CORNEAL REACTIONS TO BACTERIUM GRANULOSIS AND OTHER MICROORGANISMS

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PLATE 31

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During the course of studies on the relationship of *Bacterium granulosis* to trachoma, it has been possible to produce lesions in monkeys and apes which closely resemble the conjunctival lesions of the human disease (1–3). Pannus, considered by many ophthalmologists as indicative of trachoma, has not, however, been demonstrated in the experimental disease.

Pannus is generally regarded as a circumscribed, vasculonebulous keratitis. As defined by Cuénod and Nataf (4): Pannus tenuis (or pannus vasculosus) is a type of lesion in which delicate, new-formed blood vessels lie in a faint opacity of the corneal surface. Pannus crassus, occurring infrequently, is an opaque thickening of the corneal epithelium with more extensive, yet less evident, vascularization. Fuchs (5) describes the microscopic lesion as a "vasculo-granular" infiltration of the corneal layers above and below Bowman's membrane. There is no uniformity of opinion, however, concerning the cause of this corneal change. Moretti (6), for example, believes that pannus is the result of propagation by contiguity to the cornea of the granular reaction in the conjunctiva, the alteration in appearance being due to the different anatomical substrate of the cornea. Many ophthalmologists support the opinion that the condition is caused by mechanical irritation: the repeated rubbing of rough, granular lids over the cornea eventually leads to injury of the membrane with later lymphoid infiltration and formation of blood vessels. De Schweinitz (7) states, however, that traumatic irritation may be only a predisposing factor.

Since corneal changes play such an important rôle in trachoma, and inasmuch as similar lesions have not been reproduced experimentally, we have studied the effects of injury to the cornea by various agents. In this way we have sought to determine the type and degree of stimulus necessary to produce the delicate, vascularized, corneal opacity characteristic of trachomatous pannus.

There are certain reasons for regarding the corneae of the lower animals as more resistant to injury than the human cornea. They are exposed to eye injury from foreign bodies and other agents and yet, under natural conditions, inflammatory and destructive corneal lesions are rarely encountered in them. Even when gritty and abrasive substances or material from cages in which the animals are confined find their way into the eyes producing occasionally superficial lesions of the cornea, no severe effects follow. As Noguchi (1) and ourselves (3) have shown, repeated subconjunctival injections of cultures of organisms which are found in the conjunctival sac of monkey and man suffering from different kinds of granular conjunctivitis (3) bring about either a transient reaction or none, while repeated application of cultures of *Bacterium granulosis* to the abraded cornea is without noteworthy effect.

In the light of these facts, it is more readily understood why the animal cornea does not tend to participate in the chronic granular conjunctival inflammation which can be induced either by human trachomatous tissues or by cultures of *Bacterium granulosis*, and why it becomes essential to inject microorganisms directly into the cornea in order to study their injurious action on that tissue.[1]

Methods and Materials

The action of the various microorganisms and of the tissue suspensions was first studied in rabbits. Then monkeys, either normal or taken during the height of experimental *granulosis* conjunctivitis, were used to study the effects of *Bacterium granulosis* after intracorneal injection.

Intracorneal Inoculation.—The animal was deeply anesthetized. The conjunctival sac of one eye was flushed with warm saline solution and a lid retractor inserted. The bulbar conjunctiva near the limbus was then grasped with a curved iris forceps, and with a No. 27 gauge needle the conjunctiva was penetrated and the point of the needle carried about 2 mm. beyond the limbus, into and toward the center of the cornea. From 0.05 to 0.075 cc. of suspension was gently injected into the tissue. Care was taken to avoid escape of the inoculum into the anterior chamber, in which event the results were less regular.

Corneal Examination.—A hand slit-lamp was used in a dark room for examination of the cornea. At times it was advantageous to anesthetize an animal so as to immobilize the eyeball.

Bacterial Suspensions Employed.—The inoculum consisted of a suspension of the

[1] All operative procedures on animals were done with the aid of ether anesthesia.

full growth of bacteria on blood agar slants. The suspension was made with the condensation water of the medium in 2 cc. of saline solution. The bacteria inoculated intracorneally in rabbits were:

1. *Bacterium granulosis*, eight strains, one sent us from Tunis by Dr. Phillips Thygeson, two from cases of trachoma in Denver, Colorado, and Albuquerque, New Mexico, and five from New York cases.[2]

2. Several varieties of bacteria isolated from normal or affected conjunctivae of man and monkey were pooled. These consisted of *Streptococcus viridans*, a Gram-positive diplobacillus, a diphtheroid, *Staphylococcus albus*, *Bacillus xerosis*, a Gram-negative, spore-bearing bacterium, and a small Gram-negative, chromogenic bacillus (two types).

3. *Staphylococcus albus*, two strains, obtained from the conjunctival secretions of a monkey having experimental trachoma.

4. Minute Gram-negative bacillus recovered from the filtrate of a suspension of human trachomatous conjunctival tissue.

5. *Bacillus xerosis*, from the unfiltered material of the latter case.

6. Small, Gram-negative bacillus, motile and chromogenic, isolated from the conjunctiva of a monkey with spontaneous granular conjunctivitis; also a similar organism, recovered from a case of follicular conjunctivitis in man.

7. A Gram-negative, proteolytic, chromogenic bacillus; contaminant of the Tunisian strain of *Bacterium granulosis*.

8. *Hemophilus influenzae*, a pathogenic, meningeal strain described by Pittman as Type b (8).

9. Pneumococcus, Type I, highly pathogenic for mice, derived from lobar pneumonia in man.

10. Pneumococcus, Type II, moderately pathogenic for mice; derived from the nasopharyngeal secretions of a healthy person.

11. *Streptococcus viridans*, from normal human nasopharyngeal secretions.

12. *Streptococcus hemolyticus*, from a healthy person.

13. Gonococcus, from a case of acute bartholinitis.

14. Gram-negative, motile, chromogenic bacillus derived from a Tunisian case of human trachoma.

Most of the varieties of bacteria employed were therefore derived from the conjunctival sac of man or monkey. In addition, series of rabbits were inoculated intracorneally with sterile leptospira medium, physiological saline solution, cultures of *Bacterium granulosis* killed by heating at 56°C. for 30 minutes, tissue suspensions from a case of human trachoma, and suspensions of scrapings of tissue from a monkey having *granulosis* conjunctivitis.

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[2] For the Western American cultures we are indebted to Dr. Rowland P. Wilson of Cairo, Egypt, and for the material yielding the New York strains to Dr. Martin Cohen, of New York City. For consultations and clinical examination of experimental animals, we wish to thank Dr. Martin Cohen and Dr. H. W. Wooton, formerly of the Trachoma Hospital, New York.

Experimental Results in Rabbits

Bacterium granulosis.—Four of twenty-five rabbits inoculated intracorneally with the Tunisian culture of *Bacterium granulosis* failed to develop corneal lesions.[3] With one exception (Rabbit A), to be described, the remaining twenty-one animals reacted uniformly.

During the intracorneal inoculation, a vesicle appears at the site of injection, about 3 or 4 mm. in diameter. This flattens out in a few hours, leaving a faintly greyish, wedge-shaped macula. On the following day, moderately intense congestion of the conjunctivae, ciliary injection, and diffuse, faint clouding of the upper third or half of the cornea appear. On the 3rd day the conjunctivitis and ciliary injection persist; the diffuse clouding of the cornea becomes lighter, and the wedge-shaped, greyish macula, with its base at the limbus, is less dense. At the same time a network arises of coarse, superficial vessels in the bulbar conjunctiva, tortuous and anastomosing, but in the main running in parallel lines from the fornix to the part of the limbus adjacent to the opacity just described. These vessels are seen only over a limited area, the width of which is demarcated by the extent of the base of the corneal lesion. The episcleral vessels in general are only moderately distended. On the 3rd to the 5th days, the signs of acute inflammation have subsided, while on the 6th day, the surface of the palpebral conjunctiva appears granular, the localized injection of the bulbar conjunctiva persists, and a definite clearing of the cornea occurs except at the site of inoculation. Here is seen a faint, greyish, wedge-shaped opacity, at the base of which are newly formed, superficial blood vessels arising from the conjunctival vessels at the limbus. From one to five or more interlacing superficial vessels can be seen entering the opaque region. On the 7th day, appearances reproduced in Fig. 1 are present. From now on to the 15th day, the localized vascularization proceeds actively; the anastomosing, fine vessels extend radially and terminate quite sharply at the apical end of the opacity, which is now faint and limited to the vascular zone. After 5 or 6 weeks the eye has returned practically to normal except for this zone, about 1.5 to 4 mm. at the base and about 4 to 6 mm. long. At this time the condition resembles closely pannus tenuis or pannus vasculosus of human trachoma. The lesions are still present in six of the animals 6 months after inoculation; in the remaining rabbits the corneal condition endured from 2 to 5 or more months.

The exceptional case referred to above (Rabbit A) was one in which *Staphylococcus aureus* infection was spontaneously superimposed on that of *Bacterium granulosis*. The reaction, after 7 days, as shown by Fig. 2, was much more severe, especially in respect to the granular conjunctivitis and the corneal involvement. The effect of secondary infection on *granulosis* conjunctivitis has already been described (3).

The corneal lesion at the height of the reaction shows foci of lymphoid infiltra-

[3] This strain was also non-pathogenic in *Macacus rhesus* monkeys.

tions with occasional plasma cells and large mononuclear cells. Numerous small, newly formed blood vessels are present in the involved areas. The main infiltration and vascularization arise between the epithelial layer and Bowman's membrane, in a space where these two layers have been forced apart. The substantia propria and the epithelium adjacent to the infiltrated areas likewise show a moderate degree of similar cellular invasion. The histology agrees well with descriptions of the changes of human pannus corneae.

In four rabbits, a second intracorneal injection in the same eye was made with cultures of *Bacterium granulosis*, and in one of them, a third and fourth. The reinoculations were made 1 to 2 months after the primary injection. The general effects of the reinoculations were much less marked than those of the first injection, and small corneal lesions endured for a period of only 1 to 3 weeks. It seems, therefore, that while complete resistance does not arise a partial immunity to later injections of *Bacterium granulosis* develops.

The fact should be pointed out that granular conjunctivitis is also produced but, because rabbits frequently exhibit this condition spontaneously and the subconjunctival injection of various substances produces it, the follicular reaction cannot be considered as specific.

Other Microorganisms.—The intracorneal injection of the pooled cultures of ordinary conjunctival microorganisms listed in the second group (see "Methods and materials," above) induced, after 24 hours, marked panophthalmitis in two rabbits. In one animal suppurative, destructive panophthalmitis occurred. In the other, hemorrhagic, non-granular conjunctivitis, cyclitis, iritis, and interstitial keratitis, with generalized vascularization of the cornea, and secondary glaucoma arose. In this rabbit a secondary cataract supervened 2 months later. The more pronounced residual signs after 6 months consisted of cataract, interstitial keratitis, and marked glaucoma.

Staphylococcus albus.—Within 24 hours after inoculation with this organism, three rabbits developed suppurative keratitis, follicular conjunctivitis, cyclitis, and iritis. 1 week later there was a narrow, circumferential vascularization of the cornea which continued to extend and to cover the entire membrane. After 6 weeks cataract formed in two animals and a corneal scar in the third. The rabbits with cataract had also a residual interstitial keratitis. Other rabbits of this series will be described later.

Bacillus xerosis.—24 hours after inoculation destructive changes in the external ocular tissues were demonstrable in two rabbits, and during the following 2 weeks abscess in the cornea, diffuse vascularized keratitis, secondary glaucoma, and cataract developed. The active lesions tended to subside so that the vascularization and opacity of the cornea diminished and came to be confined to the site of inoculation. Now, after 5 months, a localized vasculonebulous keratitis resembling that produced by *Bacterium granulosis* persists. Other residual effects are cataract and corneal scars.

Gram-Negative Bacilli from Spontaneous Monkey Folliculosis and Human Folliculosis.—Only a simple, transient, greyish white macula, about 3 mm. in

diameter at the site of inoculation was induced in two animals by the bacillus derived from a monkey. In two rabbits injected with the human organism, the only effect was persistent, circumferential arborization of fine conjunctival blood vessels at the limbus, with a few vascular branches barely penetrating the cornea. The upper one-half of the limbus was affected. Complete recovery occurred in from about a week to a month. Either a similar effect or no result whatever followed the injection of six rabbits with the Gram-negative, motile, chromogenic Tunisian bacillus described on page 805.

Proteolytic, Chromogenic Bacillus.—The organism induced, 24 hours after inoculation, a greenish tinged, small, localized abscess, accompanied in one of three rabbits by follicular conjunctivitis. The abscess and subsequent vascularized ulceration endured in one animal for 3 weeks, then retrogressed and healed. Other rabbits of this series will be described later in the section on dilution.

Hemophilus influenzae.—On the day following the injection of a culture, a diffuse, suppurative reaction set in. On the 3rd day appeared intense follicular conjunctivitis, purulent keratitis with localized abscesses, and fixation of the lens with an opacity on the anterior capsule. There was profuse, thick secretion in the conjunctival sac. Marked episcleritis and iritis were also observed. 1 month after inoculation vasculonebulous, localized keratitis was visible in one of two rabbits, which at the height of the reaction resembled the corneal change induced by *Bacterium granulosis*; but after 3 weeks it had completely disappeared.

Pneumococcus Types I and II.—Pneumococcus Type I was found to be lethal for rabbits after intracorneal inoculation: all nineteen animals injected died 24 to 48 hours later. At the time of death they showed active panophthalmitis. On this account a culture of Pneumococcus Type II was substituted. Within 24 hours, the culture induced at the site of inoculation an intense hemorrhagic and follicular conjunctivitis, and suppurative keratitis with localized abscess formation. After 10 days a uniformly clouded cornea with generalized, radial vascularization was observed, the vessels extending from the limbus toward the pupil. After 16 days, examination revealed characteristic localized vasculonebulous keratitis. This endured for 2 weeks, and then receded to complete disappearance in about 1 month. Other animals of the pneumococcus series will be described in the next section.

Streptococcus viridans.—The reaction of two animals to this organism almost paralleled the changes induced by Pneumococcus Type II.

Streptococcus hemolyticus.—Rapidly destructive panophthalmitis with early signs of meningoencephalitis followed the inoculation of hemolytic streptococci. Before the death of the four injected animals, streptococcal septicemia supervened.

Gonococcus.—24 hours after injection, an intense follicular conjunctivitis appeared, accompanied by hypopyon, suppurative keratitis and iridocyclitis, and after 10 days generalized vascularization of the cornea. Within 17 days there was noted a distinct localized vasculonebulous keratitis which endured in one rabbit for only 1 week and was present in another animal at the time it was sacrificed for microscopic studies 18 days later.

Filtrable Gram-Negative Bacillus.—Inoculation of a culture of this microorganism, described on page 805, induced at the site of inoculation only a transient bleb.

Control Materials.—A similar evanescent bleb formation followed the intracorneal inoculation of eight rabbits with sterile leptospira medium, saline solution, or heat-killed *granulosis* cultures.

Tissue Suspensions.—Four rabbits were injected intracorneally with unfiltered tissue suspensions: two with the ground conjunctival tissue derived from a human case of trachoma and two with similar tissues obtained from a monkey at the height of experimental *granulosis* conjunctivitis. As one might expect from the use of material containing a number of different microorganisms (3), two of the animals, one from each series, developed destructive panophthalmitis and died shortly thereafter. The remaining two rabbits showed a clinical course similar to that of the animals inoculated with the group of ordinary conjunctival bacteria (Group 2). The employment, therefore, of such tissue inoculations in rabbits for a study of specific lesions is impracticable.

The results obtained after intracorneal inoculation of rabbits with several varieties of bacteria show a wide diversity of effects. For example, organisms such as the filtrable Gram-negative bacillus and chromogenic bacilli (or control inanimate materials) fail to induce a specific reaction. On the other hand, pathogenic species, such as Pneumococcus Type I, *Streptococcus hemolyticus*, and others produce destructive, suppurative lesions of the eye and its appendages. Among the latter organisms, however, are a group of bacteria, such as Pneumococcus Type II and *Streptococcus viridans*, which are not so highly pathogenic. They give rise to milder suppurative lesions in the cornea, accompanied by transient inflammation of the conjunctiva, sclera, ciliary body, iris, and occasionally, the lens. After subsidence of the acute inflammatory reaction, within several days to about a month, localized, vasculonebulous keratitis resembling the lesion induced by *Bacterium granulosis* remains. *Bacterium granulosis* having a particular virulence of low degree causes regularly a non-suppurative, uncomplicated, more or less enduring, localized, vasculonebulous keratitis which has a certain resemblance to the pannus tenuis of human trachoma. The degree of the corneal reaction, therefore, serves as an index of the pathogenicity of the organisms.

Effect of Dilution.—The question arises whether cultures of bacteria having a high degree of pathogenicity can be made by dilution to induce vascularized opacities of the cornea.

Three highly pathogenic strains, Pneumococcus Type I, *Staphylococcus albus*, and the Gram-negative proteolytic bacillus (Group 7) were selected. Each of these had induced highly destructive, suppurative lesions, as already noted. Dilutions of cultures were made, in the case of the first culture from 1:10 to 1:1,000,000, of the second, from 1:100 to 1:10,000, and of the third from 1:10 to 1:100. Repeated experiments were made with undiluted, standard suspensions of the cultures and with the diluted materials.

The results of tests with diluted cultures, employing 50 rabbits, are summarized as follows: With respect to Pneumococcus Type I, injection of dilutions up to 1:500 or 1:700 caused generalized panophthalmitis and death of the animal within 24 to 72 hours. With dilutions from about 1:700 to 1:1,600 a minute abscess 1 to 2 mm. in diameter promptly developed at the site of inoculation, which was completely resolved after 1 to 2 weeks. In animals receiving dilutions of 1:1,500 to 1:4,000 an arborization of conjunctival vessels arose about the upper third of the limbus, with fine vascular branches penetrating superficially into the cornea for a distance of never more than about 0.5 mm. The condition lasted, as a rule, for about a month. Finally, with still higher dilutions, no noteworthy effects were visible.

The intracorneal inoculation of the diluted cultures of staphylococci and of proteolytic bacilli gave rise to similar reactions: Lower dilutions caused minute abscesses with the vascular penetration of the cornea as described in the preceding paragraphs, and higher dilutions were inactive.

The results of the tests indicate, therefore, that dilutions of cultures that produce severe, destructive, suppurative changes in the rabbit's eye fail to bring about the distinctive vasculonebulous keratitis.

Experimental Results in Monkeys

In view of the results obtained with *Bacterium granulosis* in rabbits, we turned next to monkeys, in which the specific conjunctival lesions due to *Bacterium granulosis* appear.

Four normal monkeys and three with experimental trachoma were each inoculated in the cornea of one eye with H. D. strain of *Bacterium granulosis*—a strain which consistently produced pannus-like lesions in the rabbit.

Two of the normal monkeys showed in from 6 to 13 days after inoculation the characteristic, small, limited, wedge-shaped keratitis similar in appearance and development to the lesion seen in rabbits. No suppurative or other involvement of the cornea was detected. After about 2 weeks, the conjunctivae of the inoculated eyes revealed congestion, edema, roughness, and a number of follicles, simulating experimental trachomatous conjunctivitis. The third monkey showed early hypopyon, episcleritis, and cyclitis. It is possible that some of the material entered the anterior chamber, under which condition these changes might have been produced; in any event, after 2 weeks, the monkey exhibited a pannus-like

lesion and characteristic granular conjunctivitis. The fourth monkey died of tuberculosis shortly after inoculation.

The three monkeys showing experimental granular conjunctivitis, which were inoculated intracorneally with the same strain of *Bacterium granulosis*, yielded similar corneal changes. In addition, the congestion and edema of the conjunctiva became more marked, showing more numerous and succulent follicles in the palpebral, as well as in the bulbar conjunctivae of both eyes (Fig. 3).

At the present time, 6 months after inoculation, three of the five animals which showed corneal lesions still have pannus-like changes, and two have completely recovered after the condition had persisted for 3 or 4 months. One animal, inoculated about a month ago, is still exhibiting localized vasculonebulous keratitis.

The two animals reported in the preceding paragraph as having recovered have been reinoculated intracorneally with the same organisms, 4 months after the original injection. Although both eyes were inoculated, in neither has any reaction been obtained. Thus, as already shown in the rabbit, a certain resistance to reinoculation can be secured in the monkey.

The direct intracorneal inoculation of *Bacterium granulosis* in *Macacus rhesus* monkeys induces a vasculonebulous keratitis which is indistinguishable from the lesion obtained in rabbits, and is similar in the degree of reaction, at least, to pannus tenuis or vasculosus of human trachoma. Furthermore, this procedure can give rise in normal monkeys to granular lids resembling the experimental trachomatous disease. In monkeys showing granular conjunctivitis before corneal injection, there is an exacerbation of the signs of the preexisting conjunctivitis.

DISCUSSION AND SUMMARY

The conclusions which may be drawn from the results of the experiments here presented are:

1. The cornea of the rabbit is highly sensitive to the action of various injected bacteria. The lesions vary from insignificant, transient changes to severe, destructive panophthalmitis, with fine gradations from the mildest to the violent form of inflammation. Moreover, animals that receive the same organisms show like changes.[4]

[4] As early as 1880, Councilman (9), applying caustics, such as silver nitrate or cautery, to the corneae of frogs and cats, found that the cornea "offers special advantages . . . . from the comparative ease with which it can be investigated both in the fresh and prepared condition, from the facility with which inflammation *varying in extent and intensity* can be produced here and from the unity of its cellular elements."

2. The varying degree of inflammatory reaction is related to the pathogenicity of the special culture employed; as, for example, is shown by the reactions to Type I pneumococci and to *Bacterium granulosis*. It is evident that when a microorganism having a certain degree of virulence is used, a lesion of localized vasculonebulous keratitis resembling pannus tenuis or vasculosus of human trachoma can be induced. Thus *Bacterium granulosis*, *Bacillus xerosis*, *Hemophilus influenzae*, Pneumococcus Type II, *Streptococcus viridans*, and gonococcus can cause the pannus-like corneal changes in the rabbit. Of these organisms, however, only *Bacterium granulosis* induces early, uncomplicated and enduring keratitic lesions;[5] the others cause first, diffuse keratitis with suppurative lesions; then, as a residual effect, transient, localized, vasculonebulous changes in the cornea. These changes, in contradistinction to the *granulosis* lesions, are, therefore delayed, complicated, and transient. When, on the other hand, the invasiveness and infecting power of the organisms are low, as is the case with the filtrable, Gram-negative bacillus and the small, Gram-negative bacilli ultimately derived from cases of folliculosis, no marked effect is produced by their intracorneal inoculation. If the pathogenicity of bacteria is high (as shown by Pneumococcus Type I, hemolytic streptococcus, and the remaining bacteria), intracorneal inoculation of the microorganisms leads to serious suppurative or destructive changes.

3. The results of experiments with monkeys indicate that while pannus is not a sequel of experimental trachomatous conjunctivitis, a lesion resembling it follows intracorneal inoculation of *Bacterium granulosis*.

4. One can infer from these results, therefore, that the stimulus necessary to produce corneal changes in animals, similar to those of

[5] The extent of the typical *granulosis* reaction was found to be limited to the area in which the initial injection was made. Thus, if the upper sixth of the corneal surface was inoculated, only that part was involved, while if a series of injections were made around the entire margin of the cornea, the whole membrane became affected. The lesion in any one part, then, was identical with that in any other. That several of the reactions obtained were smaller than some of the lesions seen in human trachoma, appeared to be dependent only upon the size of the inoculation bleb. This condition did not hold for highly pathogenic organisms.

trachomatous pannus, is an agent having a definite but extremely low power of invasiveness and infectivity.

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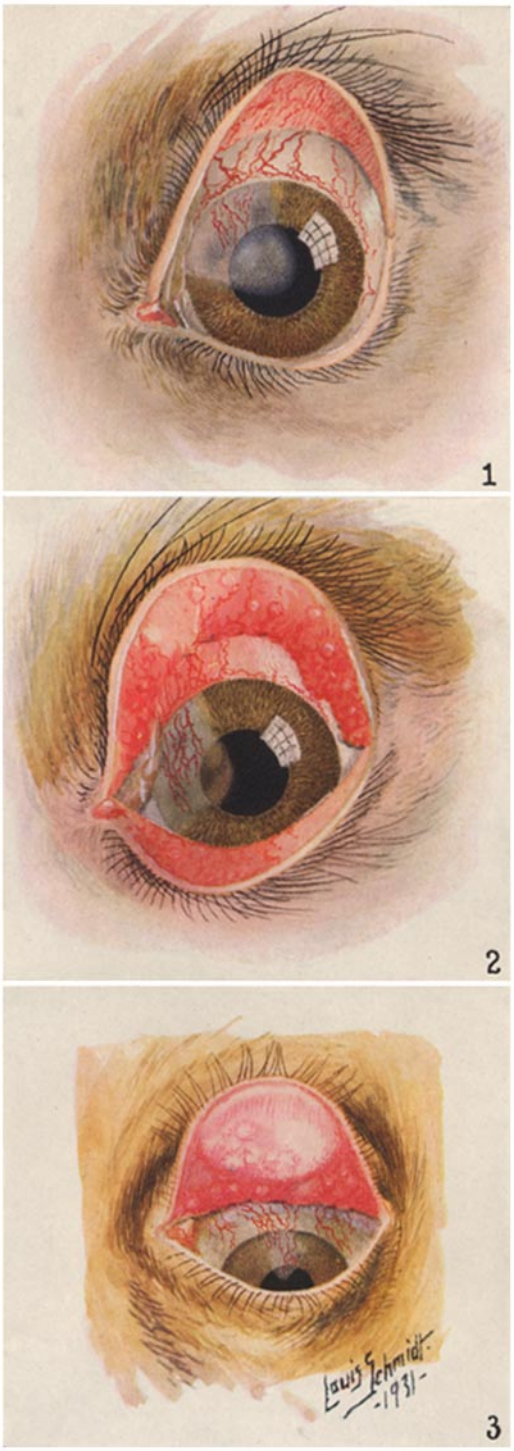
EXPLANATION OF PLATE 31

All drawings about twice natural size.

FIG. 1. Eye of rabbit inoculated intracorneally with a culture of *Bacterium granulosis*. 7th day of reaction. Outstanding features are the congested, edematous, and roughened conjunctiva; the coarse, anastomosing vessels in the bulbar conjunctiva, and the focal vasculonebulous keratitis. The opacity of the cornea later became fainter and smaller, so that within a month the lesion resembled that shown in Fig. 3.

FIG. 2. The same as in Fig. 1, except that a spontaneous secondary infection with *Staphylococcus aureus* occurred. The follicular reaction in the palpebral, and the vascular lesion in the bulbar conjunctiva, as shown, are more marked.

FIG. 3. *Macacus rhesus* monkey, having experimental granular conjunctivitis as a result of subconjunctival inoculation of *Bacterium granulosis*, was injected intracorneally with this organism on the 38th day of the disease. The follicular conjunctival reaction then became more pronounced and follicles were also seen on the bulbar conjunctiva. The drawing was made about a month after the intracorneal inoculation. It shows a marked granular conjunctivitis; two small scars in the palpebral conjunctiva; coarse, anastomosing vessels in the bulbar conjunctiva, limited to the area of the corneal lesion; succulent, large follicles in the bulbar conjunctiva, and the characteristic focal, vasculonebulous keratitis.



(Olitsky *et al.*: Corneal reactions to *Bacterium granulosis*)