EXPERIMENTAL SYPHILIS IN THE RABBIT.

IV. CUTANEOUS SYPHILIS.

PART 2. CLINICAL ASPECTS OF CUTANEOUS SYPHILIS.

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PLATES 59 TO 77.

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The character of the cutaneous affections which have been described following local inoculations of Treponema pallidum in the rabbit is sufficient to identify these conditions as manifestations of a syphilitic infection and to throw some light upon processes of reaction in the experimental animal. However, the lesions are but the objective signs or the elements of the cutaneous infection, and it will be necessary to give some account of the clinical history of these conditions before a definite place can be assigned to them as integral parts of a generalized infection.

It is the purpose of this paper, therefore, to present such facts concerning the occurrence, distribution, and fate of cutaneous lesions as will enable one to formulate a general conception of cutaneous syphilis in relation to other phases of the experimental infection. In following out this plan of presentation, detailed statements of quantitative relationships will be omitted for the sake of simplicity as well as to avoid any prejudice which might be created from an attempt to assign such values upon the basis of the material which is at present available. Obviously, this aspect of the subject is of importance in itself and will be considered in due time.

Character and Distribution of Cutaneous Lesions in Different Parts of the Body.

From the description of cutaneous lesions which has been given, it is perhaps apparent that these affections tended to preserve a cer-
tain order of distribution and that the character of the lesions present differed somewhat according to their location.

The parts most frequently involved were the hind feet and legs, the head, the front feet and legs, and the tail. This order of distribution was subject, however, to rather wide variations which corresponded in a measure with similar fluctuations in the incidence of different types of cutaneous affections. This is a fact of some importance, since the distribution of the lesions or the character of the lesions present in a given case was undoubtedly influenced to some extent by the particular organism with which the animal was infected. Further than this, the lesions did not occur indiscriminately over those parts of the body which have been mentioned but were confined, for the most part, to a few selected areas.

Lesions of the Head.

Among the animals studied by us, there was a large number which showed involvement of the skin about the head, and the lesions seen in this locality represented practically every form of cutaneous affection which has been described but with a decided predominance of processes of an infiltrative character. The points of especial predilection were certain parts of the face, the brows, the lids, the lips, the base and free portions of the ears, and the cheeks, and the affections peculiar to these areas will be taken up in the order given.

Face.—The lesions which occurred in the skin extending from the nose up over the forehead were chiefly small flattened areas of infiltration or slightly elevated papules, the usual location of which was the sides and bridge of the nose. The appearance presented by animals with affections of this type and the general distribution of the lesions may be illustrated by the photographs reproduced in Figs. 1 to 8. Some of these conditions were so apparent as to be recognized at a glance, but not infrequently there were no visible signs of abnormality and lesions could be detected only by careful palpation of the parts. Thus, the papule on the nose of the animal in Fig. 5 was made conspicuous by its location on a prominent part of the nose and in an area where the hair is short, while a lesion of essentially the same character in Fig. 6 gave no visible sign of its presence.

Lesions about the anus and sheath were not included among the cutaneous affections but with those of mucocutaneous borders, while perineal affections were entirely eliminated for reasons which will be stated below.
As a rule, facial lesions were multiple, bilateral, and symmetrical. The more common ones were of the type represented in Figs. 2, 4, 5, and 6. Occasionally, however, affections of a more pronounced character were seen such as those in Figs. 1, 7, and 8. These were usually single and occupied a position at or near the midline in the region of the bridge or sides of the nose.

Brows.—The brows were less often involved than the face but were the seat of a variety of lesions. Those which appeared to be most characteristic of this area were small indurated papules of the type shown in Figs. 9 and 14, together with focal areas of infiltration and necrosis identical with those of the face. Two such lesions are indistinctly seen in Fig. 4. In addition to these, papules of a larger type or even granulomatous lesions were observed in a few animals, a characteristic example of which is given in Fig. 10.

With two exceptions, the lesions which occurred on the brows were bilateral and were usually accompanied by similar conditions on the upper eyelids (Fig. 14).

Eyelids.—Localized infections of the eyelids, while comparatively common occurrences in the rabbit, gave rise to two groups of conditions which could not be clearly separated from one another. In some instances, the lesions arose from the cutaneous surfaces of the lids and appeared to represent affections of essentially the same status as those of the brows; in others, they were clearly marginal in origin and related to the transitional area, or the infection was confined to the conjunctival surface.

However, the general character of the conditions found upon the external surfaces of the lids may be described without attempting to make any sharp distinction as to their origin.

The simplest form of lesion on both the upper and lower lids was a small papular infiltration of the type shown in Fig. 11, and these were especially common in the marginal areas. Fleshy papules measuring several millimeters in diameter were occasionally seen on the upper lids also (Fig. 13), but the usual affection was a small indurated papule with surface ulceration (Fig. 12) or lesions of a papulosquamous type such as those in Fig. 14. These lesions were often bilateral and multiple and were not infrequently associated with similar affections of the brows.

The distinctive feature of the lesions on the lower lids was their size. As a rule, they were larger and of a more fleshy character than those of the upper lids and exhibited a constant tendency to encroach upon the free margin of the lid. Their surface was usually scaly or covered with small crusts (Figs. 15 and 16), and in two instances, large chancr-like lesions were formed which underwent central necrosis and ulceration as shown in Fig. 17.

Lesions of the lower lid were all unilateral and single.

Lips.—There were comparatively few animals which showed localized infections on the lips, with the exception of those in which the lesions were situated along the margins of the nasolabial folds. The only conditions seen were patches of infiltration analogous to those in Fig. 18 or small indurated papules of the
type shown in Figs. 5 and 6. Other conditions affecting the marginal area will be described elsewhere.

The lower lip and chin were very rarely affected. Thus far, we have seen only three animals with lesions in this location, and all of these were comparatively small papules or areas of infiltration one of which is illustrated in Fig. 19.

Base of the Ears.—The skin at the base of the ears and over adjacent parts of the cheeks and neck formed another area for the localization of cutaneous affections (Figs. 20 to 25 and 83 to 88). The lesions seen here were of two very different types and included processes varying from small papular infiltrations analogous to those in Fig. 20 to larger lesions of a circumscribed or diffuse character, (Figs. 21 to 25). In a few instances, large granulomatous masses such as those in Fig. 23 were seen, but the more common affections were small indurated papules or patches of diffuse infiltrations showing various forms of secondary alteration such as were described and illustrated in Part 1 of this paper. Not infrequently these were associated with similar processes on other parts of the ears or tended to spread from the basal area to adjacent parts of the ears as in Fig. 24.

By reference to the photographs illustrating these conditions, it will be seen that the position of greatest predilection for these affections was the lateral surface of the ears immediately below and at the sides of the intertragal incision. The lesions in this area were usually multiple; in some instances they were confined to one side, but in others they exhibited the most perfect bilateral symmetry (Fig. 23).

Ears.—The auricle was also the seat of cutaneous lesions in a number of animals. In the main, these were of the type of macular or small papular eruptions. The macular lesions have been described in detail and no further comment need be made here.

Upon the outer surface of the ears (Figs. 22 and 24 to 27), comparatively few lesions were seen, and, with the exception of that shown in Fig. 26, they were all situated on the lower portion of the ear and occupied one of four positions: the margins of the intertragal incision (Figs. 24 and 27), the medial surface of the ear (Fig. 25), and the area of the anterior or posterior marginal vessels (Fig. 22).

The majority of these lesions were flattened areas of infiltration covered by silvery or grayish yellow scales with occasional points of necrosis or ulceration covered by crusts; in a few instances they were small indurated papules.

Over the internal surfaces, three types of lesions were noted (Figs. 28 to 31). One of these was the macular erythema (Fig. 31) and another the small papular eruption (Fig. 30) which have already been described. These affections occurred chiefly upon the outer part of the ear and more often near the anterior than the posterior margin. They occurred singly, as in Fig. 28, or in groups, and occasionally exhibited a circinate arrangement or appeared to follow the course of the marginal vessels.

See Part 1 of this paper also: J. Exp. Med., 1920, xxxii, 445.
A third type of lesion which was seen only once was that shown in Fig. 29. This condition developed as a flattened area of infiltration with slightly elevated margins. The surface was first covered with epithelial scales and later by yellowish gray crusts as shown in the photograph. There was a single lesion of this type on each ear.

Individual lesions on both the internal and external surfaces of the ears varied from a few millimeters to a centimeter or more in diameter and were usually symmetrically placed upon the two ears.

Cheeks and Neck.—With the exception of the area at the base of the ears, there were few lesions seen on the cheeks and neck which could be identified as syphilitic. The small follicular lesions and their various modifications referred to in the preceding paper (Part 1) were the most common conditions observed. In addition, several animals showed a diffuse infiltration of the skin over the cheeks and sides of the neck with a loss of hair and a tendency to desquamation or exfoliation. There was one animal in which the area of involvement extended well down over the shoulder and resulted in the formation of two irregular patches of necrosis. These were the only definite lesions seen in this part of the body. One other animal showed a small flattened lesion of a scaly character in the triangular area at the back of the neck which was probably specific, since at the same time there was a profusion of definite skin lesions elsewhere.

Lesions of the Hind Feet and Legs.

The hind feet and legs of the rabbit hold the distinction of being the most common location of cutaneous lesions (Figs. 32 to 55). This applied especially to granulomatous lesions, and it was here that this type of affection reached its highest state of development. In addition to the granulomata, there were, however, rashes of various types, onychias, and paronychias.

Ordinarily, these affections produced but little change in the general appearance of the parts, and the conditions which one might note were in the main prominent swellings due to the presence of large granulomatous lesions or areas of necrosis and ulceration such as are shown in Figs. 32 to 34. Instances of this kind were comparatively rare, however, and as may be seen by reference to Figs. 35 to 38, which are photographs taken before and after removal of the hair, even marked affections of the skin usually produced only slight changes in appearance.

3 See the section on alopecia in Part 1 of this paper.
4 Fig. 8, Part 1.
The lesions on the hind feet and legs were generally located along the lateral margins of the feet more upon the dorsal than the plantar surface, and were distributed from the region of the tendo achillis to the base of the fifth toe. The positions of greatest frequency were the region of the tarsus and external malleolus, the base or tuberosity of the so called fifth metatarsal, the lateral and posterior surfaces of the heel and tendo achillis, and the region of the metatarsophalangeal joint. These peculiarities of distribution and the character of the lesions found in the various locations are brought out by the photographs reproduced in Figs. 36 to 55. It will be noted that the positions enumerated are in a sense pressure points or are skin areas overlying bony or tendinous prominences, and a very large proportion of the cutaneous lesions of the hind feet and legs occurred at these particular points.

Typical examples of the conditions described are illustrated in Figs. 35 to 38 and 39 and 40 which show the hind feet of two animals with marked skin involvement. By reference to the other figures of the series (Figs. 41 to 55), it will be seen that individual variations in the size, number, and location of the lesions were very great. In some instances, frank lesions of the dorsum of the foot or ankle were noted (Figs. 36, 37, and 50), and in their growth those which developed upon the sides of the feet extended in this direction rather than towards the plantar surface. However, plantar lesions or lesions which extended towards the plantar surface were also encountered in some instances (Figs. 51 to 53), and were usually located in the tarsal arch or more exactly in the cushion covering the head of the os calcis just posterior to the base of the fifth metatarsal. Lesions occupying this position are shown in Figs. 49, 51, and 52.

Comparatively few lesions were seen on the legs, and most of these were situated over the tendo achillis, usually not more than a centimeter or so above its attachment to the calcaneus. Occasionally, however, they occupied a much higher position, as in Fig. 46, and in two instances lesions were found on the anterior surface of the shins. One of these is shown in Fig. 36.

The characteristics of distribution described were more closely observed by granulomatous lesions than by those of an infiltrative character. The latter manifested a greater tendency to spread in a linear fashion along the outer side of the foot and might, as in Fig. 54, form an almost continuous line of lesions extending from ankle or heel to the toe, but even here the tendency to localize or to concentrate at certain points was still apparent (Figs. 53 to 55).

As may be gathered from an examination of the accompanying illustrations, lesions of the hind feet and legs were occasionally single
or multiple and unilateral, but in the vast majority of cases they were multiple, bilateral, and symmetrical in their distribution.

After what has been said in regard to similar affections elsewhere, no description of the lesions seems necessary. The illustrations are sufficient in themselves to convey the necessary impressions of the variations in size and character of the several types of lesions to enable one to form a proper conception of the subject.

In addition to the lesions described, mention may be made of the occasional presence of such conditions as onychia and paronychia.

Lesions of the Front Feet and Legs.

The prevailing lesions of the front feet and legs were of essentially the same character as those of the posterior extremities but with a larger proportion of infiltrative processes. The common location of these affections was the extensor and lateral surfaces of the fore arms and the dorsum and sides of the feet as shown in Figs. 56 to 70.

The granulomata were usually situated on the fore arms just above the carpus or on the lateral margins from the level of the carpus to the base of the fifth toe; small multiple lesions were sometimes distributed over the carpus and dorsum of the feet as in Figs. 62 and 65. Occasionally also granulomatous lesions were found at a much higher level on the fore arm (Fig. 64), and in rare instances were located on the flexor instead of the extensor surface (Fig. 59).

The general distribution of the cutaneous infiltrations was much the same as that of the granulomata, but they differed in certain respects. In the case of the infiltrations, the lesions usually appeared along the ulnar margins of the fore arm and carpus instead of the extensor surfaces; they almost invariably extended over the dorsum and sides of the feet (Figs. 66 to 73) and frequently involved the median as well as the lateral surfaces (Figs. 69 and 71). In one instance, large crustaceous lesions were formed about the elbow (Figs. 74 and 75).

The cutaneous granulomata not infrequently appeared as single lesions of a large size or as multiple affections of one fore arm. In contrast to this, the infiltrations were in all cases multiple affections and bilaterally symmetrical in their distribution.

Other conditions affecting the fore paws were onychia and paronychia which were most common on the outer or fifth toe (Figs. 74 and 75), but in several animals other toes as well were involved (Fig. 71).

In connection with lesions of the fore arms, attention may be called to the frequent occurrence of edema during periods of marked activity on the part of
various types of cutaneous lesions, since examples of this condition may be seen by reference to Figs. 59 and 61. In the first of these, a very pronounced swelling about the carpus and foot can be made out, and in Fig. 61, there is a marked edema of the skin and subcutaneous tissues which extends beyond the middle of the fore arm.

In other instances where no edema was present, it was noted that shaving an area where there was syphilitic involvement or the infliction of slight trauma by other means which had no effect upon the skin of a normal animal was frequently sufficient to cause a rapid development of edema which lasted sometimes for days. This urticarial reaction of the skin, if it may be termed such, was not peculiar to cases of cutaneous infection but occurred also in animals in which the lesions were situated in the deeper structures, as in the bones. It suggests, therefore, the action of some toxic influence upon the vascular mechanism of parts adjacent to foci of active syphilitic infection, and this feature of the infection is worthy of consideration in connection with the various cutaneous and other reactions which occur subsequent to the administration of therapeutic agents.

Lesions of the Tail.

Localized infections of the tail form a group of conditions which is somewhat obscure. Uhlenhuth and Mulzer (1) reported "tail tumors" as a frequent occurrence following generalized inoculation of rabbits, and the condition thus described was in most instances a bulbous swelling of the distal end of the tail. Except in this connection, we have seen no mention of tail lesions in the literature. Such conditions do occur, however, and are probably of rather frequent occurrence, but the difficulties surrounding an examination of this part of the body are so great that we were unable to give it the attention which it probably deserved and hesitate, therefore, to commit ourselves as to the frequency and importance of this class of affections.

Again, we have been able to recognize two conditions affecting the skin of the tail (Figs. 76 to 82). The one most commonly observed was a granulomatous lesion generally involving the ventral surface or sides of the tail, rarely the dorsal (Figs. 76 to 81). As may be seen in the accompanying illustrations, these lesions were either single or multiple, and while they occurred at various levels, they were
more often found on the proximal and middle thirds than towards the outer end of the tail.

The second type of affection was that shown in Fig. 82. In these cases, the skin involvement was of an equally marked character, especially towards the end of the tail, but partook more of the nature of a diffuse infiltration. The photograph reproduced in Fig. 82 shows a thinning of the hair and the presence of bald patches over the ventral surface of the tail which characterized this group of affections. Towards the outer end, there is also a small area of necrosis. In one case of this kind, the skin covering the entire tail underwent necrosis and sloughed away.

The six cases of cutaneous syphilis of the tail which have been used for illustration are such as might be recognized without any considerable difficulty, and it will be noted that none of them conforms to the "tail tumor" type of lesion. Bulbous expansions of the end of the tail were observed, however, in a few animals but were always of a relatively slight degree and were difficult to detect because of the fact that the physical alterations present were within the range of normal variations in tail structure. These variations are so great that unless one has an accurate record of the tail of each animal before inoculation or the pathological alterations which take place are quite marked, little can be determined by palpation and the fur must be removed before inspection will be of any material assistance. These procedures we were unable to carry out as a routine part of our work and we are not in a position, therefore, to speak with any degree of assurance as to conditions other than those observed.

Lesions of the Trunk.

With the exception of the perineum, few instances of cutaneous lesions involving the trunk have come under our observation. As previously stated, alopecia was noted in a number of animals, and after removal of the hair from localized areas some peculiar conditions were observed which may or may not have been syphilitic. This is not to be interpreted as evidence that this portion of the body remains uninvolved. On the contrary, it is known that lesions may occur upon the trunk, since a pronounced eruption on the back was one of the conditions described by Grouven (2) in the first case of generalized syphilis reported. It does mean, however, that under
ordinary circumstances, marked involvement such as one frequently observes in other parts of the body is far less common on the trunk. It should be pointed out also that the regions in which minor lesions were most frequently observed were those which were most accessible to examination, and when it is recalled that some of these lesions are extremely inconspicuous, it seems not unlikely that many such affections might escape detection altogether if situated upon the more thickly covered portion of the body. The occurrence of cutaneous lesions of the trunk must be regarded, therefore, as problematical and a field for future investigation.

As regards the perineum, it may be said that lesions in this locality, including those of the genitalia as well as the surrounding skin surfaces, were quite numerous and included two classes of affections, one representing conditions of cutaneous origin and the other affections of the mucocutaneous borders.

The first of these groups comprised lesions which for the most part were closely connected with the seat of inoculation, and we have avoided placing too much stress upon them lest some confusion might arise between extensions from primary lesions and generalization of the infection as it is commonly understood. However, the descriptions of scrotal lesions given in the preceding papers (3–6) will apply equally well to those which arise in this area as a result of generalization of the virus. Other lesions of the perineum will be described in connection with affections of mucocutaneous borders.

Clinical History of Cutaneous Lesions.

An exact statement of the time of occurrence, the duration, and the relative frequency of different types of cutaneous lesions in the rabbit can hardly be given without entering into a detailed analysis of the experimental conditions under which the lesions developed, and must be deferred, therefore, until the subject can be approached from this standpoint. There are, however, certain facts concerning the clinical history of these affections which may be recorded, some of them in greater detail than others.

Cutaneous Eruptions.—The cutaneous eruption in the rabbits usually consisted of only a few lesions occurring singly or in small
groups upon some one part of the body such as the head or the feet and legs. Occasionally, the lesions were more numerous and more widely distributed, several parts of the body being involved at about the same time or in rapid succession to one another.

The order in which the lesions appeared was somewhat irregular. It was not uncommon for several or all of them to make their appearance at about the same time. In other instances, one or two lesions developed, and no others were detected for a week or more when new lesions appeared and were followed by others at rather long and irregular intervals which at times extended over several months, or, after the appearance of the first lesions, others developed at short intervals until the eruption was complete.

How many distinct periods of eruption might occur is impossible to say, since the majority of the animals were not held for any great length of time. Among those which were kept under observation for a year or more, some showed only a single period of cutaneous eruption, while in others, there were several such periods separated by long or short intervals during which no lesions were present or no new lesions appeared.

In some instances, the consecutive eruptions consisted of lesions situated in places not previously involved, while in others, they might be regarded more as relapses than as new eruptions, since the new lesions developed at the site of older ones.

It was usually but not invariably the case that the lesions of the first eruption were of a larger type and more numerous than those of succeeding crops. This applied especially to the granulomata, an instance of which may be seen by comparing Figs. 39 and 40 with Figs. 41 and 42. Figs. 39 and 40 represent the first cutaneous eruption on the hind feet. These lesions healed completely and remained healed for between 4 and 5 months at which time two of them recurred (Figs. 41 and 42).

Another very important feature of the cutaneous eruption was the apparent influence exerted by one lesion or group of lesions upon another. This was best shown in instances where multiple lesions occurred in the same locality, as upon the fore arms and wrists of the animal in Figs. 62 and 63. When, as in this case, a number of lesions made their appearance at about the same time, the growth of most of
them was abortive, and only one or two developed to any considerable extent. It may be recalled that this same condition was pointed out in connection with the development of multiple lesions of the scrotum.

The inhibition thus exerted by one focus of reaction upon another is a phenomenon of the most fundamental importance and furnishes the key to an explanation of many conditions which characterize the experimental infection. In the present instance, it probably accounts for the existence of so few lesions and the unusual size which individual lesions frequently attain.

From this description of cutaneous eruptions, it is apparent that they were exceedingly variable as to the number and character of the lesions present at a given time, the manner of their appearance, and the number of eruptions which might occur in a given case.

Time of Occurrence of Cutaneous Lesions.—Cutaneous lesions were among the earliest manifestations of a generalized infection, but the time of their appearance was subject to very wide variations. This appeared, however, to be partly due to differences in experimental conditions. The first cutaneous eruption usually appeared between the 2nd and 4th months after inoculation and on the whole was earlier in the case of the granulomata than with lesions of an infiltrative character. The earliest recorded time for the appearance of cutaneous lesions was 3 weeks after inoculation, and the longest interval between inoculation and the first cutaneous eruption was 2 years and 8 months; the next longest was between 6 and 7 months. It may be said, therefore, that the first cutaneous eruption appeared at from 6 weeks to 6 months after inoculation with occasional cases occurring earlier or later, depending upon the conditions of the infection.

As regards the occurrence of subsequent eruptions, or the interval between eruptions, very little can be said. In the few animals which were held for any considerable length of time, the period of active eruption rarely extended beyond 4 to 6 months after inoculation. One case has been mentioned, however, in which the first lesions were noted 2 years and 8 months after inoculation. A second eruption occurred in this animal 3 years and 5 months after inoculation, and a third eruption 2 months later. Lesions of this second group are shown in Fig. 52.
Two other animals of our series showed repeated periods of active cutaneous eruption extending over more than 2 years from the time of inoculation, but during this time they were never entirely free from lesions. A third animal now under observation has followed much the same course for a period of 8 months. In a fourth animal, as in the case of the one cited above, there were three sharply separated periods of eruption spaced at intervals of approximately 7 months. These few cases will serve to indicate the difficulty in attempting to set any time limits upon the occurrence of cutaneous lesions when so few animals were kept under observation for any considerable period of time, but they also indicate that cutaneous affections may occur during the late as well as the early stages of the infection.

Clinical Course of Cutaneous Lesions.—The clinical course of the cutaneous infection was essentially the same as that of the testicular or scrotal lesions. The tendency to pursue a periodic or relapsing course was apparent in the development and resolution of individual lesions as well as in the recurrence of healed lesions and the development of successive crops of eruptions.

These features of the skin reaction were again most evident in the granulomata, the growth of which usually proceeded by irregular stages interrupted by periods of inaction or even regression. Relapse of partially or completely healed lesions, which is but an exaggerated form of this reaction, was a comparatively common occurrence and may be illustrated by the series of photographs reproduced in Figs. 83 to 88 representing the state of a lesion at intervals of 90, 97, 105, 133, 141, and 160 days respectively after inoculation. This type of phenomenon was practically constant, but we have little evidence upon which to base an estimate of the frequency of relapse of completely healed lesions. It may be mentioned, however, that of the few animals kept under observation for a year or more, a number showed recurrence, and with three of them there were several periods of complete healing of individual lesions followed by relapse.

Duration of Cutaneous Lesions.—Spontaneous regression and healing were the common fate of all cutaneous lesions, but great differences were found in the duration of different types of lesions as well as of individual lesions. As was mentioned elsewhere, the macular erythemata were characteristically of short duration, sometimes dis-
appearing within 24 to 48 hours and rarely persisting for more than a few days. In like manner, small infiltrations not infrequently disappeared spontaneously within a few weeks after they were first noted.

On the other hand, granulomatous lesions and many of the infiltrations, especially the papular lesions of the brows and lids, were more enduring as a rule. For example, the papular lesions of the brows and lids shown in Fig. 14 lasted more than a year before they completely disappeared, and the lesion at the base of the toe in Fig. 48 is one of a small group which showed an even greater persistence, having lasted for more than 2 years. These were exceptional cases, however, and from the data available, it would appear that the average duration of cutaneous lesions was hardly more than 2 to 4 months, although in a fair percentage of animals, this period might be prolonged by several months.

The duration of active skin infection was somewhat longer than that of the individual lesion, since all the lesions present did not pursue a parallel course of changes. The available data bearing upon this feature of the infection, however, are insufficient to permit of an estimation of the time which such infections might endure.

Detection and Diagnosis of Cutaneous Lesions.

In view of the great frequency with which cutaneous lesions appear to follow local inoculations of *Treponema pallidum* in the rabbit and the fact that so few of these conditions have been described, it seems well to refer briefly to the detection and diagnosis of this class of affections.

The first essential to the detection and diagnosis of cutaneous lesions is obviously a knowledge of the character and distribution of these affections, and this we have attempted to supply. Large granulomatous lesions such as those in Figs. 32 to 34 which produce striking irregularities in the contour of the affected parts, or lesions which have resulted in a considerable destruction of the skin surface, as in Figs. 74 and 75, may be seen almost at a glance if one knows where to look for them. Prominent swellings and surface erosions are not always present, however, and at all events are late phenomena. The great majority of the lesions which affect the feet, legs, and tail are
concealed from view and can be detected only by palpation, rarely by inspection. Lesions about the head are more exposed as a rule, and careful inspection of the regions in which they are known to occur is highly essential, but with the exception of a few areas such as the ears and the eyelids, even here the chief reliance for the early detection of cutaneous lesions must be placed upon palpation.

The technique of this operation consists in picking up the skin and gently rolling it between the thumb and finger. In this way, one is soon capable of detecting the slightest thickening or irregularity in the skin, and if the hair is removed and these initial changes are carefully followed from day to day, little difficulty will be experienced in arriving at a diagnosis.

If the animals are separately caged and well cared for, few conditions will arise which are apt to be confused with typical syphilitic lesions, even the smaller infiltrations and erosions. Apart from diseases of the skin, such as mange, and traumatism inflicted by the animal itself, which are very readily recognized, the only three conditions which need be considered are small focal abscesses, old scars, and focal thickenings due to a new growth of hair. The first two conditions are, in the main, trunk affections and should not be confused with syphilitic lesions. The third condition may occur anywhere and is especially troublesome about the face, but clipping of the hair and careful observation will usually enable one to arrive at a correct diagnosis. Examination for spirochetes may or may not prove helpful in these cases and may even defeat the object of the examination by causing regression of a syphilitic lesion before a characteristic condition has been established.

CONCLUSIONS.

The description of cutaneous syphilis in the rabbit following local inoculation is incomplete in many respects but is sufficient to indicate that a generalized infection of the skin does occur in a large number of animals—just how often and under what circumstances we shall not attempt to say.

It is apparent, however, that the cutaneous affection is a very characteristic one. The lesions themselves bear the marks of a varied
but definite pathological process identical in all respects with the reaction set up in the scrotum by local inoculation of *Treponema pallidum*. The character of the lesions and, withal, their great multiplicity, the time relations existing between inoculation and the appearance of the cutaneous lesions, the occurrence of successive crops of eruptions, the relapsing course of the disease, and the preservation of a fixed order of distribution of the lesions, are highly suggestive of cutaneous syphilis in man, and it is believed that as more is known of the experimental infection and with better adaptation of organisms, the analogy will become even closer.

**SUMMARY.**

From the study of a large number of rabbits with generalized cutaneous syphilis following local inoculation with *Treponema pallidum*, lesions were found most often about the hind feet and legs, the head, the front feet and legs, and the tail. There was further evidence of a selective distribution of cutaneous lesions in the fact that, on a given part of the body, the lesions were usually confined to a few restricted areas. About the head, they occurred almost exclusively on the sides and bridge of the nose, the lids, the brows, the lips, and the base and free portions of the ears. On the front feet and legs, the seat of predilection was the extensor and lateral surfaces of the fore arm, the carpus, and the feet, while on the posterior extremities they were situated upon the dorsum and lateral surfaces of the feet and ankles from the level of the tendo achillis to the base of the fifth toe. The positions of greatest frequency were the region of the tarsus and external malleolus, the base of the fifth metatarsal, the lateral and posterior surfaces of the heel and tendo achillis, and the base of the fifth toe. In many instances, the positions of predilection were exposed positions or areas of skin covering bony or tendinous prominences.

It was also found that the character of the lesions differed somewhat in the various locations. The lesions of the head were mostly small circumscribed papules or processes of diffuse infiltration; on the fore arms and feet, affections of this type were about equally divided with larger granulomatous masses of a chancre-like character, while on
the hind feet and legs, granulomatous lesions were far more numerous than those of any other type and frequently reached a very large size.

The cutaneous eruption usually consisted of only a few lesions confined to some one part of the body, but occasionally they were more numerous and more widely distributed. In this connection, it was noted that when multiple lesions appeared in a given area at about the same time, the growth of most of them was abortive, and, as a rule, only one or two developed to any considerable size. Special emphasis was placed upon this phenomenon of inhibition as a factor of fundamental importance in the experimental infection.

From clinical observation, it was found that, as a rule, the first cutaneous eruption occurred at from 2 to 4 months after inoculation but might occur either earlier or later, depending upon the circumstances in the individual case. The earliest eruptions appeared 3 weeks after inoculation and the latest 2 years and 8 months, but, as a rule, the time between inoculation and the appearance of the first eruption did not exceed 4 to 6 months.

Successive crops of cutaneous lesions appeared in a number of animals usually within the first 6 months after inoculation. In a few instances, however, there were repeated eruptions extending over a period of 2 years or more, the longest recorded period being 3 years and 7 months.

The duration of individual lesions was found to be extremely variable, ranging from a few days in the case of a macular erythema to more than 2 years in the case of a few granulomatous lesions. The average duration of the lesions appeared to vary somewhat with the nature of the lesion but on the whole was not more than 2 to 4 months. No limits could be fixed, however, for the duration of an active skin infection as a whole.

Again, it was found that the cutaneous infection tended to pursue a periodic or relapsing course. This was seen in the mode of growth and resolution of individual lesions, the occurrence of successive periods of eruption, and the recurrence of completely healed lesions, all of which was interpreted as evidence of the essential relapsing nature of syphilitic infections.
BIBLIOGRAPHY.


EXPLANATION OF PLATES.

With the exception of Fig. 31 the illustrations are from unretouched photographs which represent the objects at their natural size. The time given is estimated from the date of inoculation unless otherwise stated.

PLATE 59.

FIGS. 1 to 4. Clinical appearance of animals with syphilitic lesions about the face.

FIG. 1. 58 days. An extensive infiltration of the frontal region showing loss of hair and exfoliation over the affected area.

FIG. 2. 138 days. Multiple foci of infiltration and necrosis distributed over the sides and bridge of the nose. There was a similar condition on the left side of the face.

FIG. 3. 249 days. A diffuse area of infiltration with some loss of hair and desquamation of epithelium involving a portion of the lip and the skin over the side of the nose.

FIG. 4. 188 days. Multiple focal lesions over the lower portion of the nose, the right upper lip, and the brows. Lesions were also present about the nares.

PLATE 60.

FIGS. 5 to 10. Syphilitic lesions of the face and brows.

FIG. 5. 69 days. Early papular lesion on the side of the nose.

FIG. 6. 98 days. Small nodular lesion, side of the nose, which was not visible until the hair was removed.

FIG. 7. 128 days. Circumscribed nodular lesion with central necrosis, situated on the lower portion of the bridge of the nose.

FIG. 8. 169 days. Extension and transformation of the lesion in Fig. 7.

FIG. 9. 138 days. Small papular lesions with apical necrosis on the brow.

FIG. 10. 112 days. Large nodular syphilide with central necrosis and ulceration on right brow.
PLATE 61.

Figs. 11 to 19. Syphilitic lesions of the lids, brows, and lips.

Fig. 11. 98 days. Early papular lesions on upper and lower lids. There are two small lesions on the margin of the upper lid and a single larger lesion on the lower lid.

Fig. 12. 108 days. Small indurated papule with surface ulceration on the margin of the upper lid.

Fig. 13. 134 days. Large papular syphilide, upper lid, with slight necrosis at the center and considerable desquamation of surface epithelium.

Fig. 14. 13 months. Multiple lesions of the upper lid and brow. These lesions were of the nature of small papular infiltrations covered by heavy epithelial scales.

Fig. 15. 80 days. Large nodular lesion, lower lid. This lesion was of an intense copper color with small patches of scales over its surface.

Fig. 16. 113 days. Nodular lesion of the lower lid similar to that in Fig. 15, showing foci of necrosis covered by crusts.

Fig. 17. 84 days. Large granulomatous lesion of the lower lid. The center is necrotic and covered by a thick crust.

Fig. 18. 65 days. Circumscribed area of infiltration, right upper lip. The surface of the lesion is necrotic and covered by a crust.

Fig. 19. 8 months. Multinodular area of infiltration on the chin. This lesion was of a deep copper color and showed several areas of exfoliation.

PLATE 62.

Figs. 20 to 23. Syphilitic lesions of the ears, basal region.

Fig. 20. 53 days. Two small areas of infiltration in the skin marked by arrows. These lesions developed no further than the condition here shown.

Fig. 21. 113 days. Multiple nodules in the skin at the base of the ear.

Fig. 22. 101 days. Small circumscribed area of infiltration with central necrosis just below the intertragal incision. A second lesion is seen posterior to this and a third on the anterior surface of the ear. All these lesions showed a central area of ulceration and a marked tendency to accumulation of epithelial scales.

Fig. 23. 128 days. Large granulomatous lesions at the base of the ears showing bilateral symmetry of this class of affection. A few small areas of infiltration are also seen above the nodular lesions on the left ear.

PLATE 63.

Figs. 24 to 29. Syphilitic lesions on the free portions of the ears.

Fig. 24. 8 months. The same animal as in Fig. 22. Spreading patches of infiltration on the lateral surface of the ear.
FIG. 25. 8 months. The same animal. Syphilitic lesions on the median surface of the ear. One of these was a very small area of infiltration (marked by arrow). The other shows an area of necrosis surrounded by a zone of infiltration.

FIG. 26. 104 days. Indurated nodular lesion on the anterior and outer surface of the ear.

FIG. 27. 13 months. Diffuse area of infiltration with exfoliation and necrosis spreading along the anterior margin of the ear.

FIG. 28. 60 days. Circumscribed nodular lesion on the inner surface of the ear, at an early stage of its development.

FIG. 29. 140 days. Circumscribed area of infiltration with raised edges and necrotic center situated on the anterior margin of the inner surface of the ear.

PLATE 64.

FIG. 30. 97 days. Multiple papular lesions on the inner surface of the ear showing circinate arrangement and bilateral symmetry.

FIG. 31. 132 days. Erythematous patches in the ears showing bilateral symmetry.

PLATE 65.

FIGS. 32 to 34. Clinical appearance presented by animals with large granulomatous lesions of the hind feet.

FIG. 32. 122 days. There are four large granulomatous nodules along the outer side of the right foot; on the left, there is a single large lesion in the region of the metatarsal and a second on the outer side of the heel.

FIG. 33. 122 days. Lateral view of the right foot of the same animal.

FIG. 34. 177 days. The same foot at a later date showing the appearance presented after extensive necrosis and ulceration had taken place.

PLATE 66.

FIGS. 35 to 38. Nodular or granulomatous lesions of the hind feet and legs.

FIG. 35. 69 days. Anteroposterior view before removal of the hair.

FIG. 36. 81 days. Appearance presented at a slightly later date with hair removed. The nodular swellings over the outer portions of the fifth metatarsals are due to periosteal lesions.

FIGS. 37 and 38. Lateral views of the same feet. Note especially the character and distribution of the lesions.

PLATE 67.

FIGS. 39 to 42. Nodular or granulomatous syphilides of the hind feet and legs.

FIGS. 39 and 40. 115 days. Right and left hind feet of the same animal showing the character and location of lesions and bilateral symmetry.
FIGS. 41 and 42. 10 months. Hind feet of the same animal showing recurrent lesions at the base of the fifth metatarsals. Note the relative size of the lesions as compared with the original lesions in Figs. 39 and 40.

PLATE 68.

FIGS. 43 to 46. Granulomatous lesions of the hind feet and legs.

FIGS. 43 and 44. 154 and 148 days respectively. Right and left hind feet of the same animal showing single chancre-like lesions, one over the external malleolus and the other on the lateral and posterior surface of the tendo achillis just above the heel.

FIG. 45. 76 days. Granulomatous lesions over the tendo achillis, side of the heel, and base of the fifth metatarsal.

FIG. 46. 125 days. Large granulomatous lesion situated high up on the lateral and posterior surface of the tendo achillis.

PLATE 69.

FIGS. 47 to 50. Atypical distribution of granulomatous lesions on the hind feet.

FIGS. 47 and 48. 2 years and 2 months. The same animal. Single granulomatous lesions involving the heel of the left foot and the base of the fifth toe on the right. These lesions are the same as those shown in Figs. 32 to 34.

FIGS. 49 and 50. Left and right hind feet of the same animal.

FIG. 51. 75 days. Large granulomatous lesion on the outer and plantar surfaces of the tarsus and a smaller lesion over the tuberosity of the fifth metatarsal. There is a third lesion on the plantar surface at the base of the fifth toe.

FIG. 52. Lesions identical with those in Fig. 51. The point of chief interest is the time of their occurrence which was 3 years and 5 months after inoculation.

FIG. 53. 68 days. Discrete infiltrations over the lateral surface of the foot with a tendency towards a plantar position.

FIGS. 54 and 55. 15 months. Hind feet of the same animal. Multiple infiltrations distributed over the lateral margin of the foot. In Fig. 54, the lesions show necrosis, some exfoliation, and a tendency to fuse with one another.
PLATE 71.

Figs. 56 and 57. Nodular or granulomatous lesions of the front feet and legs.
Fig. 56. 81 days. Multiple nodular lesions over the extensor and lateral surfaces of the fore arms and feet. Note character and location of the lesions.
Fig. 57. 69 days. The same feet at a slightly earlier period before removal of the hair.

PLATE 72.

Figs. 58 to 61. Lateral views of the same animal as that in Figs. 56 and 57. Note the presence of a lesion on the flexor surface of the fore arm and the edematous swelling shown about the carpus and foot in Fig. 59 and extending to the middle of the fore arm in Fig. 61.

PLATE 73.

Figs. 62 to 64. Nodular and granulomatous lesions of the fore arms and feet.
Fig. 62. 113 days. Early multinodular affection with lesions on the extensor surface of the fore arms, carpus, and dorsum of the feet.
Fig. 63. 128 days. Later stage in the development of the same lesions. Note the disappearance of most of the lesions shown in Fig. 62 and marked development of single lesions on each fore arm.
Fig. 64. 84 days. Large chancre-like lesion on the extensor surface of the fore arm situated at an unusually high level.
Fig. 65. 60 days. Early nodular syphilides, dorsum and lateral surface of the foot. The prominent swelling over the carpus was due to a periosteal lesion.

PLATE 74.

Figs. 66 to 70. Infiltrative lesions on the fore arms and feet.
Figs. 66 and 67. 202 days. Right and left front feet and legs of the same animal. The lesions here shown were in the beginning parchment-like areas of infiltration (Fig. 66) which underwent necrosis and ulceration (Fig. 67).
Fig. 68. 138 days. Appearance presented by an early lesion similar to those in Figs. 66 and 67. The presence of a lesion is suggested by partial loss of hair and discoloration of the skin shown on the lateral surface of the carpus.
Fig. 69. 157 days. Diffuse infiltration on fore arm, carpus, and dorsum of the feet. Hair clipped.
Fig. 70. 184 days. Lateral view of the lesion in Fig. 69, taken during a period of marked activity.

PLATE 75.

Figs. 71 to 75. Cutaneous infiltrations, front feet and legs.
Fig. 71. 15 months. Frontal view of the feet to show lesions present over the median surface of the toes.
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FIGS. 72 and 73. The same as Fig. 71, showing lesions on the lateral surface of the fore arm and at the base of the toes.

FIGS. 74 and 75. 8 months. There is an area of widespread infiltration over the elbows with surface necrosis, exfoliation, and the formation of weeping patches; there is also a well marked paronychia of the fifth toe on both sides.

PLATE 76.

FIGS. 76 to 82. Syphilitic lesions of the tail.

FIG. 76. 77 days. Early multiple granulomatous lesions on the ventral and lateral surface of the tail.

FIG. 77. 76 days. A large granulomatous lesion near the base of the tail with diffuse infiltration of the skin over the outer portion indicated by the glistening character of the surface.

FIG. 78. 65 days. Multiple lesions of a nodular character on the distal portion of the tail. There are beginning necrosis and ulceration of the largest of the lesions.

FIG. 79. 76 days. The same animal, showing extension of the tail involvement together with necrosis and ulceration of the affected area.

FIG. 80. 113 days. Circumscribed nodular lesions, middle and outer third of the tail. The scar of a former lesion is seen in the area marked with an arrow.

FIG. 81. 68 days. A group of three nodular lesions situated on the ventral and lateral surfaces near the base of the tail.

FIG. 82. 109 days. A diffuse infiltrative process involving the skin of the tail over its entire extent. Note the alopecia over the ventral surface of the tail and a small area of necrosis and ulceration near its distal extremity.

PLATE 77.

FIGS. 83 to 88. Periods in the history of a cutaneous lesion.

FIGS. 83 to 85. Stages of active development of the lesion. 90, 97, and 105 days.

FIG. 86. 133 days. Marked regression of the lesion.

FIG. 87. 141 days. Definite renewal of activity.

FIG. 88. 160 days. A further stage in the growth of the lesion.
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