EXPERIMENTAL SYPHILIS IN THE RABBIT.

IV. CUTANEOUS SYPHILIS.

PART I. AFFECTIONS OF THE SKIN AND APPENDAGES.

BY WADE H. BROWN, M.D., AND LOUISE PEARCE, M.D.

(From the Laboratories of The Rockefeller Institute for Medical Research.)

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In the preceding papers of this series (1-4), experimental syphilis in the rabbit has been presented from the standpoint of the phenomena of the infection which develops about the site of the inoculation. Ordinarily, these are the only manifestations of infection which are observed in the rabbit, but under certain circumstances, a generalized disease may be produced which is analogous in many respects to that of man, and in taking up the generalized infection, it will be necessary to give a brief résumé of the development of this phase of the subject in order that our work may appear in the proper relation to that of other investigators.

When it had been clearly established that the syphilitic infection could be transmitted to rabbits and maintained with undiminished virulence through successive generations of transfers, interest began to be centered upon problems of a generalized infection. From the outset, opinion was divided as to whether the infection in the rabbit became generalized as in man or remained essentially a localized infection. This division of opinion was in part an outgrowth of the controversy in regard to generalized infections in the lower monkeys and in part a result of experimental observation.

At all events, the development of lesions at points remote from the site of inoculation appeared to be an exceptional occurrence. The first instance of an infection of this kind was reported by Grouven in a series of communications beginning in 1907 (5-8). This case has become classic, and it is worthy of note that it still is the most pronounced example of a generalized infection following local inoculation which has been recorded in the literature. In fact, with a few exceptions, this animal exhibited all the manifestations which have since been
recognized as characteristic of generalized syphilis in the rabbit. In brief, the conditions noted included weakness, emaciation, dyspnea, alopecia, papular and maculopapular lesions of the skin, infiltrations and rhagades about the anterior nares associated with a mucopurulent discharge, conjunctivitis, a metastatic keratitis, and an infection of the testicles, epididymis, and regional lymph nodes, all developing from a unilateral infection of the eye and subsequent enucleation of the infected organ. The first manifestations of a generalized infection appeared 8 months after inoculation and active lesions were still present when the animal died 9 months later.

These observations of Grouven stimulated a great deal of discussion concerning generalized syphilis in the rabbit. Grouven himself reported two other cases (8), and in 1909, a fourth case consisting of a double keratitis originating from a testicular inoculation was reported by Menzincescu (9). About the same time, Uhlenhuth and Mulzer (10) reported a case of metastatic involvement of the scrotum of an uninoculated testicle with papular lesions about the anus, and Truffi (11) reported two cases of keratitis in animals inoculated in the scrotum. Subsequently, other cases of generalized infection were added to this list, but the total number of cases recorded in the literature has remained comparatively small, and most of the animals have shown only a few lesions of a minor character.

In addition to occasional instances of animals showing generalized lesions, there were other facts, however, which indicated that the infecting organism itself was not confined to the region of inoculation. As has been mentioned, Ossola (12) and Truffi (11) demonstrated the presence of spirochetes in the inguinal lymph nodes of rabbits inoculated in the scrotum in 1909, and as early as 1908, Neisser (13) reported successful inoculations of monkeys with material from the spleen and bone marrow of three out of seven rabbits killed 7 to 8 weeks after inoculation with a spleen-bone marrow emulsion from monkeys. These rabbits had been inoculated in the testicles, and although no local lesions had been detected up to the time they were killed, it was claimed that the virus was recovered from the internal organs. As reported by Neisser, these experiments might not be regarded as conclusive, since the only evidence of a specific infection submitted was the production of lesions in the inoculated monkeys which were said by Siebert to be typical primary lesions. At first, other investigators had difficulty in verifying these results, but eventually Truffi (14) succeeded in one instance (number of attempts not stated) in producing a definite infection by inoculation of bone marrow from an animal infected in the scrotum, and similar results have since been obtained by other investigators, notably by Uhlenhuth and Mulzer (15). The obvious objection which might be raised to these experiments, however, is that the results obtained appear to have been inconstant, and no one could say what proportion of the animals would have developed generalized lesions had they been permitted to live.

The occasional case of an animal with manifestations of a generalized infection or the recovery of the virus from the blood and internal organs of even a small
proportion of infected animals was sufficient, however, to establish the fact that
generalization of the virus did occur in some instances, but no large series of
experiments was carried out, so far as we are aware, for the purpose of determining
the time and frequency or the extent of the generalization which took place, and
this type of information was much needed to place the question of a generalized
infection upon a proper basis.

Further than this, there has been little effort to correlate the phenomena of
generalization and the production of generalized lesions. All that was deter-
mined was that some animals did show a dissemination of the virus, but in the
experience of most observers the appearance of lesions other than those at the
site of inoculation was the exception rather than the rule. For example, out of
some hundreds of rabbits studied by Uhlenhuth and Mulzer (15), there were com-
paratively few which showed generalized lesions other than a metastatic infec-
tion from one testicle to the other or an occasional case of keratitis, and again
Baeslack in 1916 (16) reported that there were no cases of generalized lesions in
about 800 rabbits which he had studied.

On the other hand, a few investigators have observed generalized infections
with greater frequency. In 1914 Nichols (17) reported the occurrence of gen-
eralized lesions of various types in one-half of a series of animals inoculated
with a nervous strain of Treponema pallidum. Among the conditions men-
tioned were papular lesions of the eyelids, metastatic lesions of the scrotum and
testicles, and lesions of the eyes. In this last group, there was included a new
form of lesion of the eye ground recognizable by ophthalmoscopic examination.
Unfortunately, neither the relative nor the absolute frequency of the various
types of lesions was given, but the investigations were continued by Reasoner
(18) who mentions among the manifestations produced by this organism “fundus
involvement in about 75 per cent of the rabbits, extension to the opposite testicle
in 10 per cent of cases, keratitis occasionally, involvement of the nasal mucosa
frequently, with the presence of organism in the nasal discharge. Periostitis of
the nasal bones is a later manifestation. There are eyelid lesions in 5 per cent.
This strain also may cause mucous lesions of the penis and sheath. It occasion-
ally causes a paronychia, and often a moderate degree of alopecia.” But here
again, Reasoner frequently refers to the use of repeated and combined testicular
and intravenous inoculations, and it is not clear whether the facts recorded above
represented results of testicular inoculation alone or included also results ob-
tained from mixed and repeated inoculations of various kinds. In his conclu-
sions, he states that “ordinarily the rabbit develops only an initial lesion, follow-
ing inoculation in the genitalia, eyes and eyebrows.”

On the whole, therefore, our knowledge of generalized syphilis in the rabbit
resulting from local inoculation has rested to a large extent upon a proven dis-
semination of the infecting organisms, the time, frequency, and extent of which
were unknown, and the occasional development of a few lesions at some point
more or less removed from the site of inoculation, but no comprehensive descrip-
tion has been given of the infection thus produced.
Uhlenhuth and Mulzer (19, 20) described a generalized infection in the rabbit produced by a distinctly different mode of procedure, but even here the picture presented is incomplete. Since these investigators were unable to obtain a severe generalized infection from a local inoculation, they attempted to produce such a condition by resorting to a generalized inoculation, using intracardial and intravenous injections of very large doses of organisms. In this way, they succeeded in producing with considerable frequency what were in reality multiple primary lesions, first in young rabbits and then in adult animals. Considering the mode of inoculation employed, these infections were, of course, more analogous to intrauterine than to postnatal infections. Clinically, they were characterized by emaciation and weakness, especially in young rabbits, associated with lesions of the skin and appendages, the mucous membranes, the genitalia, the eyes, and tumor-like masses about the nose and tail. The extent of the involvement as well as the number and character of the lesions present varied considerably in different animals; there was an especial tendency to exudative affections of the mucous membranes, and the nose and tail tumors together with affections of the nails were the chief additions to the list of syphilitic manifestations which had been previously described. In other words, the lesions produced in these animals were of much the same character as those which had been reported in cases resulting from local inoculation but were, on the whole, more marked and could be produced with much greater frequency.

These experiments appear to have been accepted as a basis for constructing the picture of generalized syphilis in the rabbit and lent considerable support to the contention that marked generalized infection from local inoculation did not occur except in an occasional animal. Of course, the fallacy in this line of reasoning lay in the apparent assumption that a widely disseminated primary infection such as that produced by Uhlenhuth and Mulzer was comparable to conditions which obtained in the secondary diffusion of organisms from an established focus of infection. This error of conception, as will be seen, was a very serious one and had the effect of diverting attention from fundamental problems of the infection.

Since the publication of the work of Uhlenhuth and Mulzer, interest in experimental syphilis has abated somewhat and the only contributions of note which have appeared during the past few years are those of Nichols and of Reasoner.

While these earlier observations were doubtless correct as far as they went, the impressions created were founded upon an imperfect understanding of the experimental infection; they not only left unsettled many questions relative to the generalized infection but gave an erroneous impression as to the nature of the infection produced by local inoculation.

We have been able to collect a large amount of material bearing upon this phase of experimental syphilis which will be presented in
the following series of papers dealing with clinical manifestations of generalized syphilis in the rabbit. We regret that the pathology of these conditions cannot be presented in connection with their clinical history. We have, however, an abundance of material and hope that eventually we may be able to return to this phase of the subject and supply the pathological connection.

**Source and Nature of the Material Studied.**

The material which forms the basis for our description of generalized syphilis in the rabbit is composed of two groups of cases. Up to September 1, 1919, we had been able to collect 126 rabbits with outspoken manifestations of generalized syphilis developing from local inoculations in the testicles or scrotum. This list of animals included only those in which visible or palpable lesions were present at points entirely removed from the site of inoculation. Thus, metastatic lesions of the testicles and scrotum were not included among the generalized affections on account of the possible confusion of true disseminated lesions with extensions or transformations of processes arising from the primary focus of infection.

This first series of animals came from stock transfers and routine experiments connected with the use of the experimental infection in the rabbit as a means of studying the action of drugs against syphilitic infections and was composed of three classes of animals: (1) those in which the infection ran an undisturbed course; (2) those in which the generalized lesions developed subsequent to castration or excision of primary lesions; and (3) those in which the lesions followed drug administration.

From observations made in the course of routine work, together with an analysis of this group of cases, it appeared that the entire problem of animal resistance to *pallidum* infections, and hence the occurrence of generalized lesions, was intimately connected with the nature and extent of the reaction which took place at the site of inoculation, and that any influence which was capable of modifying this reaction might be expected to react upon the phenomena of the infection as a whole. In particular, it appeared that any condition which tended to lessen, to restrain, to inhibit, or to suppress this reaction without exerting a comparable effect upon the organisms them-
selves might be expected to favor the production of generalized manifestations of disease.

Accordingly, a series of experiments was carried out, aimed primarily at the fundamental problem of the nature of the animal infection and the mechanism of animal resistance. Thus, it was found that such simple means as a unilateral instead of a bilateral inoculation, unilateral or bilateral castration, or the use of therapeutic agents capable of inducing resolution of the primary lesions without destroying the infecting organisms, would completely alter the character of the infection and lead to the production of generalized lesions in a very large proportion of the animals inoculated.

From these experiments, a second group of animals with generalized syphilis has been collected which places the total number of cases available for study at well over 200.

The study of these animals was chiefly clinical. In the majority of cases, the lesions were allowed to pursue an uninterrupted course; in individual instances, they were excised for histological study, and some animals were killed at various periods of the infection in order to make a more thorough examination of existing conditions. The period of observation varied very considerably. Under the circumstances of our work, it was impracticable to hold most of these rabbits for any great period of time. The length of observation in most instances varied from a few weeks to several months; some animals were held for a year to 18 months and a few for more than 2 years.

The identification of syphilitic lesions rested upon the general character and clinical course of the lesions, the demonstration of spirochetes, and histological examination. In a few instances, therapeutic tests were used in the study of conditions of doubtful or uncertain character and as confirmatory diagnostic measures.

The manifestations of disease which we were able to recognize during the life of the animal fell into the five following groups and will be considered in this order: (1) affections of the skin and appendages; (2) affections of the mucous membranes and mucocutaneous borders; (3) affections of tendons, tendon sheaths, periosteum, cartilage, and bone; (4) affections of the eyes; and (5) lymphadenitis. In addition, certain visceral lesions, notably of the heart and of the central nervous system, were discovered at autopsy. This group of conditions will be reported later.
In presenting this material, we shall confine ourselves for the present to a general presentation of the subject, since it has been found that the incidence of different groups of affections, the character of the lesions present in a given case, their time of occurrence, and the general course of the disease are all more or less influenced by the circumstances under which the generalized disease makes its appearance.

Lesions of the Skin and Appendages.

The first group of conditions to be considered are the affections of the skin and appendages including alopecia, paronychia, onychia, and lesions of the skin proper. Affections of this class occurred in a large proportion of the animals showing manifestations of generalized syphilis, and it will be necessary to divide the subject matter of these conditions into two papers the first of which will be confined to a description of the individual affections, while the second will deal with the clinical aspects of cutaneous syphilis.

Alopecia.

Local or general roughening of the coat and falling out of the hair are among the conditions most frequently mentioned as manifestations of generalized syphilis in the rabbit and are extremely common among rabbits infected with Treponema pallidum, but occur also from many causes in uninfected animals, the chief ones being moulting, diseases of the skin, systemic disease, and uncleanly habits. While we are reasonably certain, therefore, that a large number of our rabbits showed abnormalities of the coat referable to their syphilitic infection, we realize that it is very difficult to identify such cases with absolute certainty. In studying these affections, we first attempted to exclude the four causes mentioned, which can be done without much difficulty in all except the moulting, or shedding, of the animal. It was found that under laboratory conditions, rabbits were very irregular in this respect and might shed their coats at almost any time from early March to late November, which left only about 3 months of the year during which one was not constantly confronted by this possibility. As far as we were able to determine, there was no pathognomonic sign of syphilitic alopecia in the rabbit. Among the animals studied, there were comparatively few in which we felt justified in making such a diagnosis, and in nearly all instances the diagnosis was supported by the presence of other lesions whose character could be established with absolute certainty.

As nearly as could be determined, there appeared to be at least three conditions which might be regarded as syphilitic alopecia. The most common of these
was one in which the coat became roughened or unkempt; the hair was dry and without luster and was continually falling out. This condition might affect the entire coat, as in Fig. 1, or only some smaller area, and was especially common about the head and ears, giving to these parts a characteristic moth-eaten appearance (Fig. 2). This form of affection is probably the one usually referred to as syphilitic alopecia in the rabbit.

No true baldness was noted in affections of this kind. In exceptional instances of diffuse alopecia, there was decided thinning of the hair over certain areas of the body such as the thighs, the thorax, the abdomen, or about the elbows (Fig. 3). Facial alopecia, alopecia of the ears, and of the cheeks were more marked as a rule, and the hair frequently came away from these areas in considerable masses (Figs. 3 and 4) or with gentle rubbing patches were left which were entirely denuded of hair.

A second form of alopecia which might be referred to a syphilitic infection was characterized by no other manifestation than looseness of the hair. The coats of these animals appeared to be in perfect condition but upon gently plucking at the hair, it was found to be so loose as to come away in handfuls, leaving the skin perfectly bare or covered with a short stubby growth of hair as in Figs. 5 and 6. This condition was so marked in some animals that it was possible to pluck the fur from large areas of the body without inflicting the slightest traumatism to the skin. In some instances, the skin itself appeared entirely normal, while in others, removal of the hair revealed the presence of unsuspected lesions (Fig. 5). A similar condition was found to occur in some animals at the time of shedding. In these cases, however, the growth of new hair was nearly always well advanced before the old hair could be removed, which was not the case with the supposedly syphilitic affection.

Both these forms of alopecia were only temporary affections as a rule, and after a few weeks or months, the coat returned to a normal condition. They appeared to be intensified, however, at the shedding periods of normal rabbits, which in itself is not surprising. In one animal of our series, which was held under observation for about 18 months, there was no time at which the entire region over the hips, thighs, and loins could not be picked entirely free of hair, and as fast as the hair returned, it could be plucked out again with but the slightest tension. A similar condition existed over other portions of the body, but otherwise the coat appeared to be in remarkably good condition, as may be seen by reference to Fig. 6.

A third form of alopecia which bordered upon a true baldness was seen in a few animals. This condition was usually confined to an area a few centimeters in diameter and was characterized by what might be called a peeling of the fur, the roots of which were matted together by superficial layers of the epidermis. By rubbing these areas, masses of fur came away, leaving a bare skin covered with fine epithelial scales. The skin showed a variable degree of thickening, and in some instances focalized infiltrations and necrosis as well. A typical
though rather pronounced case of this kind is illustrated in Fig. 8. The condition here shown extended from the cheeks down over the neck and shoulders where there were two well defined areas of infiltration and necrosis of the skin.

With recovery of these lesions, there was a thin stubby growth of hair but no return to normal as in the preceding cases. This condition might be classed as a true skin lesion rather than as an alopecia, but the alteration in the skin was so variable and in some instances so slight that the alopecia appeared to be the most characteristic feature of the condition.

There was one other condition noted which may be mentioned, the etiology of which could not be determined with certainty. It affected the hair of the face and especially that over the bridge of the nose, and was characterized by a thinning of the hair over the affected area while that remaining appeared broken and irregular much as in the case of tinea infections (Fig. 7). The skin of the affected part showed a slight infiltration in some cases, but in others was thin or atrophic. The only causative factor which suggested itself besides that of a specific infection was the rubbing of the animal against the cage, and this seemed unlikely. Once the condition developed, there was little or no tendency toward a return to normal.

*Onychia and Paronychia.*

Onychia and paronychia have been mentioned among the manifestations of generalized syphilis in the rabbit, but in our experience, affections of the nails which could be definitely ascribed to syphilitic infection were comparatively rare—only seven cases having been recorded among 126 rabbits and only one of these could be regarded as a true onychia.

Paronychia was first recognized by a slight reddening and swelling of the skin about the base of the nails. The skin then became thickened or infiltrated and was covered with yellow or yellowish gray scales or crusts producing a condition like that shown in Figs. 9, 10, and 12. In extreme cases, the reaction about the base of the nail was much more marked and resulted in the formation of granulomatous masses which underwent secondary necrosis and ulceration with consequent disturbance of the nutrition of the nails themselves (Figs. 11 and 12).

These conditions were usually bilateral and symmetrical and affected the nails of both the front and hind feet.

Syphilitic paronychia was found to be difficult to distinguish in some instances from a non-syphilitic affection of a similar character which is comparatively common among rabbits. This fungus or parasitic disease of the nails develops sooner or later in all rabbits with fungus or parasitic infections of the skin or external ear. While
these affections occur upon the hind feet as well as the front, they usually make their appearance about the toes on the median side of the front feet and are not confined to the region of the nails but spread diffusely over the interdigital surfaces. In contrast to this, syphilitic paronychia appeared to be more common about the nails of the lateral toes and was sharply confined to the base of the nail. Again, the parasitic disease is a steadily progressive affection and never clears up spontaneously, while the syphilitic condition is variable in its course and clears up completely without any treatment. If spirochetes can be found, they are helpful in making a diagnosis, but in their absence, one has to rely upon clinical characteristics.

A true onychia, as has been mentioned, was recognized by naked eye observation in only one of our first group of rabbits. In this case, the condition was associated with a marked paronychia of some of the toes, and the alterations in the nails were so pronounced as to leave no doubt as to the etiological factor concerned (Fig. 11). A similar but less marked condition was also presented by the animal shown in Fig. 12. In other instances it was noted that the nails showed signs of wearing short or appeared roughened and broken towards their ends and tended to split and scale just as in the case of the outer and inner toes of the animal in Fig. 11. An example of nail involvement of this type with no associated paronychia is shown in Fig. 13.

At the time these observations were made, no relation could be established between this condition and the syphilitic infection. Subsequently, however, it was learned that alterations such as these might arise from involvement of the nail bed. In the rabbit, the nail fits closely over the terminal phalanx, and periostitis with considerable destruction of these bones may take place without giving rise to any external evidence of the existence of such an infection other than an alteration of the nails of the affected toes. Onychia in the rabbit appears, therefore, to be most often associated with a periostitis and is difficult of recognition by the use of ordinary means of diagnosis. If the involvement is slight, the nail may eventually recover, but if the destruction is extensive, the effect appears to be permanent or at least of long duration.

These observations were made by Dr. W. H. Brown, Dr. L. Pearce, and Dr. W. D. Witherbee in the course of a series of investigations of deep seated bony changes by the use of the x-ray, the results of which will be reported later.
Cutaneous Lesions.

The cutaneous lesions formed a very large and varied group of affections. They included lesions of the macular, papular, and nodular or tubercular varieties, and while they possessed many features in common with the cutaneous lesions of man, they differed from them in so many respects that it would be difficult to attempt a complete correlation of the two classes of lesions upon the basis of the material which is at present available. The only classification of cutaneous lesions of the rabbit which seems justifiable at this time is one based upon very broad lines of differentiation such as that afforded by developmental or pathological characteristics.

As was pointed out in connection with scrotal infections, one of the most striking features of the skin reaction of the rabbit to localized infections of *Treponema pallidum* is the tendency to proliferation on the part of the fixed tissue cells and the formation of large granulomatous lesions; a second characteristic of the skin reaction is the tendency to a more or less diffuse infiltration associated with varying degrees of desquamation of surface epithelium, exfoliation, and surface erosion, or necrosis and ulceration; while a third feature of the reaction is a localized hyperemia or even hemorrhage which is associated with varying degrees of exudation expressed chiefly in the form of an edema.

These characteristics of the primary reaction in the scrotum find their counterpart in the reaction to localized infection in other skin areas and form, therefore, an acceptable basis for a consideration of the cutaneous lesions of generalized syphilis. Upon this basis, cutaneous lesions will fall into three classes, the hyperemias, the infiltrations, and the granulomata. It should be understood, however, that there is no sharp line of distinction between these three classes of conditions as there is always a tendency to a combination of the three processes, and such distinctions as can be made must be based upon the predominance of one or another of the three forms of reaction.

In taking up the discussion of cutaneous lesions, the above sequence will be reversed in order to begin with those conditions which are the most obvious; namely, the granulomata.
Cutaneous Granulomata.

The lesions classed as cutaneous granulomata (Figs. 14 to 20 and 22) included those affections which developed in consequence of a reaction which was marked by proliferation of fixed tissue cells and the formation of circumscribed elevated nodules of a fleshy character varying from a few millimeters to several centimeters in diameter. Lesions of this type were quite common. They usually occurred singly or in small groups and as a rule were few in number, but occasionally they were fairly numerous and as many as twenty-eight lesions have been counted in a single animal at one time.

The granulomata appeared either in the form of rather diffuse areas of thickening which involved a considerable depth of the skin or as sharply circumscribed and indurated nodules (Figs. 14 and 17). The more diffuse lesions and the larger nodules were usually of a rose-pink or copper color or were paler than normal and of a faint yellow color, while the small discrete nodules were generally pale and opaque or of a decided opalescent appearance. In exceptional instances, the early lesion was of a deep violet-red color or appeared almost as thickened purpuric spots in the skin. In general, the surface of the lesion was smooth and rather translucent, but during the early stages of its growth there was no marked disturbance of the hair covering its surface. These several conditions are illustrated in the accompanying photographs (Figs. 14 to 19) which show various forms and developmental stages of typical granulomatous lesions.

The evolution of the cutaneous granulomata was usually rapid and within a week or so led to the formation of large oval or irregular spherical masses showing various types of secondary alteration such as are illustrated in Figs. 14 to 23. It is important to note, however, that not all the lesions present in a given case exhibited these changes to an equal degree. As a rule, only a few of those present developed to any considerable extent, while the others underwent involution and completely disappeared. This is a phenomenon worthy of note, since it illustrates the inhibitory influence exerted by one lesion or group of lesions upon another, as was pointed out in connection with the development of multiple scrotal lesions.

The growth of granulomatous lesions took place chiefly from the deeper layers of the skin and tended to be of a concentric type so that surface alterations were usually confined to a relatively small area. The most common changes observed were those due to necrosis. In some instances, this was very superficial and produced no more than a slight exfoliation of epithelium or surface erosion; in others, it extended to a greater depth, and the skin over the center, or even a larger portion of the lesion, became converted into a dry, adherent crust, or a depressed ulcer was formed which converted the lesion into a typical chancre-like mass.
While, as a rule, the area thus involved was small, occasionally a large part of
the lesion was destroyed in this manner—the necrosis keeping pace with the
growth of the lesion (Figs. 18 and 19).

Another noticeable feature of this class of affections was the preservation of
the hair over a large part of the lesion which was obviously due to the nature of
the skin involvement. With the advent of infiltration and necrosis of the outer
layers of the skin, the hair first became thin and broken and was then lost over
the affected area, but, as may be seen by reference to Fig. 19, many lesions
showed practically no disturbance of the hair outside the zone of necrosis. In
other instances, however, there were a more extensive involvement of the outer
layers of skin and an obliteration of papillae extending well beyond the area of
necrosis. In these cases, the loss of hair was more pronounced and lesions were
formed which, with their smooth and infiltrated surfaces, bore an even more
striking resemblance to the typical scrotal chancre (Fig. 20). Usually the ob-
literation of skin papillae and the loss of hair merely preceded the appearance of
other changes, but not infrequently they marked the extent of the surface alter-
ation, and the lesions thus formed were quite analogous to unulcerated nodular
chancrees of the scrotum (Fig. 22).

In many ways, the cutaneous granuloma of the rabbit may be viewed as an
expression of a vigorous reaction to infection analogous in all respects to that
which characterizes the reaction at the primary focus of infection. Objectively,
the force of this statement may be appreciated by comparing Figs. 20 and 21
and Figs. 22 and 23 which represent corresponding cutaneous and scrotal lesions
of two animals photographed at the same time. The significance of the striking
similarity between these two processes of reaction will be made clear when we
come to consider the factors in animal resistance and the mode of expression
of this resistance.

Before leaving the subject of cutaneous granulomata, reference may be made
to a similar group of lesions which originated within the subcutaneous tissues and
reached a considerable size before any skin involvement took place (Fig. 24).
These lesions were, of course, more analogous to ordinary gummata, or the so
called tertiary skin lesions of man, than to those of earlier stages of the disease,
and the few cases seen in the rabbit also appeared late in the course of the infec-
tion. For example, the animal shown in Fig. 24 had a succession of cutaneous
lesions, the first appearing about 3½ months after inoculation. There were no
lesions in the subcutaneous tissues, however, until 25 months after inoculation
when the lesion upon the nose developed and was followed 3 months later by
other lesions of a similar character.

In all granulomatous lesions, spirochetes were numerous and could
be demonstrated without difficulty as long as the lesions were active.
Cutaneous Infiltrations.

The second group of cutaneous lesions to be described (Figs. 25 to 41) includes a variety of conditions ranging from small discrete papules on the one hand to large weeping or crustaceous patches on the other, the common basis of which was a cutaneous infiltration in contradistinction to the proliferative reaction which characterized the lesions of the preceding group. According to available data, these affections occurred among our first series of animals about as frequently as the granulomata, but their incidence has steadily declined with changing conditions until, under present circumstances, they might be regarded as comparatively rare affections. It should be pointed out, however, that lesions of this class were often less clearly defined and much more difficult of detection than the granulomata, and hence it is not unlikely that many may be entirely overlooked.

At the time of their appearance cutaneous infiltrations may differ very slightly if at all from early granulomatous lesions. As in the case of the granulomata, two forms of lesions could be distinguished from their mode of origin, one appearing as a somewhat diffuse process and the other as a very minute and sharply circumscribed nodule, and these characteristics tended to be preserved in the fully developed lesions of this class. There were thus formed two fairly well defined groups of conditions, the one a flattened or lenticular lesion, the other a more elevated and indurated papule.

Flattened Papular Lesions.—The initial lesion of this group (Figs. 25 and 26) presented the appearance of a simple infiltration of the skin, involving the papillary layers and varying from a few millimeters to a centimeter or more in diameter. These spots were usually of a faint pink or copper color, but in exceptional instances, the discoloration of the skin was quite pronounced, approaching in intensity the violet-red color occasionally seen in early granulomatous lesions (Fig. 26). At this stage, the affected area was raised but slightly above the surrounding skin level, the elevation being greatest at the center of the lesion and diminishing towards its periphery.

Changing conditions in the life history of the organisms and the particular circumstances under which generalized lesions make their appearance in a given case are undoubtedly potent factors in determining the character which these lesions assume.
Very soon the appearance of the lesions changed, the color becoming a pale yellow or gray or deepening to a copper or brown as the case might be. At the same time, the infiltration increased and the hair over the affected area was lost to a considerable extent, while the skin became smooth and glistening and of a parchment-like consistency or was covered by thin scales of a yellow or yellowish gray color (Fig. 27).

Subsequently, numerous modifications of these lesions occurred as a result of growth or extension or from secondary alterations taking place within the affected area. The characteristic mode of growth of the flattened papular lesion was a peripheral extension of the infiltration which in itself gave rise to a variety of conditions. Most often there was produced a small but fairly well defined area of infiltration analogous to some of those shown in Figs. 28 and 31. Occasionally, however, the process assumed more extensive proportions and from one or more small lesions, there developed a widespread affection such as that seen in Fig. 28. Not infrequently, the original lesions or the center of the lesion in such cases underwent resolution with the peripheral extension of the process as may be seen by an examination of Figs. 28 and 29. There was thus formed a single annular lesion, as in Fig. 29, or an affection composed of a series of lesions grouped in similar fashion about the area in which the infection first appeared (Fig. 28).

In addition to conditions such as those described, numerous modifications of these lesions occurred which were attributable to secondary alterations. Among these may be mentioned a squamous type of lesion, a suggestion of which is given by the accumulation of scales about the margins of the lesion in Fig. 29. Another condition which was of frequent occurrence in this class of affections was exfoliation of the epithelial coverings which gave rise to moist or weeping patches or to areas of infiltration covered by thick yellowish gray or yellowish brown crusts (Figs. 31 and 33). In other instances, necrosis of a more pronounced character occurred and resulted in the formation of an ulcer, as in one of the lesions in Fig. 29, or the entire area of infiltration was converted into a dry, necrotic eschar, a condition which is suggested in Fig. 8.

While in many instances the flattened papular lesions were rather small and few in number, they were occasionally quite numerous and tended to spread and to fuse with one another, as has been described, or were processes of a rather diffuse character from the beginning and covered an area several square centimeters in extent. As might be expected from the nature of the process, this particular type of lesion was especially prone to exfoliation and necrosis and the formation of weeping patches or of lesions of a crustaceous character such as that shown in Fig. 33.

As was pointed out in connection with the cutaneous granulomata, it is important to note again that many of the infiltrative processes which have been described are closely analogous to certain forms of primary scrotal lesions. In order to emphasize this point, two sets of photographs have been inserted to enable one to make the comparison between the primary and the generalized...
Raised Papular Lesions.—The raised papular lesions of the skin (Figs. 34 to 41) analogous to the miliary or follicular syphilides of man were of three varieties. The simplest of these and the one from which the others usually developed was a small shotty nodule averaging from 1 to 3 mm. in diameter and raised a millimeter or so above the surrounding skin level (Figs. 34 to 36 and 38). These lesions were very sharply demarcated and were of a grayish white or faint copper color. In most instances, they were rather dense and opaque but occasionally were of a semitranslucent or opalescent appearance. The crest of the lesion tended to be rounded or pointed, but in exceptional instances there was a slight umbilication as in Fig. 36. Some of the lesions were also surrounded by a rich vascular network as is clearly shown in this same figure (Fig. 36).

These papules rarely persisted in the condition described for any considerable period of time but tended to undergo one of two types of alteration. Many of them underwent a central or apical necrosis with the formation of a small crust or ulcer. This was particularly the case with lesions situated about the face or ears (Fig. 37). The second modification seen was of a squamous type, and this was especially common with lesions of the upper eyelids and brows (Figs. 38 to 41). In some of these, a thick layer of epithelial scales was formed upon the crest of the lesion (Fig. 40), while in others, the entire nodule was incased in a covering of horny epithelium (Fig. 39). This group of conditions presented the general appearance of small vegetations, and their prominence was due largely to the accumulated epithelial coverings which upon removal left an unexpectedly small and rather flattened body of infiltration.

Another feature of these lesions was the tendency to occur in groups such as those shown in Fig. 39. In two animals of our series, one of which is shown in Fig. 37, the papules showed a definite circinate arrangement and a very striking bilateral symmetry.

Routine examinations for spirochetes were not made upon all the lesions of this group which were encountered, since it was desired to follow the clinical course of the lesions as far as possible, and it was found that the traumatism inflicted either by aspiration with a needle and syringe or by scarification was sufficient to disturb the development of the smaller lesions and predisposed to rapid regression or healing. However, spirochetes were demonstrated in lesions of all the types described. They were most easily demonstrated in the moist or weeping patches of infiltration and in the fleshy papules but were more difficult to demonstrate in the dry necrotic lesions and the small follicular papules. When once familiar with this group of lesions,
however, the clinical history was usually sufficient in itself to enable one to make a perfectly definite diagnosis.

While, in attempting to point out the salient features of various types of cutaneous eruptions, a distinction has been drawn between cutaneous infiltrations and cutaneous granulomata, it must be said that no complete division between these two classes of affections could be made. In reality, they tended to merge one with the other, and while the great majority of the lesions seen in the rabbit could be assigned to one or the other of these two groups, there were borderline conditions which would be very difficult to classify upon this basis.

As our investigations advanced, the difficulties encountered in this respect were increased due to a change in the character of the lesions produced by the two strains of organisms employed. This was especially noticeable in a decrease in the relative incidence of lesions which have been described as infiltrations and a corresponding increase in lesions which clinically might be regarded either as small granulomata or as unusually marked processes of infiltration. Mention is made of this fact on account of the bearing which it may have upon any interpretation which may be placed upon such conditions as manifestations of a reaction to infection.

**Macular Erythema, or Roseola.**

A macular erythema has never been described among the cutaneous lesions of the rabbit so far as we are aware, but in the course of our observations, a pronounced rash of this type was seen upon the ears of a number of animals with manifestations of generalized infection. As yet, no conclusive proof of the syphilitic nature of these lesions has been obtained. Thus far, we have been unable to demonstrate spirochetes in the lesions, although we have not had an opportunity of making a thorough search for them in section. The evidence which we have rests upon clinical and histological examinations.

In its typical form, the macular erythema first appeared as slightly thickened, rose-colored spots or patches situated in the deeper layers of the skin or in the subcutaneous tissues of the outer third of the ear. The color of the rash deep-
ened to a dusky red or purple, then changed to a coppery hue, and faded, leaving a faint stain in the tissues. Occasionally, there were small petechial hemorrhages associated with the lesions and a central opaque white spot or ring which persisted after the general color of the rash had faded. A typical though rather pronounced case of macular erythema is shown in Fig. 42.

As a rule, the hair was loosened over the affected area or over a much greater area than appeared to be involved, and, in a few instances, the surface of the skin was also affected, becoming roughened and covered with scales, a condition which was especially noticeable upon the inner surface of the ears where the skin is normally quite smooth. Ordinarily, no other changes were noted, but in two instances, there was a well marked infiltration of the affected areas which made its appearance just as the rash began to fade. The ear of one of these animals and the areas of infiltration are shown in Fig. 43.

In their distribution, the macular lesions usually preserved a fair degree of bilateral symmetry. Aside from the ears, the only positions in which definite purpuric spots of the character described have been seen were the trunk and the thighs of two animals.

During the early stages of the erythema, the color was diminished by pressure or by vascular constriction and increased with dilatation of the vessels, but such influence had little if any effect upon the appearance of the rash after the purpuric stage had been reached. In general, these lesions suggested a reaction similar to the early reaction described in the scrotum following inoculation with a virus emulsion.

This macular erythema was usually fleeting and rarely persisted for more than a few days, and frequently a slight roseola disappeared within 24 to 48 hours after it was first noted. In most instances, the roseola developed early in the course of the infection, but in one animal, it was observed as late as 16 months after inoculation. Another characteristic feature of these lesions was a marked tendency to recurrent periods of eruption.

After a long series of observations, it was found that a very large proportion of the animals which showed eruptions of this type belonged to one of three classes: first, those which had shown other manifestations of generalized infection, second, animals in which such lesions were still present, or third, animals which subsequently did develop lesions of a definite syphilitic character.

Histologically, three types of change were found in these lesions. In the early stages of the erythema, the vessels of the region were
dilated and the surrounding tissues were edematous. At a later period, there was stasis as well as dilatation of the vessels and slight extravasation of red blood cells along with the edema, and the endothelial cells of the vessels were swollen. These were the usual changes, but in the most marked cases, there were in addition a slight migration of leucocytes and an accumulation of round cells. These changes are precisely those which occur with the initiation of the specific reaction in the testicle and scrotum.

The chief source of difficulty in relating the macular erythema to infection with *Treponema pallidum* is the occurrence of erythematous and vasomotor disturbances of various sorts in the ears of normal rabbits. The non-specific condition usually develops from the base of the ears and radiates outward along the marginal vessels but may assume a macular form not unlike that of the early roseola described. These conditions were found to occur especially during periods of moultng, or shedding, and at such times, thickened erythematous patches may be found on any part of the body where new hair is beginning to grow. However, the purpuric type of eruption was never observed except in infected animals, although very many normal rabbits were examined with this point in view.

As the matter stands, therefore, we feel reasonably certain that a true macular lesion does occur in the rabbit, but the difficulties of making a positive diagnosis are so great that we have confined our listing of such conditions to animals which showed some other manifestation of generalized syphilis, and among these, to those animals in which the rash appeared in typical form.

Lesions of Uncertain Etiology.

The cutaneous lesions thus far described include only those affections whose etiology we have been able to establish with absolute certainty or, as in the case of the macular erythema, with a strong degree of probability. This group of manifestations would hardly be complete, however, without mention of several conditions which may

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3 It is possible that therapy exercised some influence upon the occurrence of macular erythema, since eight of the first thirteen animals in which an outspoken eruption of this character was observed, were drug-treated animals.
bear some relation to *pallidum* infections but whose etiology we have not been able to establish to our own satisfaction.

The first of these conditions is that illustrated by Fig. 44 which shows a bare area of skin in the lumbar region from which the hair has been plucked. In this area, there were two definite nodular masses, one covered by a short growth of hair, the other entirely bare and of a decided red color. A similar reddened and thickened area projects beyond the margins of the upper edge of the denuded skin area. These conditions were comparatively common and especially so at the time of moulting.

It will be noted that the peculiar condition of the skin in this animal is not unlike the early stage of a syphilitic skin lesion but analogous conditions are known to occur among uninfected rabbits. In the presence of a negative examination for spirochetes, obviously no diagnosis of the nature of such affections could be made. Granting, however, that conditions of this kind are entirely phenomena of a new growth of hair, it still appears possible that they may be influenced to some extent by the presence of a syphilitic infection. Whether such is the case cannot be said. The conditions were confined almost entirely to the face, where known skin lesions usually present a very characteristic appearance, and to the trunk, a region in which almost nothing is known of syphilitic lesions. The condition is mentioned mainly to avoid confusion between affections of proven origin and conditions of unknown etiology which may simulate them.

The second group of conditions to which we may refer concerns more especially certain of the hair follicles or possibly the sebaceous glands of the cheeks and, to a lesser extent, the neck. In a considerable number of infected rabbits, it was found that an abnormal condition of the skin developed about the roots of certain hairs, usually late in the course of the disease. The condition was characterized clinically by the formation of an exudate which glued together small tufts of hair irregularly distributed over the cheeks and sides of the neck. This material extended a millimeter or so up the shaft of the hair and resulted in the formation of dry, hard projections which were very easily palpable and were of a cream-yellow or lemon-yellow color. When the hair was clipped, the appearance presented was that shown in Fig. 45.

This condition might persist for a very long time or might clear up after only a short duration. In the process of clearing, the hair came out, and one found beneath these masses of exudate, faint circles in the skin similar to those seen in Fig. 46.

A condition which appeared to be of the same nature developed in several animals whose cheeks had been shaved as a means of investigating suspected skin lesions. One of these animals is shown in Fig. 47. The lesions formed under these conditions were minute points of elevation surmounted by a small crust. It was found that by applying pressure or tension to the skin, a small droplet of clear or slightly turbid fluid exuded from these points. This fluid contained a
large number of polynuclear and mononuclear cells, but no spirochetes could be found.

In this particular animal, it may be of interest to note the existence of another abnormality in regard to the growth of the hair of the area shown. This animal with two others was shaved several weeks before the photograph in Fig. 47 was taken. At that time, there were several small syphilitic lesions at the base of the ears. The hair of the other two animals (both with specific lesions) returned very promptly, but in this animal, there was practically no growth of hair for many weeks which in itself is indicative of disturbed nutrition of the hair, and is a condition which has been repeatedly observed in animals with marked generalized syphilis.

This group of conditions suggests the possibility of a follicular syphilide, possibly a pustular eruption, but at present, it is no more than a suggestion. Similar conditions were found in uninfected rabbits but were far less common and were usually associated with other evidences of abnormality. In infected animals, this condition showed no relation to other diseases. For example, the rabbit in Fig. 45 was in perfect condition except for the presence of two small lesions upon the hind feet. A year previous, however, it had been the subject of a most pronounced cutaneous syphilis.

We are of the opinion that some of these conditions may be directly or indirectly related to infection with *Treponema pallidum*. We have had no opportunity, however, to make a thorough investigation of them and in the absence of any definite proof of a syphilitic origin, they must be left as conditions of uncertain etiology.

**SUMMARY.**

From the study of a large series of rabbits with outspoken manifestations of generalized syphilis, lesions of the skin and appendages were found to constitute one of the largest and most varied groups of such affections. The conditions noted consisted of alopecias, onychia and paronychia, and lesions of the skin proper.

It was found to be a matter of some difficulty to make a positive diagnosis of syphilitic alopecia, but there were three and possibly four conditions which appeared to be attributable to such an infection. The first of these took the form of a general or local roughening of the coat with falling of the hair which produced the typical moth-eaten appearance associated with syphilitic alopecia in the human subject. A second form of alopecia was essentially an abnormal looseness of the hair which permitted large areas of the body to be completely
denuded. The third type of alopecia was associated with definite skin changes, and the hair was readily removable together with an adherent mass of epithelial scales.

Paronychia was comparatively rare but was readily recognized by a characteristic infiltration and exfoliation of the skin about the base of the nails.

The incidence of onychia is uncertain. Late in the course of the investigation it was found that alterations in the nails which were not entirely characteristic in themselves might occur in consequence of a syphilitic involvement of the nail beds which could not be detected by ordinary methods of examination. The cases which were recognized as syphilitic were those which showed an associated paronychia.

Lesions of the skin were found to be one of the most frequent manifestations of a generalized infection in the rabbit. These lesions were divided into three classes: first, granulomatous lesions, second, infiltrations, and third, erythemata.

The granulomata were lesions of a fleshy character which tended to grow to a very large size and presented all the characteristics of circumscribed primary lesions of the scrotum.

The conditions described as cutaneous infiltrations included two general types of lesions, one a flattened and rather diffuse process, the other an elevated and sharply circumscribed papule. As a class, these lesions were very prone to secondary alterations and in this way gave rise to a great variety of conditions which in general resembled the diffuse primary lesions of the scrotum and the papular lesions resulting from local dissemination.

A third type of lesion resembling the macular erythema of man was observed in a small number of animals, and while no definite proof of the specific origin of these lesions was obtained, the evidence available was strongly suggestive.

In addition, several other cutaneous affections were noted which have not as yet been thoroughly investigated. It is suggested, however, that these processes may bear some relation to infection with *Treponema pallidum*.
BIBLIOGRAPHY.

13. Neisser, A., Dermat. Z., 1908, xv, 73.

EXPLANATION OF PLATES.

All the illustrations are from unretouched photographs which, with the exception of Figs. 1 and 6, represent the objects at approximately their natural size.

Figs. 1 to 8. Alopecias in the rabbit. Abnormalities of the coat which may be referable to a syphilitic infection. All the animals here shown had active manifestations of generalized syphilis, other than the alopecia, at the time these photographs were taken with the exception of one in Fig. 6 and in this case there was a double keratitis at the time the alopecia first appeared.

PLATE 47.

Fig. 1. An abnormal condition of the coat frequently observed in rabbits infected with Treponema pallidum. A diffuse alopecia.

PLATE 48.

Fig. 2. Alopecia areata, showing a slightly moth-eaten appearance of the hair about the face and ears. This condition may be simulated by ordinary processes of moulting.

Fig. 3. Diffuse alopecia, showing a marked thinning of the hair over the thigh and a slight roughening of the skin.
EXPERIMENTAL SYphilIS IN THE RABBIT. IV

PLATE 49.

Fig. 4. Alopecia areata associated with desquamation of surface epithelium, a condition also seen at the time of moulting.

Fig. 5. An animal in which the hair was plucked from the region of the head and shoulders. Elsewhere the hair was firmly set. Note the cutaneous lesions on the face. An affection as pronounced as this is rarely observed in a normal animal but is comparatively common among those infected with Treponema pallidum.

PLATE 50.

Fig. 6. An affection of the coat characterized by abnormal looseness of the hair which persisted over a period of more than 18 months. The region over the hips, thighs, and loins of this animal were plucked clean a number of times. Note the excellent appearance of the coat of the animal.

PLATE 51.

Fig. 7. A peculiar thinning of the hair over the lower portion of the nose.

Fig. 8. The same animal as in Fig. 7. Alopecia areata associated with a slight diffuse infiltration of the skin, desquamation of epithelium, and focal necroses. An unquestionable syphilitic affection.

Figs. 9 to 13. Affections of the nails.

Figs. 9 and 10. A bilateral paronychia of the front feet.

Fig. 11. Left hind foot. Marked paronychia and onychia of the nails on the two middle toes and onychia of the inner toe. Hair clipped.

Fig. 12. Right hind foot. Paronychia of first and third toes. Onychia with loss of the nail. Hair clipped on the third toe.

Fig. 13. Simple onychia of hind foot. Hair over the toes clipped. This animal showed a periostitis and necrosis of the terminal phalanges.

PLATE 52.

Figs. 14 to 19. Cutaneous granulomata analogous in many respects to the grouped nodular or tubercular lesions of the so called secondary and tertiary periods of human syphilis.

Figs. 14 to 16. Stages in the development of a typical cutaneous granuloma as seen at intervals of 1 week. Fig. 14 shows an area of diffuse thickening in the skin, the surface of which was of a decided copper color. In Fig. 15, there is beginning surface necrosis, and Fig. 16 shows a well developed chancre-like lesion with central necrosis and depressed ulcer. Area shaved.

Fig. 17. A group of six early granulomatous lesions on the dorsum and side of the right hind foot with an older lesion over the tendo achillis as seen after removal of the hair. These lesions were all sharply demarcated but varied in appearance from pale opalescent nodules to nodules of a deep violet-red color. Note the tense appearance of the skin and glistening surface of the two largest lesions.
Fig. 18. A group of granulomatous lesions on the right hind foot representing various stages of development. The lesions in this animal were characterized by an intense violet-red color and by rapid and widespread necrosis. The enlargement of the fifth metatarsal seen in the photograph is due to a syphilitic periostitis. Hair removed.

Fig. 19. Granulomatous lesions of the foot illustrating various stages of necrosis and ulceration and the persistence of the hair over this class of lesion. Hair clipped.

PLATE 53.

Figs. 20 and 21. A cutaneous granuloma and the scrotal lesions of the same animal. The animal was inoculated in the testicles and subsequently the left testicle was removed, but large scrotal lesions developed on both sides, presenting essentially the same appearance as the generalized lesions of the skin.

Figs. 22 and 23. An unulcerated granuloma of 4 months duration with a bald patch on its surface and the corresponding lesion of the scrotum 11 months after inoculation. The two lesions were photographed at the same time. A similar lesion in the right scrotum had been excised.

Fig. 24. A subcutaneous granuloma, or gumma, freely movable between the skin and the nasal bones, 26½ months after inoculation. Hair clipped.

Figs. 25 to 41. Cutaneous infiltrations. The lesions in this group represent processes which are perhaps more analogous to the cutaneous lesions of man than those of the preceding group.

PLATE 54.

Fig. 25. Large copper-colored patches of infiltration just appearing on the right ear. Ears shaved.

Fig. 26. A very early but pronounced area of infiltration on the dorsum of the right front foot. The lesion was of a violet-red color and at this time presented much the same appearance as an early granulomatous lesion. The nodular mass at the carpus is a syphilitic lesion of the ulna. Hair removed.

Fig. 27. Small cutaneous infiltrations at the base of the ears showing accumulation of epithelial scales. An early secondary transformation. Area shaved.

Fig. 28. Multiple lesions of the fore arms and feet grouped in irregular circles with the most active lesions towards the periphery. The affection first appeared in the region of the carpus and subsequently extended as shown in the photograph. The lesions were profusely covered by fine epithelial scales most of which were unavoidably lost in shaving the affected area.

PLATE 55.

Fig. 29. The same animal as in Fig. 28. An annular lesion, the margins of which are partly covered with epithelial scales, and a smaller area of infiltration with a necrotic center covered by a scab. A third lesion is seen in profile upon the anterior surface of the ear. Area shaved.
Fig. 30. The primary lesions of the scrotum in the same animal as that in Figs. 28 and 29, intended to show a similarity in the cutaneous reaction of various parts of the body or between the so-called primary and secondary lesions of the skin.

Fig. 31. Multiple cutaneous infiltrations on the right front and hind feet showing some loss of hair and various degrees of necrosis and ulceration. The hair has been clipped but not shaved.

Fig. 32. The scrotum of the same animal and the lesions which developed following inoculation. (See legend of Fig. 30.)

Fig. 33. A large crustaceous lesion over the elbow and paronychia of the fifth toe. Natural appearance.

Plate 56.

Fig. 34. An early papular lesion on the posterior margin of the ear, showing the pale body of the lesion with a narrow zone of color at its base. Area shaved.

Fig. 35. A small papular lesion of a few days duration on the inner surface of the ear.

Fig. 36. Two small papules with central umbilication surrounded by a network of vessels. Lesions of only a few days duration.

Fig. 37. A group of small papular lesions showing circinate arrangement and bilateral symmetry.

Plate 57.

Fig. 38. A fleshy papule of the upper eyelid.

Fig. 39. Multiple papular lesions of the upper lid and brow covered by heavy epithelial plaques, a transformation which frequently affects lesions such as that in Fig. 38.

Fig. 40. A fungus type of lesion which appears to be due to a continuous piling up of epithelial debris intermingled with a serous exudate. The body of this lesion was hardly more than 2 mm. in diameter.

Fig. 41. The same lesion at a later date showing a very irregular but still somewhat scaly surface. This figure is given to illustrate modifications which may take place in a given lesion.

Fig. 42. A macular erythema, or roseola, of the ear.

Fig. 43. Cutaneous infiltration following the fading of a roseola. There was still a distinct copper color in these areas.

Plate 58.

Figs. 44 to 47. Abnormalities of the skin frequently observed in rabbits infected with Treponema pallidum whose connection with the pallidum infection is still undetermined.

Fig. 44. An area of alopecia in the region of the loin showing irregular patches of thickening in the skin analogous to those which occur with a new growth of hair. These conditions are especially frequent in infected animals.
Fig. 45. Multiple follicular lesions over the cheek and neck. These lesions develop about the roots of certain hairs, and while they are quite common in infected rabbits, they are occasionally seen in apparently normal animals. Hair clipped.

Fig. 46. Alopecia of the cheek and pale circles in the skin occurring with the healing of lesions such as those in Fig. 45.

Fig. 47. A bare area of skin showing several minute crusts with a bristle protruding and numerous irregular areas of thickening and mottling in the skin. The one marked by the arrow was a definite syphilitic papule. The upper part of the area was shaved about 7 weeks before this photograph was taken but there had been practically no growth of hair within this time, which is most unusual.
(Brown and Pearce: Experimental syphilis in the rabbit. IV.)
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