

STUDIES ON THE ETIOLOGY OF SPONTANEOUS CONJUNCTIVAL FOLLICULOSIS OF RABBITS

I. TRANSMISSION AND FILTRATION EXPERIMENTS

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PLATES 4 AND 5

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In previous articles (1, 2) we have described spontaneous conjunctival folliculosis as it occurs in *Macacus rhesus* monkeys and in chimpanzees. This condition, prevalent among certain dealers' stocks of animals (1, 3), was identified as a disease *sui generis*, which is localized wholly to the conjunctiva and is transmissible from simian to simian by contact or by the inoculation of affected tissues. It was found to be due to a bacterium, not to a virus, and a new organism, tentatively designated as *Bacterium simiae*, was shown to have an intimate relationship to the infection.

A spontaneous conjunctival folliculosis exists widely distributed in various species of rabbits: chinchilla, New Zealand and domestic, either albino, black or pied. For example, in two groups of animals, 52 in one and 129 in the other, only six of each group had smooth conjunctivae; and again, inspection of rabbits in dealers' stocks revealed that of 115 animals, only about 25 per cent, consisting chiefly of the suckling or the newly weaned, and those born of mothers with smooth lids, were free from this conjunctivitis.

The occurrence of folliculosis in rabbits has been recorded by others. Weiss stated that follicles have been seen in "normal" animals by Finnoff and Thygeson, Bengtson, and himself (4). Cuénod and Nataf (5) mentioned that the affection occurred frequently and classified it as "pseudotrachoma." The writers cited have not reported any experimental investigations.

A laboratory study of the condition was, however, made by Nicolle and Lumbroso (6). They termed the rabbit affection *conjunctivite granuleuse naturelle* and

described two forms: one in which follicles were massed at the canthi, the follicles being considered as normal (*follicules normaux*); and the other in which the lesions were scattered over the entire lid. In either case the upper, tarsal, conjunctiva was always clear. This absence of lesions in the upper lid was considered by them as a differentiation of the rabbit disease from human trachoma, since they could determine no distinction in the type of follicles in both affections.

Nicolle and Lumbroso also found that the disease was transmissible from rabbit to rabbit either by inoculation of affected conjunctival material or by contact; the new-born being frequently attacked as a result of contact with infected mothers. They reported, furthermore, that rabbit folliculosis was transmissible to monkeys (*Macacus sinicus* and *rhesus*) and a papion (baboon). A single animal of each species was employed for this test. Although they concluded in a first article (6) that *Macacus inuus* monkeys were not reactive to inoculation of rabbit folliculosis material, they reported in a second paper (6) that two *inuus* monkeys had been infected with such material, the effects, however, differing from those in the other simians. The period of incubation was at least 10 weeks, instead of 2, and the lesions appeared in both the upper and lower lids, instead of only in the lower. However the recognition of the specificity of the reaction in the *inuus* animals is important, since the writers asserted that isolated follicles appeared spontaneously among their monkeys, and that in their hands mere scarification of conjunctivae harboring such lesions induced an intensified folliculosis over the entire membrane. These aspects of the problem as they concern spontaneous granular conjunctivitis of monkeys have already been discussed in one of our previous papers (1). Nicolle and Lumbroso believed that there might be a telluric or humic origin of the rabbit disease (*des maladies telluriques ou mieux humiques*). In their opinion, the fact of its spread by contagion from rabbit to rabbit does not render untenable the view that the origin of folliculosis is in the soil or humus with which the animal comes in contact.

After completion of the investigation on spontaneous follicular conjunctivitis of *rhesus* monkeys and chimpanzees, with results as given in the introductory paragraph of this paper, we began a similar study of rabbits, with the object of determining the etiology of the malady as well as any possible relationship of the conjunctivitides among different species. In the present paper, we shall describe the clinical and pathological appearance of the disease and the attempts to identify the nature of the causal agent. In a second article we shall report bacteriological investigations and discuss the significance of the results.

Clinical Observations

We have found, like Nicolle and Lumbroso (6), that the conjunctivitis as it occurs in rabbits exists in two forms, which we designate

respectively as the localized (Type I) and the diffuse (Type II). In either case, were it not for the disclosure of the lesions after eversion of the lids, and occasionally for the presence of abnormal secretion at the inner canthus or the caruncular region of the eye, the rabbits could be considered as wholly normal.

The Localized Form of the Disease.—In Type I of the spontaneous disease eversion of the lids discloses apparently normal conjunctivae except for an occasional case in which there is a mild degree of edema with injection of the vessels descending from the palpebral arterial arch. A closer examination, however, reveals at the canthi, more often the inner, three or four follicles in vertical alignment, like a chain of beads, or they may be irregularly massed, in a minute, hummock-like clump. The latter consists of four or five follicles of different sizes, the entire clump measuring from 2 to 3 mm. across the widest part. One or two isolated, small follicles may appear also in the mid-section of the conjunctiva. While Nicolle and Lumbroso have found the upper lids to be always free from lesions, we have observed, on the contrary, that about half of the animals examined reveal follicles situated in the upper palpebral conjunctiva in positions similar to those in the lower. In the upper membrane, however, the more frequent congestion and mild edema may mask the granulations. Considerable aid in such instances is afforded by the use of an ophthalmologist's loupe.

The essential lesion in the first form of the disease is the follicle. It appears as an elevation of minute, pin-point size which, discrete and located in the mid-section of the membrane, may measure up to 1/2 mm. in diameter. In general, the follicles resemble semitransparent, gelatinous sago-like granules, light greyish in color, with an even, smooth surface. Pressure between glass slides ruptures them, expressing a greyish, grumous substance which on microscopic examination will be seen to consist of cellular elements, notably large epithelial cells and monocytes. The follicles are never dark red and hemorrhagic, as are those occasionally met with in monkey folliculosis. The bulbar conjunctiva and the cornea are not involved in any way: there are no visible scars, pannus, ulcers or pits. The follicles may be transitory and disappear after several weeks but remission with newly formed lesions is the rule. In some animals the affection remains stationary for indefinite periods; in others more marked activity results in the development of all of the characteristics of the diffuse form of the disease. We shall describe later the transition of Type I to Type II.

The Diffuse Form of the Disease.—Type II of rabbit conjunctival folliculosis, although less often seen in nature than Type I, is more persistent and is usually associated with a progressive inflammatory reaction. While the type of follicles is similar in both forms of the disease, their distribution is different. In Type II the lower conjunctiva is also more markedly involved than the upper. The mucous membrane, dark red in color, presents injected blood vessels and a surface roughened and thickened by the underlying edema. It is covered in its entirety

by granulations of various size which may lie in parallel rows or be irregularly distributed. Here, as in Type I, the upper conjunctiva is also affected and reveals more marked congestion and edema with a resultant velvety appearance. Characteristic follicles, although scattered over the surface and especially at the inner canthus, are less numerous than those in the lower conjunctiva. There is often present a drop of greyish or faintly yellowish, mucopurulent secretion at the inner angle of the eye.

This description applies to the form of disease as it is ordinarily seen in nature. After the disease has become chronic, the entire lower membrane becomes studded with uniform sized granulations, not unlike a gravel stone mosaic in appearance. In such instances the membrane assumes the greyish color of the massed follicles. Pannus of the cornea, ulcers, pits or visible scars also do not develop in this form of the disease. In most of the animals an ovoid network of injected blood vessels, measuring about 5 mm. in the longest axis, is present in the bulbar conjunctiva at the upper pole of the corneal limbus.

In the diffuse type of spontaneous rabbit folliculosis, the disease lasts, as a rule, throughout the life of the animal. It is, however, essentially progressive, taking several weeks, or months, to reach a stage of stationary chronicity. During the progress of the affection infrequent exacerbations or remissions may nevertheless occur, but the general tendency of slow progression to chronicity with a fully developed reaction remains. Figs. 1, 2 and 2*a* show the lesions in the upper and lower conjunctivae in fully developed cases.

Relation of Type I to Type II of the Disease.—The question whether the lesions of the localized form of folliculosis are simply enlargements of pre-existing conjunctival lymphoid tissue (6), or whether they constitute another form of the same disease is answered by the results of the following experiments.

Two series of tests were undertaken. In one, 25 stock rabbits showing characteristic Type I folliculosis and kept under quarantine were observed for the purpose of noting the progress of the disease over varying periods of time. Ten of the animals developed, during the natural course of the affection, in the 4th to the 6th week of observation, the diffuse or Type II form of folliculosis.

In the second test, each of three anesthetized rabbits having Type I conjunctivitis with lesions in all four lids was scarified in the upper left membrane only, by means of stippling with a No. 22 hypodermic needle.¹ From 12 to 20 days later the animals revealed the diffuse type of folliculosis in the scarified conjunctiva,

¹ All experimental procedures on animals as reported in this paper were performed with the aid of ether anesthesia.

thence spreading during a period of 2 to 3 weeks from this lid to the other, untreated, membranes. As controls, fourteen rabbits having smooth conjunctivae were similarly scarified; none of these was specifically affected.

At this point it may be mentioned that, of over 50 rabbits with definite, characteristic Type II folliculosis, four showed retrogression of the lesions; after a month it became clearly evident that the disease took on the form of the localized type. This, as we have already stated, is an unusual occurrence; the diffuse form of folliculosis is, as a rule, progressive and persistent.

It would appear from the foregoing that the Type I affection is an expression of a mild form of the malady, and the diffuse type of a relatively marked form, one being convertible into the other by natural or artificial means. Whether the type of folliculosis which develops in an animal is correlated with the degree of its resistance or with environmental factors is unknown.

Histopathology

The results of microscopic examination in the two types of the disease offer additional evidence that both consist essentially of varying degrees of the same pathological changes. In Type I the lesions, chiefly follicular, are limited to only part of the conjunctiva, the remainder of the membrane being normal; in Type II, the entire lid is involved but with the same kind of follicular reaction (Figs. 3, 4, and 5). A description of the lesions existing in the diffuse form should suffice therefore.

The epithelium loses its continuity; here and there are observed more or less extensive areas of complete denudation of the membrane or its thinning out to a single cell layer, especially over a superficially placed follicle. Papillary hypertrophy does not occur; nor do the pseudocystic formations, known as post-trachomatous degenerations (concretions formed in epithelial pseudocysts due to papillary hypertrophy). In areas in which the follicles do not protrude beyond the lining epithelial zone, there is a mild degree of infiltration mainly with lymphocytes, but also with monocytes and polymorphonuclear leucocytes containing acidophilic granules.

The follicles are either discrete or confluent and develop in the more superficial layers of the conjunctiva. They consist chiefly of cells having clear homogeneous cytoplasm and vesicular nuclei without much chromatin. These clasmatocytes are more abundant in the center of the lesion in which may also be found lymphocytes and an occasional plasma cell. The lymphocytes show, however, a more pronounced disposition towards the periphery; but the orderly arrangement of a

definite center of clasmotocytes surrounded by a well defined zone of lymphocytes, such as is seen in other conjunctival follicular diseases, does not occur in rabbit folliculosis. A slender, fibrous capsule encircles the follicle. The blood vessels throughout the conjunctiva are dilated and distended with blood. In general, the lesion appears superficially like a granuloma, but granulation tissue and giant cells are absent (Fig. 6). On the other hand, bacteria are often seen, lying either free or intracellularly in the follicle. These will be described in the next paper of the series. We should state here, however, that *Bacterium granulosis* or *simiae* was not recovered from the affected tissues.

The cellular infiltration in the case of follicles that are in a relatively earlier stage of development is predominantly lymphocytic, although monocytes, primitive connective tissue cells and a few clasmotocytes are also visible; but encapsulation is not evident (Fig. 7).

Diet as a Causal Factor

In view of the fact that dietary insufficiency has been advanced as the causal factor of conjunctival folliculosis (7), an attempt was made to find whether an insufficient diet would cause the rabbit disease.

Nine rabbits having smooth conjunctivae and in an apparently healthy condition were quarantined. One or all of the conjunctivae were scarified once at the beginning of the test and then the animals were placed on a diet limited solely to oats. They rapidly became thin, the average loss of weight after 34 days being 483.3 gm. from an initial average weight of 2039 gm. None developed follicular conjunctivitis.

Restriction of the diet to oats did not give rise to folliculosis. Tests now to be described indicate that the disease can be conveyed from rabbit to rabbit by contact or by inoculation of folliculosis tissues. This being so, it is difficult to assume that the rabbit disease is telluric in origin (6) or that it is an expression of generalized adenoidism (8).

Transmission Experiments

(a) *By Inoculation of Affected Tissues.*—The entire affected conjunctivae of anesthetized rabbits having spontaneous folliculosis were removed and ground in a mortar with 0.9 per cent sodium chloride solution, in proportion of 1 cc. of the solution to four conjunctivae; the resulting tissue suspension was injected into the left lower conjunctiva and was also applied to the scarified conjunctivae of normal rabbits. In general, the methods used followed those of Noguchi (9) in his studies on trachoma.

For 3 or 4 days after receiving the affected tissue, the conjunctiva of the rabbit shows the acute, irritative effects of the inoculation and scarification; namely, congestion, edema and roughening of the membranes. This acute condition sub-

sides promptly and after another day or two, or 5 to 7 days after injection, a definite follicular conjunctivitis develops. The early stages reveal a membrane roughened in appearance with minute granulations especially at the inner and outer canthi and on the semilunar fold. From these marginal areas, the follicular reaction spreads over the entire palpebral conjunctiva in a period of from 1 to 3 weeks. Meantime the uninoculated conjunctivae become involved with the same type of inflammation, and within about a month all of the palpebral membranes are affected. The experimental disease is then indistinguishable from the affection occurring in nature. Infrequently the period of incubation of experimental folliculosis is prolonged to 2 or 3 weeks. Abscess formation does not occur following inoculation.

The following summarizes numerically the results of the tests.

The tissues were obtained from 20 rabbits having characteristic Type II folliculosis. As a rule, the material from two animals was pooled before injection. It was inoculated into the conjunctivae of 22 rabbits in all, two or three receiving each material. One of the 22 died early, one (of a group of three) was unaffected, and the remaining 20 reacted in the manner just described and developed the diffuse form of the disease. In one series of tests the affection was initiated in two rabbits having smooth conjunctivae by means of the subconjunctival injection of folliculosis tissue derived from a stock rabbit. By this means the disease has been transferred through six passages to date—each passage consisting of two rabbits—with positive results in all. Fig. 5 represents the lesions induced in one of the rabbits of the second passage.

On the other hand, conjunctival material showing localized folliculosis (Type I) seldom gave rise to the diffuse form of the disease. Thus, only one of three rabbits having Type I folliculosis evoked the diffuse form in two normal animals. Transfer of such material from the other two affected rabbits showed no specific effects in four normal animals.

The inference that the rabbit is highly sensitive to the agent causing diffuse conjunctival folliculosis is justified, since all but one animal showed characteristic diffuse folliculosis after injection with affected tissues. The agent producing the localized form of the disease proved to be less active.

(b) *By Instillation of Suspensions of Affected Tissues.*—The scraped follicles derived from two rabbits with the Type II disease were suspended in 1 cc. of saline solution and such a suspension was freshly prepared for use on each of 4 consecutive days. This was dropped into the conjunctival sac of three normal rabbits with gentle massage for some seconds. From 5 to 11 days after the last instillation, signs of folliculosis appeared and in 2 or 3 weeks developed into the characteristic, diffuse type. The same material inoculated subconjunctivally into two additional rabbits, as controls, induced diffuse folliculosis in both within a week.

(c) *By Contact.*—Two stock rabbits showing spontaneous diffuse folliculosis were placed in the same cage with two rabbits having smooth conjunctivae. After 15 days, both of the latter showed characteristic Type II folliculosis. As controls, three animals with clear conjunctivae were caged together; during 5 weeks' observation none was affected. The tests were repeated with the same outcome. The extension of the disease from the inoculated conjunctivae to the uninoculated membranes in other experiments, as already mentioned, is another example of contact infection, autogenous in origin.

The conjunctival folliculosis occurring spontaneously in rabbits is manifestly an infectious disease. It is not only transmissible by means of inoculation or even instillation of a suspension of the affected tissues, but it is also contagious: animals with smooth conjunctivae acquire the infection when merely caged with folliculosis rabbits.

The fact that the disease can be spread by contact emphasizes the necessity for rigid precautions during experimental work. For this reason, as well as because of the widespread distribution of the disease in nature, the choice of animals for such work is difficult. The best material is provided by the 2 or 3 month old litters of does free from conjunctival affections in that they are least likely to have the spontaneous disease. Animals are kept, as a rule, from 3 to 5 weeks in strict isolation and quarantine before use. In spite of these precautions, five of 204 animals developed localized follicular conjunctivitis during the early stages of quarantine.

Control Experiments.—The following control experiments would seem to indicate that rabbit folliculosis and the induced disease are a clinical entity resulting from a specific infectious agent.

In fourteen anesthetized animals the palpebral conjunctivae were merely scarified; in nine, the membrane was scarified and normal rabbit conjunctival tissue applied to it; and in nine, subconjunctival inoculation of similar material was made in addition to its application to the scarified tissue. None of these 32 rabbits developed folliculosis.

Twenty-eight animals were inoculated subconjunctivally with various bacteria encountered in cultures of conjunctival tissue obtained from monkeys or rabbits with or without folliculosis; and in addition, fourteen with cultures of either *Bacterium granulosis* or *Bacterium simiae* and seven with suspensions of sterile leptospira medium. Characteristic lesions were not produced in any of these animals.

Six rabbits received suspensions of human trachomatous tissues with negative results.

Suspensions of the conjunctivae of three *rhesus* monkeys showing characteristic spontaneous folliculosis (1) proved inactive on injection into the conjunctivae of six rabbits. Conversely, the tissue from the affected lids of six rabbits having fully developed folliculosis, which in each case evoked the experimental disease in other rabbits, failed to infect four *Macacus rhesus* and three *Macacus cynomolgus* monkeys. The issue of this last experiment adds to the list of control tests and does not accord with the finding of Nicolle and Lumbroso (6) that the rabbit affection is transmissible to monkeys.

Filtration Experiments

After the specific, infectious nature of spontaneous conjunctival folliculosis of rabbits was determined, we undertook a study of the filtrability of the causal agent through Berkefeld V candles or Seitz membranes. Cultures of *Serratia marcescens* (*Bacillus prodigiosus*) could pass through the former but not through the latter.

In all instances hormone broth, which favors the filtration of viruses and bacteria, was employed as diluent. The mucous membrane of the conjunctivae removed from rabbits having fully developed folliculosis was ground in hormone broth, 5 cc. being added to tissue derived from two to four lids. The thin suspension so obtained was allowed to stand in order to sediment the larger particles, and the supernatant fluid was then placed in a Seitz apparatus or in a Lilliput, size No. 5 Berkefeld V filter, the candle of which was covered with a fairly close fitting, inverted test tube so that nearly all the material could be passed through. Filtration was done at a negative pressure of 60 cm. Hg, and continued for about 10 minutes, the time required to obtain sufficient material for experimental purposes. The filtrate was seeded in leptospira medium but in no case was growth of any bacteria obtained.

Seven separate tests were made; in four, small size Berkefeld V filters were used, and in three, a single Seitz disc. In all but one experiment the affected conjunctivae obtained from two rabbits were pooled to prepare the suspension to be filtered. The unfiltered and filtered material was inoculated into two rabbits for each sample.

To summarize: In the seven tests all rabbits, fourteen in number, receiving unfiltered folliculosis material developed the characteristic experimental disease of the diffuse type. Of the corresponding fourteen animals injected with filtrates, thirteen were unaffected and only one showed folliculosis. The question may well be raised of whether this rabbit became infected accidentally through contact with the active agent of the disease.

It can be said, therefore, that the infectious element does not, as a rule, pass through Seitz filters which retain *Serratia marcescens*, or through Berkefeld V filters which are pervious to this organism.

Absence of Inclusion Bodies.—In view of the fact that filtrability by itself is not always an indicator of the character of an ultramicroscopic virus (10), we extended the study to include an examination of stained film preparations and sections of tissue from folliculosis cases, for the peculiar cytotropic effects which are characteristic of the action of many viruses (11).

Twenty-two rabbits showing fully developed folliculosis in early and late stages were examined by means of Giemsa-stained film preparations of follicular material. Two to four such slides were made from each rabbit and the microscopic examination included the contents of the entire film. In addition, sections of affected tissues removed from over 25 animals and stained with eosin and methylene blue or by the Giemsa method were studied microscopically. We could not find in these film preparations or tissue sections, either intra- or extranuclear inclusion bodies which might be referable to the action of an ultramicroscopic virus. Nor were the primary cellular changes caused by various viruses observed.

The evidence as given indicates that an ultramicroscopic virus is not the cause of the disease.

CONCLUSIONS

Spontaneous conjunctival folliculosis is widespread among various species of rabbits. It exists in two forms: Type I, in which the lesions are localized and the disease is relatively inactive, and Type II, in which the follicles are closely distributed over the entire surface of the conjunctivae and the affection is more active and characterized by extensive inflammatory reactions. One type can be converted into the other either by experimental methods or by natural processes.

The disease can be transmitted from rabbit to rabbit by means of subconjunctival inoculation of suspensions of the affected tissues or by instillation of such material into the conjunctival sac, or even by mere contact of folliculosis animals with rabbits having smooth conjunctivae. It is plain that the disease is an infection.

The causal agent of the infection is not filtrable through Seitz discs that retain *Serratia marcescens* nor through Berkefeld V candles that permit the passage of this organism. Furthermore, the lesions of the

spontaneous or of the experimental disease do not exhibit the cytotoxic effects or the inclusion bodies suggestive of the action of an ultramicroscopic virus. They are characterized, on the other hand, by a persistent and progressive chronicity and show certain resemblances to the granulomata.

The evidence suggests that the spontaneous conjunctival folliculosis of rabbits is due to a microorganism—one having a low grade pathogenic action. In a paper shortly to be published, a bacterium capable of reproducing folliculosis in normal rabbits will be described.

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EXPLANATION OF PLATES

All sections are stained with hematoxylin and eosin, except Fig. 4 which is stained with eosin and methylene blue.

PLATE 4

FIG. 1. Eye of stock rabbit having fully developed diffuse conjunctival folliculosis (Type II). The upper lid shows the velvety appearance of the conjunctiva, associated with numerous follicles. Natural size.

FIG. 2. Same rabbit, lower lid. Granulations diffusely scattered over the entire conjunctival surface. Natural size.

FIG. 2 a. Same as Fig. 2, in another rabbit.

FIG. 3. Localized conjunctival folliculosis (Type I) in a stock rabbit. The solitary follicle is to be noted. The remainder of the conjunctiva was practically normal (as shown in Fig. 4). $\times 122$.

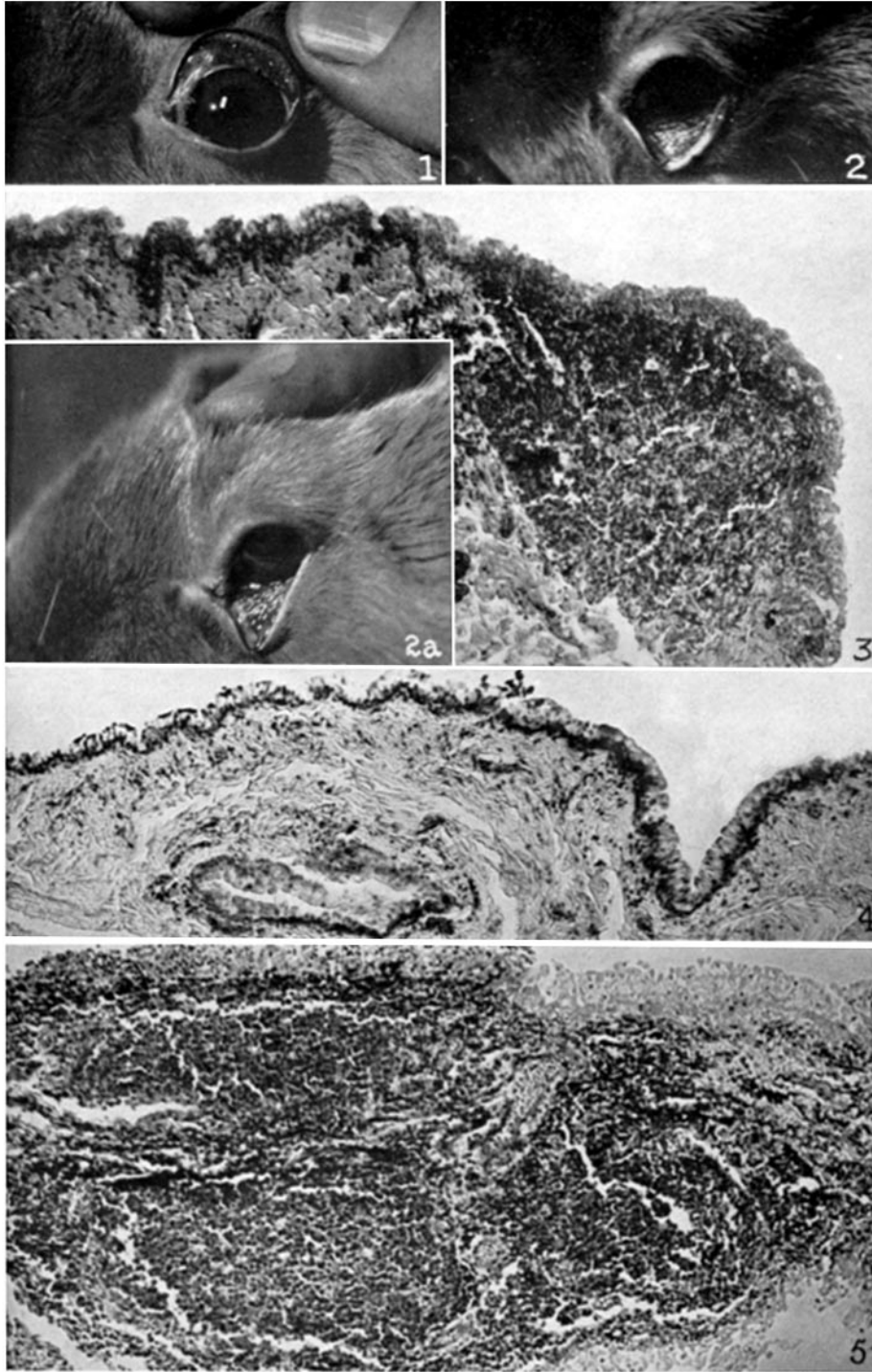
FIG. 4. Same as Fig. 3. The conjunctiva is normal in the portion free from follicles. $\times 122$.

FIG. 5. Rabbit conjunctiva, inoculated with affected tissue, showing diffuse folliculosis Type II. There is a marked follicular reaction with widespread inflammatory changes. $\times 122$.

PLATE 5

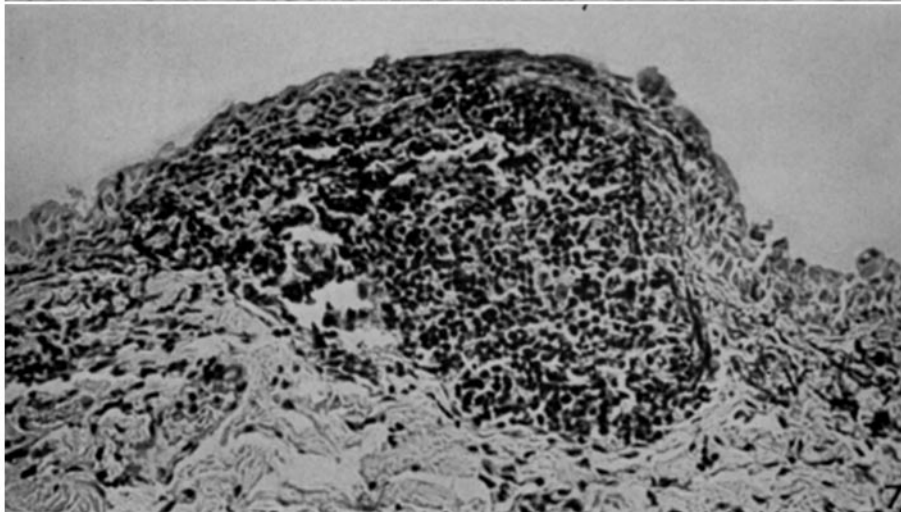
FIG. 6. Same specimen as Fig. 5. A higher magnification of the follicular structure which consists of light staining clasmatocytes, some lymphocytes and plasma cells. A fine fibrous capsule can be seen to be limiting the follicle. $\times 300$.

FIG. 7. A follicle in its earlier stages of development; Type I folliculosis. One sees monocytic infiltration with lymphocytic accumulation, at the margin more especially. Fibrous capsule absent. $\times 300$.



Photographed by Louis Schmidt

(Olitsky *et al.*: Conjunctival folliculosis of rabbits. I)



Photographed by Louis Schmidt

(Olitsky *et al.*: Conjunctival folliculosis of rabbits. I)