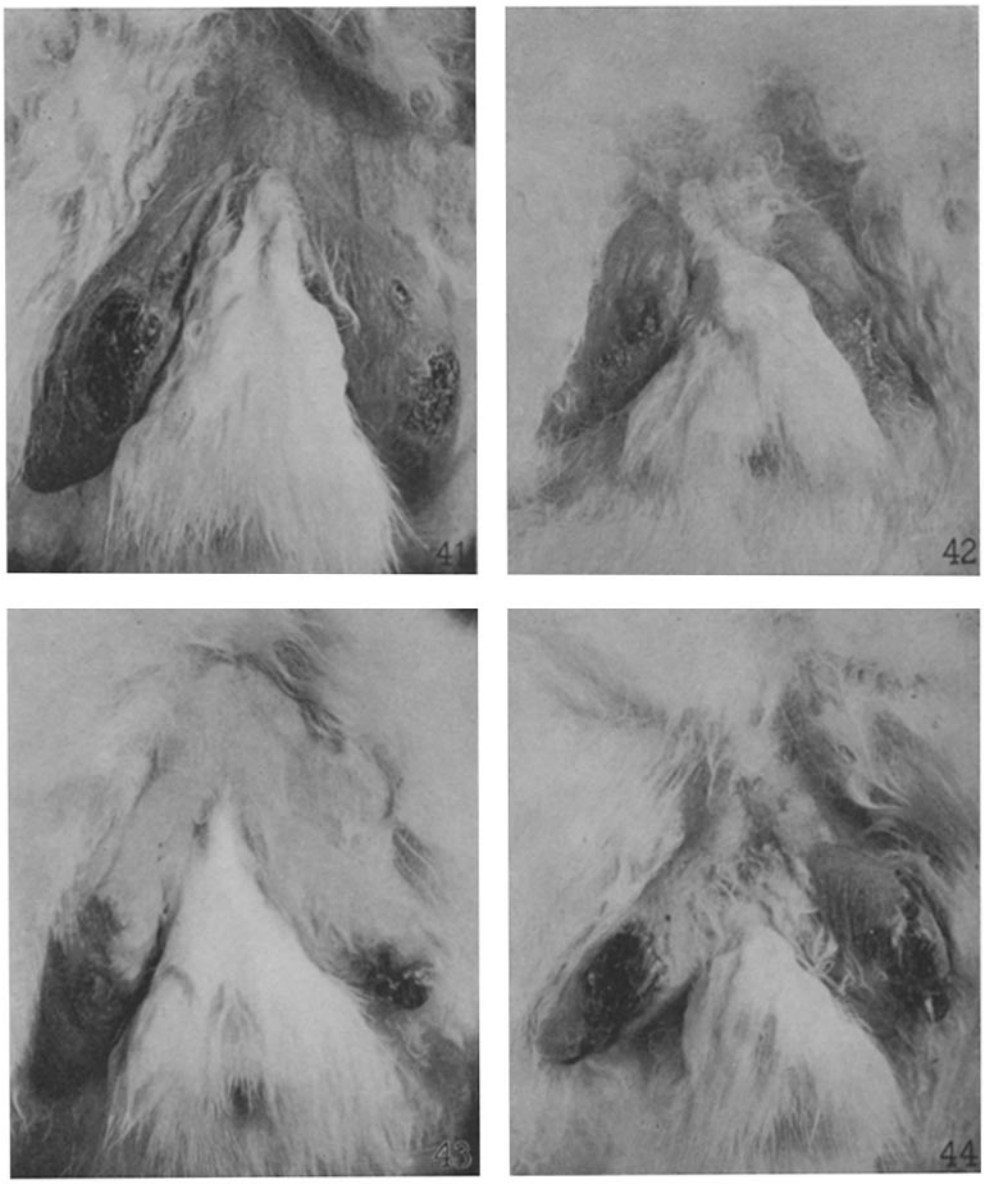

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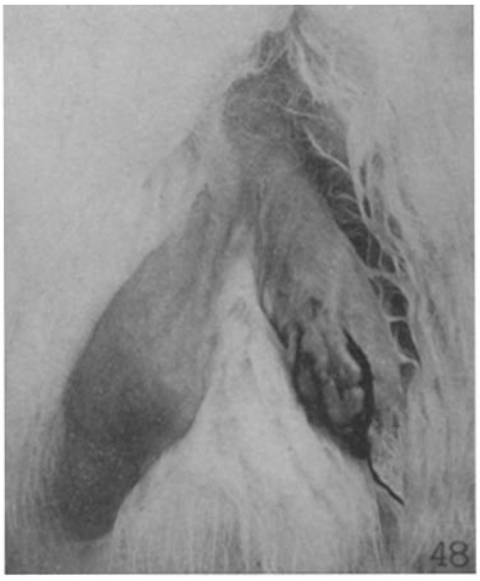

(Brown and Pearce: Experimental syphilis in the rabbit. II.)