

To Dr. Jas. S. Billings, U. S. Army, *abl*
Randolph (R.L.) with the compliments
of R.L. Randolph

A CONTRIBUTION TO THE PATHOGENESIS OF
SYMPATHETIC OPHTHALMIA; AN
EXPERIMENTAL STUDY

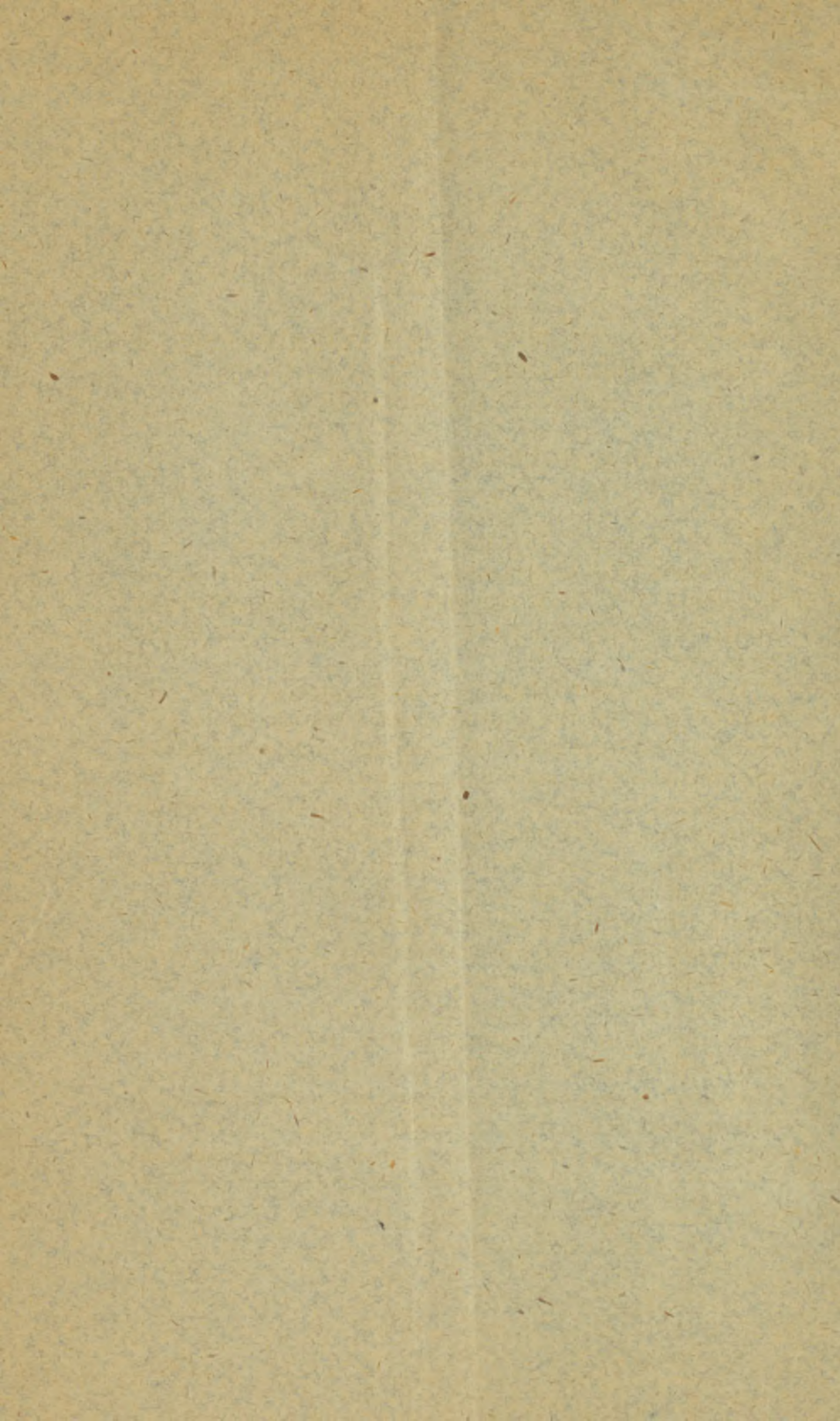
BY

ROBERT L. RANDOLPH, M.D. ✓

ASSISTANT SURGEON TO THE PRESBYTERIAN EYE AND EAR CHARITY HOSPITAL, BALTIMORE, M.D.



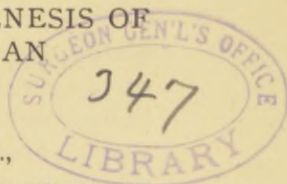
[Reprinted from the ARCHIVES OF OPHTHALMOLOGY, Vol. xvii., No. 2, 1888]



A CONTRIBUTION TO THE PATHOGENESIS OF
SYMPATHETIC OPHTHALMIA; AN
EXPERIMENTAL STUDY.

By ROBERT L. RANDOLPH, M.D.,

ASSISTANT SURGEON TO THE PRESBYTERIAN EYE AND EAR CHARITY HOSPITAL, BALTIMORE, MD.



FORTY years ago William Mackenzie summed up his conception of sympathetic ophthalmia in the following words¹: "I think the chief medium through which sympathetic ophthalmitis is excited is the union of the optic nerves."

This theory found most general acceptance among ophthalmologists till the appearance of Heinrich Müller's investigations fifteen years later. Müller² endeavored to find the channel of communication in the ciliary nerves. His conclusions were drawn from the anatomical examination of three eyes, which had been enucleated through fear of sympathetic disease in the fellow eyes. While conceding the possibility of inflammatory transmission along the optic nerves, "the irido-choroiditis of the first eye," he says, "has progressed so far that advanced atrophy of the optic nerve is present. The nerve is nothing more than a fibrous cord incapable longer of conducting an irritation, or indeed any other process, so that simply cutting through the optic nerve will not lessen the chances of sympathetic trouble. The ciliary nerves, on the other hand, do not easily atrophy. The majority of eye diseases attack the anterior half of the eye, and consequently the ciliary nerves from their position

¹ Mackenzie: "Diseases of the Eye," 4th edition, p. 597, 1885.

² v. Graef's *Archiv für Ophthalmologie*, iv., S. 367-370.

would be more exposed to irritation. And when the inflammation of the second eye makes its appearance under the garb of irido-choroiditis, as it frequently does, it is far more logical for us to assume that the inflammation was brought about through the ciliary nerves than through the optic nerve. It is not improbable, that the ciliary nerves exercise some direct influence upon the nutrition of the retina and optic nerve."

The fact (if it be a fact) that changes in the structure of the ciliary nerves are rarely seen, I look upon as one of the strong points in favor of the ciliary-nerve theory, though many of the opponents of this theory think differently. They regard the lack of pathological changes in the ciliary nerves as proof positive of their non-participation in the inflammation, having the idea that the inflammation travels along the ciliary nerves from one eye to the other, producing structural changes throughout its course. But this is hardly possible, certainly not probable. We are only at liberty to assume that the inflammation in the injured eye calls forth a functional irritation of the sensitive ciliary nerve fibres, and this influence finds its way through reflex action to the fellow eye. Pathological changes in the ciliary nerves would interfere with the propagation of such an irritation or influence—their soundness then speaks for and not against the theory. It should not be lost sight of that the ciliary nerves of one eye transmit influences or conditions to the fellow eye through reflex action, and not, as it is possible in the case of the optic nerves, through direct continuity.

The ciliary-nerve theory found a most ardent supporter in v. Graefe, and I might say in the majority of ophthalmologists up to within twenty years ago.

The subject of sympathetic eye troubles was ably discussed by Mauthner in his well-known monograph, "Sympathetic Diseases of the Eye," which appeared in 1879.

In speaking of the possibility of transmission through the blood-vessels, he thinks that the inflammatory process, starting in the choroid of one eye, might be carried over through the choroidal vessels to the ophthalmic artery;

from this point to the internal carotid, and from thence to the circle of Willis. The inflammation then passes along the anterior arch of this circle into the opposite ophthalmic artery, and so to the choroidal region of the second eye. He seems to think though that this is the least tenable of the theories, and consequently lays very little stress upon it. In discussing the optic- and ciliary-nerve theories, his arguments are characterized rather more by diplomacy than by a pronounced individual opinion, for he commits himself to neither of the two. "We have, on the whole," says he, "no right at all to ask whether the sympathetic affection is transmitted along the optic nerves or along the ciliary nerves; nor can we ask whether the transmission takes place along one path more frequently than along the other, for the transmission may be affected in both ways."

The subject was most exhaustively treated from an historical standpoint, but, from the unsettled tone of the work, the Vienna professor leaves his readers, barring a better insight into its history, with as vague an idea as possible of the pathogenesis of sympathetic ophthalmia. Not long after this the old Mackenzie theory was revived by Horner¹ and Knies,² and, while convincing some, it had probably quite as healthy an effect in stimulating investigation in this probably the darkest field of eye pathology. The revival of this theory was the result of observation of a case of iritis serosa in a girl nineteen years old. In the left eye there were deposits about the size of pins'-heads on the membrane of Descemet. Nothing of the fundus could be seen with the ophthalmoscope. She counted fingers at a distance of six feet. In the right eye there were slight deposits in the lower half of the cornea about Descemet's membrane. The corpus vitreum was clear. The papilla was markedly red and somewhat foggy. There were no synechiæ on either side. The patient was seized with violent bronchitis, and died soon after from gangrene of the lungs. From sections made the following was noted. The

¹ *Correspondenzblatt für Schweizer Aerzte*, ix., Jahrg. 9, No. 21.

² *Archiv für Augen- u. Ohrenheilk.*, ix., 1.

entire iris was immensely infiltrated with round cells, so also the ciliary body and the choroid as far as the optic nerve. The latter showed evident neuritis and cell infiltration, which continued on into the orbit and as far as the chiasm. At this point the pial sheath of the nerve was markedly infiltrated.

This condition was present in both eyes, and, in consequence, the idea suggested itself that, between the two eyes affected alike, a channel of communication through the medium of the optic nerve might exist. And particularly as sympathetic eye inflammation most frequently makes its appearance under the garb of iritis serosa and premonitory papillitis, Knies concluded that the inflammation had travelled from the originally injured eye up its optic nerve to the chiasm, across the latter to the other optic nerve, and from there down to the fellow eye. Horner and Knies thought that they had found still further foundation for their theory when, on injecting a colored fluid into the sub-arachnoid space of one nerve, it was found to have forced its way through the chiasm into the other nerve sheath.

"The pathologico-anatomical fact and the experiments will at least justify us," says Horner, "in explaining the transmission of the sympathetic process as having occurred through the lymph spaces, and we ought now to abandon the uncertain field of reflexes, vaso-motor disturbances, and neuropathic inflammations."

In 1881 the subject was given still further impetus by the researches of Snellen, Berlin, and Leber.

These three advanced the opinion that the inflammation was of parasitic origin, and hence the appearance of the disease in the second eye must rest upon an infectious basis. They all agreed as to the nature of the ophthalmia, though they did not entertain the same opinion as regards the mode of transmission. Snellen¹ held that it was a specific inflammation, metastatic in nature, where the organisms were peculiarly adapted to the choroidal tissue, and were transmitted through the lymph spaces of the optic nerve, and furthermore, he says, "if this theory of infection is the

¹ Transactions of the International Medical Congress, London, 1881.

true one, the only path for the transmission of the organisms is the optic nerve."

Berlin¹ contended that a portion of the inflammatory products of the first diseased eye was taken up into the general circulation. These products can remain anywhere stationary in the organism without further development, simply because they do not find the conditions suitable for their nutrition. If, however, they get into the capillary region of the uveal tract of the other eye, they there find circumstances analogous to their mother soil, and develop and give rise to inflammation. Leber² said that typical inflammations of the coats of the eye are promoted in their development chiefly through the blood-vessels, it making no difference whether the cause of the inflammation was of septic, rheumatic, or tuberculous origin.

Such an assumption, says he, is quite as admissible for sympathetic ophthalmia.

Berlin's hypothesis that the inflammation is a specific metastatic one, and transmitted through the blood-vessels, opens up the possibility of inflammatory appearances in other parts of the body. But this is never the case. The other eye alone becomes involved. Such an hypothesis, then, would only be tenable when we suppose that the nutrition and circulation in the eye differ from those of the rest of the body, that the eye possesses unique conditions for the growth of lower organisms, and that these organisms, in consequence, can attain their growth in the second eye, and nowhere else in the body. We cannot assume this peculiarity for the circulation in the eye in contradistinction to that of the rest of the body. The mere fact that the other eye alone is attacked, leads us to believe that the cause must be a local one. By far the greater number of sympathetic eye troubles are caused by the entrance of foreign bodies. Clinical experience shows us every day that wounds resulting from infectious foreign bodies cause the most violent inflammations, and, on the contrary, wounds caused by aseptic matter, result in comparatively little disturbance.

¹ *Vollmann's Samml. klin. Vortr.*, No. 186, 1880. *v. Graefe's Archiv für Ophth.*, xxvii., S. 327.

² *Ibid.*, vol. xxvii.

Not long ago I took occasion to perform some experiments on dogs for the purpose of establishing this fact. After sterilizing a cataract knife I made an incision at the upper border of the cornea about half an inch below its junction with the sclera. I passed the knife into the iris and cut upward entirely through the corneo-scleral junction as far as the ciliary region, and in several instances into the latter. The cornea healed up promptly; so also the iris, the healing process in the latter being exactly similar to that after a successfully performed iridectomy. The media always remained clear, and not a symptom of cyclitis followed the operation. Naturally for thirty-six hours after the experiment there was some slight photophobia and lachrymation, but these soon passed away. Leber¹ has shown very conclusively that aseptic foreign bodies may remain in the eye indefinitely without giving rise to inflammatory symptoms. Against the ciliary-nerve theory, says Leber, there remains unexplained the fact that a fixed time, six or eight weeks, passes between the inflammation of the first and second eye, and this is just the time required for the transmission of the inflammation along the optic nerve. Another fact against the ciliary-nerve theory. How can we explain the occurrence of sympathetic trouble after the enucleation of the injured eye? If we attribute the sympathetic inflammation to the presence of the injured eye acting as an irritant to the ciliary nerves, should we not suppose that after the enucleation of that injured eye, all danger of subsequent trouble in the second eye was removed immediately and for all time? As regards the outbreak of the disease years afterward,² Leber attributes it to a subsequent attack of the old process, or possibly to a fresh infection of the originally inflamed eye. He thinks that too much stress has been laid upon the sensitiveness to touch in the ciliary region as indicating excessive ciliary irritation, regarding this sensitiveness as due simply to the inflamed condition of the whole eye. This is a most reasonable supposition—for almost any inflamed organ or part would be abnormally

¹ *Von Graefe's Archiv für Ophthalmologie*, xxx., 1.

² "v. Graefe's Archiv für Ophthalmologie," xxvii., 1., S 333.

sensitive to pressure, and why not the ciliary region? We undoubtedly have sympathetic ophthalmia without increased sensitiveness in the ciliary region. Another strong point against the ciliary-nerve theory seems to me the condition we have in glaucoma. In this disease, as is well known, irritation of the ciliary nerves is of so violent a type, that its reflex influence is seen not only in the most excruciating facial neuralgia, but even in parts as remote as the stomach we have functional disturbance manifesting itself in nausea and vomiting. And yet no similar condition of affairs as a result of sympathy is seen in the other eye.

Wounds in the ciliary region are thought to peculiarly predispose to sympathetic ophthalmia. I thought in connection with this latter idea that I would make some experiments simply to observe the result of wounds inflicted in the ciliary region. My experiments were made on dogs. In every case the instruments were sterilized and introduced through the corneo-scleral junction. The wound was extended from this point up through the ciliary region. I purposely produced a prolapse of the iris into the wound, inasmuch as this kind of wound—*eingeklemmte Wunde*—is thought to be by some a most favorable condition for the development of sympathetic trouble. In none of the cases did any excessive inflammatory reaction follow. Hyperæmia of the iris,—but no adhesions—photophobia, lachrymation, and some slight injection in the vicinity of the wound were the only results. Two weeks afterward, on examination with the ophthalmoscope, I found the media perfectly clear, and the iris had healed in the corneo-scleral wound, no sensitiveness to light or to touch. The fundus was in every respect normal. The dogs were kept under observation for four or five weeks, and at different times I examined them, but never found any further pathological change. This fact appears undoubtedly significant, for it at least shows that injuries to the ciliary region are not, in themselves, sufficient to produce a sympathetic disturbance, something else is necessary, a something modifying the character of the wound itself.

Of all the contributions to the pathology of this subject,

the work of Prof. Deutschmann, has probably attracted the most widespread attention ; and his results have been regarded by many ophthalmologists as settling the question beyond a doubt.¹ His earliest experiment was made with the spores of the *aspergillus fumigatus*, and consisted in making repeated injections of a suspension of these organisms into the corpus vitreum of a rabbit. Choroido-iritis followed the first injection, and at the end of four weeks, or a few days after the fourth injection, he discovers choroido-iritis and opacities in the vitreous of the fellow eye. The animal is killed, and the microscopic examination confirms in every respect the diagnosis. Evidences of an inflammatory process are seen throughout the inoculated eye. Neuritis interstitialis extending on up to the chiasm, with an involvement of the latter, is observed, the process passing on down to the other eye by way of its optic nerve. The iris and ciliary region of the sympathetically affected eye were not examined ; the posterior half of the eyeball showed abundant signs of inflammation in round cell infiltration. He concluded, therefore, that a sympathetic inflammation may be produced in one eye by the introduction of infectious matter into the other eye, and that the track of this inflammation is along the optic nerve and its sheaths. Being convinced, though, that the inflammation produced by the *aspergillus fumigatus* was the result of chemical irritation, and knowing that such an irritation is rarely, if ever, concerned in the production of sympathetic ophthalmia in human beings, he resorted to the pus² or ganism for the inoculating material. He injects then two or three drops of a suspension of *staphylococcus pyogenes aureus* into the corpus vitreum of one eye. On the following day posterior synechiæ and corpus vitreum opacities are observed. On the second day the animal shows signs of meningitis, no new feature, as far as could be seen, showing itself in the inoculated eye. The papilla of the fellow eye, however, was very red and injected, the vessels enlarged and tortuous. The animal dies on the third day.

¹ v. Græfe's *Archiv für Ophthalmologie*, xxviii., 2 ; xxix., 4.

² v. Græfe's *Archiv für Ophthalmologie*, xxx., 4.

The microscopic examination reveals purulent infiltration of the inoculated eye, this infiltration extending on up toward the chiasm with diminishing intensity, to increase in intensity, however, in its passage from the chiasm down the second optic nerve. In the infected eye both optic nerves, the chiasm, the pia mater of the base of the brain, and in the papilla of the fellow eye the presence of microorganisms is proven, viz.: the staphylococcus pyogenes aureus. To avoid the complication of meningitis, he makes a very dilute suspension of the micrococci, and inoculates five rabbits. Only one of the animals gives a negative result; negative in so far that after remaining alive for several weeks, no change was observed in the fellow eye. The other four animals die at periods ranging from five or six days to two or three weeks. The participation of the second eye shows itself in papillitis, cloudiness of the retina, narrow pupil, and sluggish iris. There is no symptom of meningitis, but the animals lose their appetite and die after a few days. Cultures from the blood of the animals reveal the staphylococcus aureus. The cause of death, then, is a general infection. As regards the microscopic examination of the eyes and optic nerves. The fate of the first eye is generally iridochoroiditis, followed by phthisis bulbi. Round cell infiltration with micrococci were to be found in both optic nerves, chiasm, and in the posterior half of the second eye,—a typical sympathetic ophthalmia, he concludes, in all but one feature, namely, in the non-participation of the iris and ciliary region of the fellow eye. And the reason the iritis is absent, says he, is because the animals die before the organisms have time to reach the anterior portion of the eye. If, then, he can shorten the path which the organisms take in their journey to the anterior portion of the uveal tract of the second eye, he will be able to produce an iritis before the death of the animal, and will have proven that had the animal lived long enough, a sympathetic iritis would have developed itself. For this purpose he makes the following experiment: After a tenotomy of the superior rectus muscle, he passes in a delicate blunt instrument, and pulls forward the optic nerve, which

he severs as close as possible to the optic foramen. Into the cut end he injects a very small quantity of a suspension of staphylococcus aureus, and ties up the cut end to prevent the escape of the fluid into the orbit, and then replaces the parts. It is sufficient to say that on the third day he establishes the existence of iritis with hypopyon, and the microscopic examination shows purulent infiltration of the iris and ciliary region.

In eight or ten cases where one eye had been enucleated on account of imminent danger of sympathetic ophthalmia in the fellow eye, Prof. Deutschmann detects the presence of the staphylococcus aureus and albus. He concludes then that sympathetic ophthalmia in man is most probably an inflammation propagated through the optic nerve and that the "Entzündungserreger" are micro-organisms.

Such striking results would seem to promise an easy confirmation, and with this idea I determined to repeat the experiments of Deutschmann. My earlier experiments were made upon dogs. I chose dogs as I supposed they would be less likely to succumb to the effects of a general infection and in consequence they would enable me to follow out more accurately the theory of Deutschmann. My technique was the same as that employed by Deutschmann—and consisted in injecting a suspension of staphylococcus aureus into the corpus vitreum. The instruments employed were always thoroughly sterilized previous to the operation. About two minims of the inoculating fluid were injected. After fixing the ball of the eye with a pair of forceps, I pulled the eye forward and passed in a hypodermic needle half an inch posterior to the ciliary region. I may add that the organisms were obtained from a furuncle and were identical with the staphylococcus aureus of Rosenbach.

I have selected for this paper the clinical history of those cases killed at periods ranging from three weeks to two months, as covering the most probable time in which a sympathetic trouble would develop.

CASE I.—June 16th. Inoculated a small black bitch in the right eye, injecting two minims of the suspension in sterilized water. A slight clouding of the vitreous was observed a few hours

later. The morning after the operation the media had become so cloudy that it was impossible to get a view of the fundus. Iridocyclitis ensued, followed by panophthalmitis and rupture of the eyeball, the latter occurring on the third day after inoculation. Healing of the ruptured eye was very prompt. I examined the other eye with the ophthalmoscope every day, but never detected any thing abnormal. The animal was killed on July 9th. The eyes were carefully dissected out with their optic nerves and chiasm. Marked phthisis bulbi of the inoculated eye was observed, but no atrophy of the nerve, indeed there was no difference in the macroscopic appearance of the two nerves. Microscopic examination showed the bulb of the inoculated eye densely infiltrated. Everywhere throughout the uveal tract, retina, and vitreous lymph cells were abundant. The papilla was very much swollen and was densely infiltrated with round cells. This cell infiltration extended on up the nerve involving not only the trunk of the nerve itself, but also its sheaths and the intervaginal space. This infiltration rather decreased in intensity as it neared the chiasm, and at this point it was hardly possible to say with certainty whether the physiological number of nuclei had been overstepped. There was certainly nothing that would be regarded as pathological in that part of the chiasm continuous with nerve of the healthy eye. Examination of the second eye and its nerve revealed a perfectly normal condition of the parts. There was no cell infiltration of the orbital tissue adjacent to the inoculated eye, nor of any portion of the brain touching upon the optic nerves and commissure. The most careful examination failed to reveal the undoubted presence of organisms.

CASE 2.—June 29th. Inoculated in the usual way a white poodle. Clouding of the vitreous in the course of a few hours. Next day the eye was enormously swollen, showing evident panophthalmitis. The eyeball ruptured on the fourth day. The dog was allowed to live till the middle of November, when it was killed. At no time did the other eye show any signs of sympathy. Microscopic examination showed the inoculated eye to be infiltrated throughout with round cells. The eye had shrunken so much that the relative position of the coats had been lost. A cheesy mass filled the space once occupied by the vitreous. The papilla was swollen. Marked papillitis and neuritis, the latter extending about one inch from the intraocular end of the nerve. The chiasm, the optic nerve of the second eye, and the latter itself were all perfectly normal. I failed to find any micrococci.

CASE 3.—June 27th. Inoculated a brown puppy (about five months old) in the right eye. Irido-cyclitis followed by rapid phthisis bulbi. The eye did not rupture. Twenty-six days after the inoculation, I observed in the left eye a clouding of the cornea. On a close examination by oblique illumination I became convinced that the clouding was not superficial, but, on the contrary, deep-seated; in other words, that there existed an interstitial keratitis. The surface of the ball of the eye was entirely free from wound, abrasion, nor indeed was any external cause visible. A cause from without would probably have given rise to a superficial inflammation, but here the superior layers of the cornea were intact. Causes extrinsic do not give rise to inflammations of the cornea limited to the parenchyma. The cause here was plainly intrinsic and I naturally supposed that I had before me a typical case of sympathetic ophthalmia, where the organisms after traversing the uveal track had passed over from the iris to the membrane of Descemet and here set up inflammation. In two or three spots on this membrane there were small white deposits.

If, however, the organisms had taken this track, there must be present also an iritis and choroiditis. Owing to the corneal clouding it was impossible to ascertain the condition of the fundus. But the iris was in every respect normal, acting promptly. After keeping the dog under further observation for forty-eight hours and noticing no new feature in the case, he was killed. The microscope showed throughout the inoculated eye dense round-cell infiltration; neuritis optica extending about half an inch from the papilla, but from this point on up the optic nerve to the chiasm and down the other optic nerve, no pathological change was to be seen. As regards the second eye, and more particularly the choroid, ciliary body, and iris of the same, I found not the faintest trace of an inflammatory process, other than the keratitis, and should say that with the exception of the cornea, the eye was perfectly normal. The keratitis then was a spontaneous process, separate and distinct in its origin from the causes which resulted in the destruction of the other eye. A close examination for micro-organisms failed to reveal the presence of the latter.

CASE 4.—July 6th. Inoculated the left eye of a large brown bitch. Soon after clouding of the media, followed by irido-cyclitis and Descemetitis. The inflammation subsided in ten days and left the eye with several thick corneal opacities and anterior synechiæ. Pthisis bulbi followed. The dog was killed September 3d. The microscopic examination revealed evidences of inflammation in

every part of the eye. There was also inflammation of the optic nerve, infiltration extending about half an inch from the intra-ocular end of the nerve. Nothing noteworthy in the nerve was observed beyond this point, nor was there any thing pathological in chiasm, the other optic nerve, or the second eye. I could find no organisms.

CASE 5.—July 15th. Inoculated the right eye of a small black bitch. Followed as usual by irido-cyclitis and clouding of the media. On the the third day diffuse clouding of the cornea. Violent keratitis. Perforation of the cornea with prolapse of the iris. Four weeks later all signs of an acute inflammation had subsided, leaving a large corneal opacity, and just at this point the iris had fallen forward into the perforation and healed. The dog was killed September 3d. The microscopic examination revealed extensive round-cell infiltration throughout the inoculated eye. Neuritis optica extending not more than a quarter of an inch from the eyeball. The chiasm with the second eye and its nerve was perfectly normal. No micrococci were to be found.

I have selected the records of the above five cases as they appeared to be fairly typical of this series of experiments extending from the early part of June to the middle of November. The other cases differed in very few particulars from the above, certainly in nothing that could be regarded as throwing any additional light on the subject.

I made fifteen experiments in all. In nine of the cases the eyeball ruptured and the contents were disgorged. The fate of the other six cases was cyclitis, choroido-iritis, ending with phthisis bulbi. The first dog was killed three weeks after inoculation, the second dog four and a half months, the third twenty-six days, and the fourth and fifth cases two months and six weeks respectively. I selected dogs, as I have said, because I thought that, unlike rabbits, they would be less apt to fall victims to a general infection. In this respect the whole aspect of my experiments on dogs resembled more nearly what we see in man, for in only one instance did I observe any thing like a constitutional effect (Case 3). The trouble remained local. All the cases were examined every day with the ophthalmoscope. Never was any thing unusual observed about the second eye. In two

cases there was noticed twenty-four hours after inoculation, an enlarged condition of the retinal vessels, associated with a general redness of the papilla. This disappeared at the end of three or four days. It certainly could not have been due to the presence of organisms, for there was not the faintest trace of an inflammatory process in the fundus, and the corpus vitreum was always perfectly clear. It was, I think, a reflex engorgement of the vessels, due, without a doubt, to the violent inflammation going on in the other eye, and there is no reason to be believe that it could ever have developed into a condition similar to that of the first eye.

Further than these two cases I observed nothing in the second eye that would suggest sympathy with the condition of the inoculated eye.

Rupture of the eyeball, and the consequent disorgement of its contents, is thought to exclude the possibility of sympathetic ophthalmia. No. 1 was the only case where cell infiltration was present in the neighborhood of the chiasm, and yet here the inoculated eye ruptured on the third day. I made a most thorough examination of the intercranial end of the optic nerve and of the chiasm in this case, but failed to find any organisms. The existing inflammation must then have spread from the point of infection by contiguity or continuity, and if produced by the micro-organisms, these must have disappeared by the date of the examination.

In one point my experiments differ from those of Prof. Deutschmann, namely, in the fact that mine were made on dogs. Thinking that this difference might impair the value of my work as a control of that of Prof. Deutschmann, I determined to repeat his experiments on rabbits.

Two months ago a man came to the eye clinic with the history of a foreign body in the eye. While working on the railroad, a week before, a piece of iron flew into the right eye. When seen at the clinic, the diagnosis of panophthalmitis was easily made, and enucleation was performed. The foreign body was a piece of steel, and was found imbedded in the retina. The whole eye was filled

with pus. I obtained a few drops, and brought them in a test tube to the laboratory, and then made plate cultures after Koch's method. I succeeded in isolating the staphylococcus aureus, and obtained a pure culture identical in every respect with the staphylococcus aureus of Rosenbach.

I have selected for this paper the following clinical histories of experiments on rabbits :

CASE 1.—*April 11th.* Injected four minims of a solution of staphylococcus aureus into the corpus vitreum of the right eye.

April 13th.—Clouding of vitreous.

April 18th.—White deposits in the pupillary space. Posterior synechiæ.

April 23d.—Blood in anterior chamber. Great injection of conjunctiva and iris. Left eye normal.

April 30th.—All the appearances of general inflammation of the infected eye.

May 10th.—The eyeball immensely swollen. Panophthalmitis. The left eye remaining throughout perfectly normal. Not the slightest evidence of sympathy. There was no change in the condition up to the 17th of May, when it was killed.

Microscopic examination.—Infected eye filled with a cheesy mass. Infiltration of corpus vitreum with leucocytes. Round-cell infiltration throughout iris and ciliary body. Choroiditis and retinitis. Papilla tremendously infiltrated. Here, there was undoubted neuritis. The neuritis extended about half an inch from the eyeball, and, from this point on, there was no appearance of cell infiltration. The chiasm and the optic nerve of the fellow eye were perfectly normal. No bacteria could be found.

CASE 2. *April 11th.*—White rabbit with gray ears. Inoculated in right eye.

April 11th.—Cloudings in corpus vitreum.

April 16th.—White deposits in pupillary space. Iritis. Left eye normal in every respect.

May 3d.—No change.

The animal was examined every day till the 19th of May, when it was killed. At date of death the pupil was entirely closed with a white deposit and the iris bulged forward, almost obliterating the anterior chamber. The fellow eye remained throughout normal.

Microscopic examination: Inflammation of all the coats of the eye, and enormous infiltration of the corpus vitreum with leucocytes. Detachment of the retina and thickening and infiltration of the choroid with round cells. Papilla swollen and densely infiltrated with round cells. Neuritis extending about a quarter of an inch from the eyeball. From this point on there was nothing abnormal in the appearance of the nerve. The chiasm was normal; so, also, the optic nerve of the fellow eye. I could find no organisms.

CASE 3. *April 11th.*—Black-and-white rabbit. Inoculated right eye.

April 13th.—Choroido-iritis. Floating opacities in the vitreous.

April 15th.—Iris very much injected. Posterior synechiæ. White deposit in the pupil. The eye remained the seat of an inflammation, marked by no new feature, till May 21st, when the animal was killed. The fellow eye never showed any signs of sympathy. Microscopically, the infected eye had somewhat shrunk. The corpus vitreum was filled with a cheesy mass. The iris and lens were bound together by synechiæ. The optic nerves were both about the same size.

Microscopic examination: Round-cell infiltration everywhere present. Almost complete disorganization of the choroid and retina. Difficult to make out the relation of the parts. Dense cell infiltration of the optic nerve extending about a quarter of an inch from the eyeball. The rest of the optic nerve, with the chiasm and optic nerve of the opposite side, were normal. A sterilized platinum wire was introduced into the interior of the eyeball after I had burnt a way for its passage through the cornea with a hot knife, and inoculations were made upon agar. Es-march's method was employed, and numerous colonies of micro-organisms were to be seen the third day afterward. They were, however, not the organisms with which I had made the inoculation.

CASE 4. *April 11th.*—Inoculated a gray rabbit in right eye.

April 13th.—Choroiditis. Opacities in the vitreous. The pupil appeared to get smaller every day, till April 26th, when it was not larger than a pin's head.

April 26th.—Iris bulging forward into the anterior chamber. Great injection of the iris. The left eye remaining perfectly normal.

May 3d.—Blood-red appearance of iris, and the latter appears as though thrown into folds.

May 7th.—No change.

No new feature developed itself from this time till June 7th, when it was killed.

Microscopic examination: Eyeball filled with a cheesy mass. Detachment of retina. Infiltration of choroid, retina, and ciliary region with round cells. Purulent infiltration of the vitreous. Papillitis. Neuritis immediately adjoining the eyeball. No organisms.

CASE 5. May 17th.—Inoculated a white rabbit in left eye.

May 21st.—Eye very much injected, and impossible to see the fundus. Dense clouding of the corpus vitreum. The right eye normal. This case was examined every day till May 31st, when it was killed. No new feature showed itself in either eye. The infected eye was cut open with a hot knife, and a sterilized platinum wire was passed in. Inoculations were upon agar, and Esmarch tubes were made. They were placed in a breeding oven, and twenty-four hours later beautiful colonies of staphylococcus aureus showed themselves. I made a stab culture and obtained a pure and typical growth in every point identical with the organism with which I had inoculated the eye.

The optic nerve and chiasm were entirely free from organisms.

To sum up then my experiments on rabbits. The first rabbit died forty-eight hours after inoculation, the second rabbit ten days after inoculation. The latter gave evidences of brain trouble before death in spasmodic movements of the neck and inability to move without falling forward. The autopsy revealed a very hyperæmic condition of the brain. The first rabbit died with all the symptoms of a general infection. Both animals were very young, hardly more than a month old, much too young for such experiments. Five rabbits inoculated on March 28th met with violent death on April 11th, killed by dogs. Careful examination every day with the ophthalmoscope and a microscopic examination of sections from the optic nerves, chiasms, and eyes of these five animals never revealed a feature differing from what was seen in the five cases just reported in full. The third series of experiments consisted in the inoculation of eight rabbits. These were killed at periods ranging from four weeks to two months; one exception, Case 5, which was killed in fourteen days. An

ophthalmoscopic examination was made every day for the first three weeks ; and afterward never were more than three days allowed to pass without such examination. Never did the fellow eye show the slightest symptom of sympathy. The fundus remained unchanged, perfectly normal ; not even did the blood-vessels take part by increase of size, in other words, no hyperæmia. Every one of the eyes suffered with irido-cyclitis in its most typical form.

There is one point in connection with experiments in general on dogs and rabbits upon which I would lay particular stress. There is great difficulty in recognizing a true inflammation of the optic nerves and the chiasm, and indeed of the choroid and retina too, unless you have normal sections of these parts right at hand with which to compare your supposed pathological conditions. In the first five experiments on dogs I was perfectly convinced that I had a neuritis extending from the infected eye around to the fellow eye by way of the chiasm. I submitted the sections to skilled microscopists, and they agreed with me. The suggestion was made though that I kill a dog and study the normal condition of the parts.

I did this, and to my surprise found that the normal optic nerve of the dog was most rich in nuclei, nuclei which gave to the nerve the appearance of dense round-cell infiltration. It is a fact worthy of note that the chief distinguishing feature of inflammation of a nerve at this stage is the increase in the nuclear elements, and upon this point we must mainly rely in making a diagnosis of neuritis. Changes in the nervous bundles themselves are not readily demonstrable features of a neuritis of three weeks' duration.

The fact then that we must regard the number of nuclei as in great measure deciding the existence of inflammation, the fact that the physiological number of these nuclei from their abundance can easily deceive us and lead us to conclude that we are looking upon a pathological number, that we have before us genuine leucocytes, all these facts, I say, point to the necessity of comparing what is known to be a normal condition with the

section under observation. And by this I mean to say, that longitudinal and cross-sections of the ball, optic nerve, and chiasm of the eye to be examined must be compared with corresponding sections in what is known to be the normal state. In the case of the optic nerve and chiasm, sections must be compared from as near as possible corresponding portions of the nerves, as I have observed a difference in the number of nuclear elements in portions of the nerve. The nuclei are rather fewer and more scattered in the neighborhood of the chiasm. They are generally most abundant at the intra-ocular end of the nerve. It will be remembered that in several of Professor Deutschmann's cases the cell infiltration decreased in intensity as it neared the chiasm, and increased in intensity on the way from the chiasm down to the other eye. This is exactly what we have in the physiological condition. The nuclei are, as I have said, abundant at the intra-ocular end of the nerve, decreasing in number toward the chiasm, comparatively scattered and few in the chiasm itself, and increasing in number from the chiasm toward the fellow eye. I do not mean to be understood as asserting that Professor Deutschmann has really mistaken the normal condition of the nerve for a neuritis descendens and ascendens. But such a mistake could readily be made. He performed five experiments. My experiments number 15 on dogs and 15 on rabbits, and in the main points my results contradict his completely. Dr. Gifford's experiments of inoculations with the pus cocci number seventeen, and his results coincide with mine. What I said of the normal optic nerve of the dog is equally applicable to the normal optic nerve of the rabbit. This also is rich in nuclei.

In short, unless the precautions which I have suggested be taken in experiments of this nature upon dogs and rabbits, a reasonable doubt must be cast upon the accuracy of a diagnosis of existing inflammation.

As regards the condition of the fellow eye: In several of his cases Deutschmann notices, with the ophthalmoscope, changes in the fundus, papillitis, retinitis, and choroiditis, though the anterior portion of the eye remains healthy. It

will be remembered that in his experiments all of his animals die of a general infection. Cultures from the blood show the presence of micro-organisms. That means that there were organisms in the kidneys, heart, and throughout the circulation. We are not surprised when we see a neuroretinitis or choroiditis or clouding of the whole fundus in a patient who we know has nephritis, or pyæmia. Pernicious anæmia, heart disease, in other words, great disturbances in the circulatory system, are prolific causes of diseases of the fundus. We have here an animal succumbing gradually to the effects of a blood poison, dying with pyæmia. Kidneys loaded with micro-organisms, heart and entire circulation alive with pus cocci. With so violent a provocation, can we regard it as extraordinary that the fundus should be the seat of inflammatory changes, especially when we consider how very liable it is to participate in vital changes in the general system?

In Case 3 (dog) I look upon the keratitis as simply a manifestation of constitutional disturbance brought about by the presence of micro-organisms in the blood. This was the only instance among the dogs, where I observed any evidence of constitutional disturbance, showing that dogs, unlike rabbits, are not liable to give way to a general infection. Furthermore, I regard a general infection as a serious objection to these experiments, not only because the animal dies before the sympathetic inflammation shows itself; but the fact that there is present a constitutional disturbance removes the analogy between the experimental process and the disease as seen in man. Sympathetic ophthalmia in man is from beginning to end a local affection.

I report here three cases which came under my own personal observation, where the injured eye was enucleated for fear of sympathetic ophthalmia. In all three cases the injury was caused by the entrance of a foreign body. I have examined several other eyes for organisms, but always with a negative result, and I do not report them, as there was no history of injury from a penetrating foreign body.

CASE I.—S. M., boy, eleven years old. Six years ago, fell on a piece of glass, a particle of which entered the right eye just above

the corneo-scleral border. Choroido-iritis ensued, followed by rapid phthisis bulbi. Six months afterward the left eye took on inflammation, and up to present date (April 28th) has been the seat of periodic inflammation, accompanied with a great deal of pain.

Stat. præsens.—Right eye very much shrunken, and not half the original size; not sensitive to touch. The left eye presented a broad band of corneal opacity running across the centre of the cornea. The pupil was bound down by posterior synechiæ, and a white deposit in the centre showed that cataract was present, cataract resulting from the frequent deposit of inflammatory products upon the anterior capsule of the lens. Tension was decidedly minus; light perception good. Inasmuch as the atrophic eye was utterly useless, and was possibly through its presence giving rise to the recurrent attacks of inflammation in the fellow eye, it was enucleated. The whole interior of the eye was filled with a cheesy mass, and the internal coats had undergone complete disorganization. It was impossible to make out the relative position of the parts. Round-cell infiltration was everywhere present, neuritis extending to point of section of the nerve. Cultures from the interior of the eye made into Esmarch tubes failed to show any signs of growth. Half of the eye was put into a tube of gelatine, but nothing grew. The bacteriological examination was made prior to cutting open the eye.

CASE 2.—May 25th, 1887.—J. C. Lewis. About six weeks ago while at work, a piece of the hatchet—with which he was driving a nail—flew off and struck him in the left eye. When seen he was suffering great pain. Light perception gone. Eyeball very much injected and sensitive to touch. The pupil was completely closed by posterior synechiæ. The diagnosis was of course irido-cyclitis. The fellow eye had been the seat of shooting pains within the past few days, and was somewhat sensitive to light. The ophthalmoscope revealed a perfectly normal fundus. The pupil responded promptly to light, *not* sensitive to touch and as far as I could see absolutely healthy. The injured eye was enucleated and the piece of iron was found imbedded in the ciliary region. The microscope showed round-cell infiltration throughout the eye, most noticeable in the ciliary region. Papillitis. Sections prepared for bacteriological examination failed to show the presence of micrococci. Cultures from the interior of the eyeball gave no evidence of the presence of bacteria.

CASE 3.—H. White, 19 years old. Lost right eye six weeks

ago in an explosion. No light perception. Large corneal wound. Prolapse of iris. Pupil very small and closed with a white deposit. Tension minus. Ciliary injection, though the eye was not particularly sensitive to touch. Enucleation. Cultures made. There were, however, no signs of growth in the tubes. Within, the eye had undergone degeneration. No microscopic examination was made.

I may here refer to a case reported by Prof. Hirschberg where the enucleated eye—after the patient had suffered two weeks with a sympathetic inflammation—was examined for organisms by Nordenson in Koch's laboratory. The result of the examination was completely negative. (*Centralblatt für praktische Augenheilkunde*, Januar, 1888, S. 20.) Also to a case of "sympathetic neuroretinitis," reported by S. C. Ayres and Adolf Alt, when not a trace of bacteria was found in spite of the most careful examination. (*American Journal of Ophthalmology*, February, 1887.) In nearly all of the eyes enucleated for fear of sympathetic inflammation, Prof. Deutschmann found micrococci.

In my cases the cultures were made from the eyes almost immediately after enucleation. Every precaution was taken to avoid contamination. In making cultures from the vitreous the cornea was first sterilized with a hot knife. The point of the blade was then passed into the anterior chamber. Through this hole a sterilized platinum wire was passed into the corpus vitreum and twisted about in every direction within the eyeball. The inoculations were upon agar, and Esmarch tubes were made. By this method or the plate mode of culture, one can be certain that one is not dealing with impurities. Any other known method is open to objections. I observed that Prof. Deutschmann never took this precaution, making simply the stab culture. It is quite possible that he inoculated an impurity, at least he can not be perfectly certain that the growth upon the gelatine had its origin within the eye. In the first two of my cases, in addition to the inoculations, the eyes were cut in half with a sterilized knife. A half from each eye was sterilized on the outside with hot knives and put into a gelatine tube. Nothing grew. The other two halves were stained and examined under the microscope with the result already mentioned.

Prof. Deutschmann observes micrococci in the tissues themselves, even in the optic nerve. This I am unable to explain. I can only say that, with the strictest precautions against contamination, I did not observe in any of the clinical cases last reported any appearances in the tissues which could be unmistakably pronounced organisms. In staining for bacteria I employed both Gram's and Weigert's fibrin method, the universal stain of Löffler, the tubercle stain, etc.

Prof. Deutschmann has never given a satisfactory explanation of how the organisms get from one eye to the other. The micro-organisms, says he, work their way forward with a certain impetus, an impetus which comes from their own growth, as well also from their power of spontaneous movement (*Eigenbeweglichkeit*). So they reach the chiasm and from thence they are carried downward to the other eye by the lymph stream. Now if the micrococci had this power of spontaneous motion we would want no better explanation. But micrococci do not possess this property.¹ "Micrococci and all those kinds of bacteria whose form of growth resembles the micrococci, are always in a state of rest, except such movements as are to be attributed to unavoidable shocks," as for example, mechanical violence to a part.

It may be a matter of surprise that rupture of the eyeball occurred in so many cases in my experiments with dogs, and not a single time with the rabbits. I think this is easily explained. In the case of the dogs the injections were made with a very coarse hypodermic needle, the point of which was somewhat blunted from constant use. In forcing the needle through the tough sclerotic much force was employed, and the eyeball subjected to a good deal of mechanical violence, and, at the point of puncture, there was always more or less of a contused condition of the tissues, ecchymoma, etc. At this point, no doubt, the tissues were infected, the nutrition of the whole eyeball was disturbed by the mechanical violence employed, and this, in conjunction with the presence of pus cocci within, afforded the conditions necessary for a general inflammation. Later

¹ "Die Mikroorganismen," von C. Flügge, S. 124.

on I obtained the finest needle that could be gotten, and I had no further trouble with the injections.

Why did so few of my animals die of general infection? Among other things they were kept in an amply large and well-ventilated apartment, and always had plenty of good food, but mainly because the quantity of cocci injected was very small. A very weak suspension was employed. In injections of pus cocci the intensity of the effect is in direct proportion to the quantity of organisms injected. This peculiarity is not associated with the history of the organism of anthrax, and here let me briefly refer to some experiments made by Dr. Gifford with the anthrax bacillus. His work appeared in these ARCHIVES (vol. xv., pp. 281-295). He takes the view that the organisms leave the first optic nerve with the vessels, and, after passing through the orbit, reach the cranial cavity. They pass from this point into the subvaginal space, and from thence along into the supra-choroidal space of the second eye. It is strange that Dr. Gifford should have used the anthrax bacillus for such experiments. He could not have selected an organism which would have given him results less valuable to the history of the subject. Twenty-five experiments were made, and every one of the animals died of general infection. In only three cases did the rabbits live long enough for the bacilli to reach the second eye. With the exception of the mouse, there is no animal that succumbs more promptly to anthrax than does the rabbit, and if all twenty-five of the cases had lived long enough, the second eye would have been found filled with bacilli, and for all that, no new fact, certainly no valuable one, would have been established. Furthermore, it would have been extraordinary had the organism not been found in the second eye, and that, too, in the supra-choroidal space, as well as everywhere else in the second eye. I examined a number of mice last summer that had been inoculated with anthrax at the *root of the tail*. The animals had died in twenty-four hours after inoculation. I selected at random pieces from different parts of both eyes and optic nerves, and in every specimen countless bacilli were to be seen.

My results then, as far as confirming the theory that sympathetic ophthalmia is propagated along the optic nerves and its sheaths, were entirely negative. As I have already said, the optic nerve of the infected eye at its intra-ocular end was always infiltrated. A moment's glance was sufficient to tell me that, but any noticeable progress of the inflammation for more than a very short distance from the eye was never observed. This portion of the nerve could hardly have escaped participation. Its proximity alone to such an inflammation would have called forth changes in its own structure. In this connection it is pertinent to call attention to experiments which have been made to determine whether or not inflammation, induced experimentally in a circumscribed part of a nerve, is capable of propagation for a long distance in the nerve trunk. Of these experiments the most exact and trustworthy are those of O. Rosenbach, who injected chemical irritants, such as turpentine, Fowler's solution, etc., into the sciatic and vagus nerves. Rosenbach's experiments were performed under Cohnheim's direction. As he used no especial antiseptic precautions, it is reasonable to believe that micro-organisms were not absent. In opposition to preceding experimenters Rosenbach failed to find that the local inflammation travelled any considerable distance along the nerve from the site of the injection. My own results are in harmony with Rosenbach's conclusions. He says: "The result of the microscopical investigation, in spite of the positive changes which it presents to us, is nevertheless, as regards the propagation of the neuritis, a completely negative one. Only so far as the chemical and mechanical action of the injection reaches is there any change, and beyond this—so far as the methods of investigation can lead us to a conclusion—is every thing intact. (O. Rosenbach: "Experimentelle Untersuchungen über Neuritis." *Archiv. für experimentelle Pathologie und Pharmakologie*, B. viii., S. 231.)

The question then arises, Does infection play a roll in the production of sympathetic inflammation of the eye? Experience in a large eye clinic for the past four years has inclined me to the affirmative side of the question. That

the optic nerve, however, is the track of the infection, my experiments have led me to doubt seriously. The experiments of Leber, and mine, of the same character, indicate quite conclusively that aseptic wounds of the eyeball, whether of the ciliary region or not, produce little disturbance. More or less violent is the result of septic wounds.

The experiments which I have reported shed no positive light upon the mode of production of sympathetic ophthalmia, for in no instance was this affection a sequel of the operation. It is reasonable to suppose that had the same insults been applied to the human eye, at least in some instances sympathetic ophthalmia would have resulted. This raises the question whether rabbits and dogs are susceptible to sympathetic inflammation of the eye. Upon this point I am unable to bring any positive evidence. I do not feel warranted, on the basis of the negative results of my experiments, in drawing any positive conclusions as to the genesis of sympathetic ophthalmia.

These experiments were undertaken in order to control the results which others had obtained by similar investigations. That the conclusions which had been drawn from these results must be corrected and revised seems to me the justifiable inference to be drawn from the experimental work presented in this paper.

My experiments were made in the Pathological Institute of the Johns Hopkins University. I take this occasion to express my thanks to Prof. Wm. H. Welch, Director of the Institute, for his kindly aid. His advice on every point I have found most useful. And I would also thank Dr. B. Meade Bolton, assistant in bacteriology, for the material assistance which he rendered me in the bacteriological part of my work.

G. P. PUTNAM'S SONS, PRINTERS
NEW YORK