Pathogenesis of sympathetic ophthalmia concerning the theories of transmission

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PATHOGENESIS OF SYMPATHETIC OPHTHALMIA

CONCERNING THE THEORIES OF TRANSMISSION

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SENIOR THESIS

UNIVERSITY OF NEBRASKA COLLEGE OF MEDICINE

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### PATHOGENESIS OF SYMPATHETIC OPHTHALMIA

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INTRODUCTION AND HISTORY
SYMPATHETIC OPHTHALMIA

Introduction

Unfortunately, there is little known positively concerning the origin of sympathetic ophthalmia, its pathogenesis is almost completely enveloped in darkness. It is important that we find a satisfactory explanation to the question, for upon this therapeutic and prophylactic measures depend. Many theories have been proposed and these are found to fall into groups corresponding to the different periods of development in medical science, several not being in harmony with current teaching. I have presented in this paper the various theories, and with each have given the opinions of their important advocates and, in some, their important critics.

Definition

Sympathetic ophthalmia is a specific bilateral ocular disease, which usually occurs after penetrating wounds that involve the uveal tract of one eye, although rarely it may follow other causes. The injured eye is known as the exciting eye, and the uninjured eye as the sympathizing eye. The disease appears in the exciting eye at a variable time after injury and synchronously or shortly afterwards, affects the sympathizing eye. The disease is confined primarily to the uveal tract. The clinical picture is fairly characteristic and the histologic picture is quite characteristic.

In defining the term "sympathetic ophthalmia", we should differentiate it sharply from "sympathetic irritation". This latter term is used to describe what is apparently a reflex disturbance in the second eye, after disease or injury of the first eye. This reflex disturbance is characterized by slight photophobia, lacrimation, and often transient amblyopia. Sympathetic irritation is rarely if ever the precursor of sympathetic ophthalmia (68).
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History

The first mention of possible sympathetic ophthalmia is in the anthology compiled by Constantius Cephalus, A.D. 1000, where in a quotation from the Agathius, Volume II, page 352, is the observation: The right eye, when diseased, often gives its suffering to the left. (68)

According to Brondeau, 1358, in a work of Thomas Bartholinus, recorded in the latter part of the 17th Century, is stated a case where the other eye became involved after a knife wound. The injured eye healed but remained without sight. (39)

George Bartsch, in 1583, wrote upon the subject and was followed by Bidloo, 1649-1713, who mentioned in his work that when the splinters of wood remained in an eye, reaction occurred in the other. (71) (39)

In 1741, LeGran speaks in a way that leaves not any doubt that he recognized sympathetic ophthalmia. He stated that if one should wait, as in the case of other abscesses, for the formation of pus, the patient might lose his sight by the inflammation which is communicated to the other eye by way of the optic nerve. He also, offered the first suggestion as to the method of transference in sympathetic ophthalmia. (41).

In 1802, Beers made the observation that where an inflammation had persisted in an eye for many years, and where sight is gone, heightened irritability and asthenopia make their appearance in the other eye. He advises that as long as the inflammation persists in the blind eye, the relative good eye should be the object of the greatest care and should be spared as much as possible, and he points to the possibility of the disease which is in progress in the blind eye, causing blindness in the other eye. (39)
In 1818, Demours reported three cases in which he establishes the existence of sympathetic blindness. One was a case of a healthy young girl struck in the eye by the end of a knife. The result was a violent and obstinate inflammation, and after several months the pupil of the eye was occluded. As to the other eye, the cornea remained clear, but the lens was opaque and the pupil was contracted, and the iris at this point was pressed forward. (39)

Wardrope, in 1818, reported a case of sympathetic iritis, briefly, and mentioned that veterinary surgery had noticed the destruction of the second eye in horses, and that it might be avoided by destruction of the first eye by lime. (57)

Von Ammon, 1835, stated that he had several sympathy cases. One of his cases was that of an old man who suffered a wide gapping wound of the sclera; the iris was elapsed and much of it lacerated. Scarcely any iritis followed, but two months later uveitis showed itself in the other eye. (39)

In 1833, Lawrence stated that penetrating wounds of the globe, unless judiciously managed from the very beginning, are generally followed by an internal inflammation which destroys sight, and not infrequently ends in atrophy of the organ. Often the sound eye is attacked by similar internal inflammation which affects the iris, lens, retina, and vitreous humor, and thus may be arranged among the general diseases of the globe. Lawrence states also that sympathetic ophthalmia may come on during the active period of the original disorder, or after cessation. The former is likely to occur if the injured eye be neglected, and especially if employment and exertion of the sound eye be continued. The constitution, state of health, and habits of living will also influence the result. (35)
Sympathetic Ophthalmia was first described exhaustively by Mackenzie in 1844. We credit Mackenzie not only for his excellent account of sympathetic ophthalmia from the clinical standpoint, but also for being the first to make definite statements as to its pathogenesis. He concluded from the cases that he had studied that it is not improbable that the blood vessels of the injured eye, being in the state of congestion which attends inflammation, communicate the condition to those of the opposite side, with which they have connection within the cranium. The ciliary nerves also of the injured eye, may be the means of conveying to the third and fifth nerves an irritation which may be reflected from the brain to the same nerves on the opposite side. He believed, however, that the chief medium through which sympathetic ophthalmia is excited, is the union of the optic nerves, since the optic nerve of the one eye, proceeds backwards and meets the optic nerve of the other eye, the two mingle their fibers and practically decussate. He also stated that it is extremely probable that the retina of the injured eye is in a state of inflammation which is propagated along the corresponding optic nerve to the chiasms, and that thence the irritation, which gives rise to inflammation, is reflected to the retina of the opposite eye along its optic nerve. (36)

Tavignol, 1849, speaking of sympathetic iritis of one eye following a wound of the other, dissents in some points from the views advanced by Mackenzie as to the symptomatology of the disease, and holds that the inflammatory phenomenon are to be attributed to the wound of the ciliary body. (39)
H. I. Faier

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THEORIES OF TRANSMISSION
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A. NERVE REFLEX THEORIES
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OPTIC NERVE THEORY

Ninety years ago, it is safe to say, there was but one view held as to the genesis of sympathetic ophthalmia. This was the doctrine of Mackenzie, and it was the first explanation offered on the pathogenesis of sympathetic ophthalmia. He believed that the chief medium through which sympathetic ophthalmia is excited is the union of the optic nerves, since the optic nerve of the one eye proceeds backwards and meets the optic nerve of the other, the two mingle their fibers and practically decussate. He also stated that it is extremely probable that the retina of the injured eye is in a state of inflammation which is propagated along the corresponding optic nerve to the chiasma, and that there the irritation which gives rise to inflammation is reflected to the retina of the opposite eye along its optic nerve. (36) However, it is difficult, from the writing of Mackenzie, to be certain whether he supported a purely nervous agency in the transmission.

Homer and Knies, 1879, agreed with Mackenzie and offered pathological evidence of this manner of transmission. (39)

While Muller was offering his new ciliary nerve theory (see below), Alt, 1876, argued in favor of Mackenzie's optic nerve theory. He brought forward an account of the pathologic changes found in 112 eyes enucleated because of sympathetic disease of the fellow eye. His conclusion, in favor of the optic nerve theory, was based mainly on the large percentage of pathologic changes in the retina and optic nerve, and the small percentage of changes in the ciliary nerves, which these eyes exhibited. It appeared to Alt that the entire nervous apparatus of an eye has the power of transmission, and even the influence of the sympathetic system must not be left out of view in this consideration because 97% of the cases have changes in
the vascular membranes of the eye. (2)

Alt's views attracted much attention, but when it was pointed out, in 1884, by Theobald, that the changes in the retina and optic nerve to which Alt attached so much significance, consisted in a large measure of detachment of the retina and atrophy of the optic nerve, retinitis and neuritis being conspicuous by the infrequency of their mention, and further, that the uveal tract as well as the optic nerve and retina, was the seat of pathologic changes, the inconclusive character of the evidence that Alt brought forward and its irrelevance so far as the question of the etiology of sympathetic inflammation was concerned, became apparent. (53)

* * * * *

CILIARY NERVE THEORY

The doctrine of Mackenzie, because of the lack of any positive evidence, was universally abandoned, and the view that the pathologic changes in the secondarily affected eye were the product of an influence, an influence of a reflex character, transmitted to it through the ciliary nerves, was as universally accepted. This theory depends upon the clinical observation that in irritation of one eye, for instance by a foreign body, its fellow eye is affected, becomes congested, and the tears flow. Such reflexes are due to the irritation of trophic, motor, sensory, and blood vessel nerve filaments as are contained in the ciliary nerves. (54) (71) (2)

This view, which had been suggested by Mackenzie as an alternative but improbable explanation of the phenomena of sympathetic ophthalmia, and had been advanced previously by Tavignol in 1849, was first brought prominently forward by Heinrich Muller in 1858. He draws his conclusions from
the anatomical examination of three eyes which had been enucleated through fear of sympathetic disease in the fellow eye. Muller concedes the possibility of inflammatory transmission through the optic nerve, though the latter, he says, all the way from the retina up into the trunk is in a condition of atrophy, so that it is not capable of conducting an irritation or, in fact, any other process. Cutting through the optic nerve, then, 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 part of the eye, and in consequence, Muller believes the ciliary nerves, from their location, 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 to assume that the inflammation was brought about through the ciliary nerves rather than the optic nerves. It is not improbable, he says, that the ciliary nerves exercise some direct influence upon the nutrition of the retina and optic nerve. Every cyclitis, whether of spontaneous or traumatic origin, whether it made its appearance in the beginning as cyclitis or developed into the latter, always keeps up a more or less persistent irritation of the ciliary nerves. It makes no difference whether the phenomena of irritation are due to a genuine cyclitis or to any influence which interferes with action of the ciliary body, such as stretching or tearing, calcareous products in the ciliary region, partial detachment of the ciliary body; under all circumstances, the sympathetic disturbance which results rests upon the same principle, irritation of the ciliary nerves, together with an influence which affects nutrition, secretion, and accommodation. Muller found ardent supporters as vonGraefe, 1862, Donders 1873, and Bowman 1872,
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who believed it sufficient and who strengthened it with their labors. (54) (39)

However, experimental evidence is contradictory. Mookèn and Rumpf 1880, irritated the exposed iris of a rabbit with spirit of mustard and the Paquelin cautery; the opposite iris showed anemia; with ether, the opposite iris showed hyperemia. (49) Jesner, 1880, cauterized the corneal margin with the silver stick; the aqueous of the other eye showed fibrinous coagula. Wessley, 1900, repeated Jesner's experiments, estimating the albuminous content of the aqueous of the other eye. In thirty-two experiments there were no abnormal increases. Bach, 1896, under similar conditions, found minute coagula and extravasation of blood in the anterior and posterior chambers and in the periphery of the vitreous. He, however, denies his adherence to the ciliary nerve theory. (71) Shaw, 1898, (50) kept up jequirity conjunctivitis and mechanical injury for six months; slight infiltration of the uveal tract of the other eye occurred but was not progressive. These experiments were crude and had many chances for error. (41)

Bocchi, 1894, states that the irritants, causing the reflex action can be mechanical, chemical, or bacterial. (41)

Many observers have found evidence of inflammatory changes in the ciliary nerves (Schmidt-Rümpel 1874, Goldzieher, 1877, Berger, 1887). In some cases inflammation has been absent. (Brailey 1885, Schirmer 1892) (41) Ayres, 1882, had several cases which he thought had a direct bearing on this idea, and showed that the incarceration of the optic and ciliary nerves would cause sympathetic irritation and plastic iritis. He also noticed changes of shape and proliferation of the interfibrillary nuclei. (41) (4) (5) According to Schmidt-Rümpel, the tenderness on pressure of the
ciliary region, which is present with hardly an exception, also testifies to their implication. (41)

Randolph, 1898, states that pathological changes in the ciliary nerves would interfere with the propagation of such an irritation or influence. He believes their soundness, then, speaks for and not against the theory. (39)

Collins, 1895, sides with the nerve reflex theory, for in a case of sympathetic ophthalmia, occurring two years after a cataract operation, the injured eye was excised and there was no evidence of infection by the most thorough methods of investigation. (11)

Theobald, in 1905, one of its few defenders, sides with the ciliary nerve theory and attempts to prove its correctness by the failures of many in trying to repeat Deutschmann's work. (14) (54) The unsatisfactory results are aids for his proof. He seems to believe that the absence of bacteria in the exciting eye; the variable period of incubation; the significance of disease and injuries involving the iris and ciliary body; the site at which the inflammation commonly begins in the sympathizing eye; the occurrence of sympathetic disease in consequence of non-penetrating injuries of the cornea, which however have given rise to painful and protracted keratitis; the arrest or favorable modification of the disease from enucleation of the primarily affected eye; its occasional development after enucleation of the exciting eye; the long continued existence of sympathetic irritation in some cases, without the development of actual inflammation, and in others the occurrence of inflammation with but little precedent irritation, are what this theory would lead us to expect. (54)
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The fact, that in some instances sympathetic inflammation begins at the posterior pole of the eye as a neuroretinitis or choroido-retinitis, has been regarded as being distinctly favorable to the theory that the disease is transmitted by way of the optic nerve or its lymph spaces; but as he pointed out in his previous paper, in 1884, (53) this is only what the ciliary doctrine would lead us to anticipate. It is, here, about the optic nerve, that the short ciliary nerves enter the eye ball and the neighboring choroid coat, between the blood vessels of which and those of the papilla there is intimate anastomoses and is especially rich in ciliary nerve supply. (54)

Theobald (54) is sure the work of the pathologists Head and Campbell, 1900 (31) on the pathology of herpes zoster, and believed by the pathologists of the time, is not any more than the advocates of the ciliary nerve theory of sympathetic ophthalmia ever have claimed; that without the intervention of bacteria or their products, inflammation may be set up in a distant part in consequence of an irritation of sensory nerves in relation with this part. One of the important remarks of Head and Campbell is that herpes zoster is produced, not by disturbances of special trophic nerves, but by intense irritation of cells in the ganglion which normally subserve the function of pain. There is no evidence that bacteria take part either in the ganglion lesions which they describe as an acute interstitial inflammation accompanied by necrosis of the ganglion cells, or in the secondary skin lesion. The contents of the vesicles, whenever examined, have been found sterile or in the consequent inflammation of the lymphatic glands. These glands have all the signs of inflammation and yet show no sign of bacterial invasion.
Thus, Theobald believes that if an irritation of ganglion cells which normally subserve the function of pain, can produce without bacterial or traumatic intervention, inflammatory changes in the skin area supplied by the sensory nerves emanating from these cells, then, is there any reason why the irritation, proceeding from an injured or diseased eye to its fellow, may not in like manner produce inflammatory changes in it? Or, reversing the sequence of events, as described by Head and Campbell, in assuming that intense and long continued irritation of sensory nerves, such as we have in a seriously injured and chronically inflamed eye, may cause inflammation in the ganglion cells with which these nerves are in relation, and this, in time, may bring about the inflammatory change in the sympathizing eye. This is what Theobald states was his doctrine in 1884. (53)

Theobald, in his paper of 1905 (54), concludes that sympathetic ophthalmia and herpes zoster are related affections. He believes, then, that these diseases are due to a common cause, disease of one or more of the ganglia in relation with the fifth nerve, oftenest probably of the ophthalmic ganglion, less often of the gasserian ganglion, or of the central ganglia themselves.

The modern idea on herpes zoster is that a filtrable virus is the cause. A virus has been definitely isolated in herpes simplex, but so far, it is only a theory with herpes zoster. If this modern theory be true, then Theobald's work is devoid of truth.

Among the critics of the nerve reflex theory, Snellens, 1881, was one of the first. He had regarded the idea that the direct action of the nervous system on the nutrition of the tissues, as the cause of sympa-
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sympathetic ophthalmia was analogous to the neuro-paralytic sloughing of the cornea after division of the trigeminal, and also, as analogous to the keratitis consecutive to herpes zoster of the frontal nerves. Both of these analogous types have lost their values as proofs of the trophic influence of nervous action. For Snellen states in 1857, he succeeded in proving that ophthalmitis after division of the trigeminal nerve, is not a neuro-paralytic phenomenon, but the result of an injury of the anesthetic eye. After cutting the trigeminal of a rabbit and closing the eye and fastening the sensitive ear before the anesthetic eye, he prevented traumatic influence, and so annihilated neuro-paralytic inflammation. In the same way, herpetic keratitis ceased to stand as a proof of nervous action; the pathologico-anatomical researches by Wyss, having shown convincingly that herpes zoster consists in continuous inflammation of the nervous fibers, propagating itself to the final ramification of the nervous tissue in the epidermis of the skin and the epithelium of the cornea. Snellen mentions that the origin of nervous irritation was sought in incarceration of the ciliary fibers in the cicatrix of the sclera; but in many cases, such compression is not to be seen. That sometimes symmetrical parts of both eyes are affected, has been accepted as another proof of nervous action, but he believes this also is not without many exceptions and may be assigned to accidental occurrence. He believes, therefore, that reflex action is devoid of proof. (51)

Gifford, in 1887, does not see reason for the haste to get rid of the ciliary theory; he believes that we should not lose sight of the probability that while genuine sympathetic inflammation is only caused by germs, its progress may be hastened or favored by reflex irritation from the other
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eye. The germ theory alone can hardly account for the numerous cases of immediate improvement of a genuine inflammation, far advanced, which have followed enucleation of the first affected eye. Just as other vasomotor disturbances, caused by a chill, may give the bacteria in the nose a chance to cause an acute coryza, so in all probability, can the reflex influence of an irritated eye favor the starting up or the progress of sympathetic disease in the fellow eye. (20) More recent articles of Gifford show that he is not any longer of this opinion. This idea of Gifford's is similar to that of Schmidt-Rimpler. (See Modified Ciliary Nerve Theory)

Finley, 1892, after examining thirty cases of eyes injured by penetrating wounds and with resulting inflammation, states that to only a few can it be attributed to purely mechanical or chemical influences. He believes that the ciliary nerve theory rests on purely hypothetical grounds not being supported by any experimental fact, and is not able to hold its own on theoretical and clinical grounds, for nowhere else in the body can we find any similar affection. He believes that three important clinical facts are unexplainable by this theory; (a) cases of sympathetic ophthalmia that are not preceded by a period of irritation; (b) cases where large aseptic foreign bodies like pieces of gun cap are imbedded in the interior of the eye for years without causing any sympathetic trouble; (c) cases of sympathetic ophthalmia occurring after enucleation. (16)

Würdemann, 1932, one of the leading modern ophthalmologists, is very critical of the ciliary nerve theory. He believes that clinical experience has shown that infection must always have occurred in order to cause sympathetic inflammation in the other eye; that every day operation wounds are made in eyes, and if these be aseptic they heal without the
slightest trouble and give rise to no risk of sympathetic inflammation; that even wounds that are made in the region of the ciliary body, such as iridectomies, iridesis, cataract operations, and others, if they be not infected, heal properly, but if they be infected, an operation wound is as liable as any other to set up destructive sympathetic disease in the other eye. Further, very painful diseases in which the uvea is affected, particularly panophthalmitis and glaucoma, do not give rise to irritation or sympathetic inflammation. Again, clinically, we find that the largest number of sympathetic inflammations have occurred within four weeks after enucleation of the first injured or diseased eye, when certainly there can be no irritation from the ciliary nerves of the other eye. Here we must suppose at least an ascending neuritis of the ciliary nerves, and pathologic anatomic examination has not shown this condition. Again, optico-ciliary neurectomy has not prevented the occurrence of, nor stopped the progress of sympathetic inflammation or irritation. (71)

Before the advent of the germ theory of disease, nerve reflex theories were used as the explanation of many of the diseases. Now, however, since the germ theory of disease has been definitely proven and , since clinical experience on sympathetic ophthalmia points towards infection, I believe the nerve reflex theories to hold no place in modern ophthalmology.
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B. BACTERIAL THEORIES
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BACTERIAL THEORIES

In 1831 the subject of sympathetic ophthalmia was given further impetus by the researches of Snellen, Berlin, and Leber. These three advanced the opinion that the inflammation was of parasitic origin, and hence that the disease in the second eye must rest on 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.

MIGRATION THEORY

Leber and Snellen, 1831, were among the first to advocate the view that sympathetic ophthalmia is a specific inflammation where the organisms were peculiarly adapted to the choroidal tissue and were transmitted through the lymph space of the optic nerve; and they went on to say if this theory is the true one, then the only path for the transmission of the organism is the optic nerve. (51)

Snellen states that the repeated observations of meningitis after extirpation of eyes with purulent inflammation makes this theory of transmission seem probable. He believes that the morbid changes of the vessels, the increase of lymphoid cells, and perhaps the accumulation of microphytal organisms, are the guiding signs that may indicate the direction in which the morbid process is propagated. (51)

Deutschmann in 1832 (41)(71)(14), by bacterial and animal experiments, was able to cause similar changes in the eyes of animals. He experimented by injecting fluid containing the spores of the aspergillus fumigatus, and later staphylococcus pyogenes aureus and albus into the sheath of the optic nerve, tracing the microorganisms across the chiasma in their course through the optic nerve of one eye to the optic nerve of the
other, in which they set up a typical sympathetic inflammation. He obtained similar results with croton's oil and concluded that the disease was caused by transmission of bacterial metabolic products.

Deutschmann (14) believed the agent in both eyes to be staphylococci. Later he changed to a gram positive diplo-bacillus as the agent; however, these have both proven to be erroneous. He believed that the second eye becomes diseased when the bacteria succeeds in passing from the first eye into the lymph channels of the first optic nerve, past the optic chiasma, through the lymph spaces of the second nerve into the orbit. He believed that the course of the bacteria passing from the eye into the optic lymph spores and vice-versa, is a twofold one; either direct from the choroid into the intervaginal space, or along the anterior ciliary vessels from the eye ball, around it, within the musculature of the orbit, and eventually back of the eye along the central vessels into the spaces of the optic nerve and vice-versa.

According to Deutschmann, chronic inflammatory changes in the meninges consist of circumscribed foci and so cause no general symptom.

The Leber-Deutschmann theory was at once widely accepted, for it explained: (1) why sympathetic ophthalmia exceedingly seldom follows any but perforating wounds of the globe, and being thus afforded to microorganisms; (2) why sympathetic ophthalmia does not start at once, but only after several weeks, this time being needed for the germs to travel up the optic nerve through the chiasma, and down the other to the second eye, there to give rise to the inflammation; (3) why enucleation of the wounded eye does not always present sympathetic ophthalmia; the germs may already have started and be on their way up the nerve or in the chiasma out of reach of the surgeon.
Gifford, 1887, (19,20), repeated Deutschmann's experiments but did not see any changes in the other eye; he obtained changes in three of twenty-five cases with anthrax bacilli. Mazza, 1889, (41) obtained negative results with staphylococci, and found them only in the sheath when the animals died of meningitis. Sattler obtained negative results with staphylococcus derived from a human sympathizing eye. Randolph, 1888, (45) believed that infection is important in sympathetic ophthalmia, but doubted the track to be the optic nerve, since his results were negative. He was also against the pus organisms as the agent and believed it was a specific organism or one of another class of organisms. Alt in 1884 confirmed Deutschmann's experiments with croton oil. Limbourg repeated Deutschmann's experiments in which sections of the optic nerve showed a continuous infiltration of the optic sheath from the eye to the brain, and he thinks his experiments greatly support the optic nerve, migration theory of sympathetic ophthalmia. (39)

Alt, 1884, Berger, Finley 1892, tend to show that in every well marked case of cyclitis there is a tendency for the optic nerve to be implicated. Berger also found the ciliary nerves involved in many cases. (39)

According to Brailey, 1834, (7) Shaw, 1898, (50) Roemer 1917 (47) and many others, the advocates of this theory can make no claim to furnish the fundamental explanation of sympathetic ophthalmia, because in the first place, it contravenes important clinical and anatomical symptoms in the clinical syndrome, and in the second place, it is contrary to the doctrine of infection.

We will first consider this theory, clinically. It is considered by all that the assumption that the first diseased eye suffers from an
infectious uveitis is not the only factor to be considered in the migration theory. Even the rare occurrence of sympathetic iritis in panophthalmitis cannot be explained well by the migration hypothesis. Deutschmann (50) supposed that the intensity of the inflammatory process destroyed the microorganisms; and Gifford (23) suggested that the channels of communication with the other eye were blocked by inflammatory products. But cocci have been found in eyes suffering from panophthalmitis by Schirmer, 1892 three weeks, by Schmidt-Rimpler, 1892 four weeks, and by Axenfield, 1896 five weeks, after the onset of the inflammation and have been detected in the optic nerve (50). Nothing could lead the migration theory to require a certain time for the migration from one eye to the other, except the purpose of explaining the fact that the earliest appearance of the inflammation in the second eye is fourteen days after the injury; but the interval between the diseases of the two eyes is explained altogether differently from the standpoint of bacteriology.

The cases in which sympathetic ophthalmia has appeared after optico-ciliary resection are also inconvenient for the migration theory. Cases recorded in which sympathetic ophthalmia occurred after optic neurctomy are: by Roemer, three weeks after, by Trousseau, 1808, thirteen weeks after, and by Schmidt-Rimpler, eighteen months after. (50) The path of the micro-organisms of the second eye is closed by the resection, and auxiliary hypotheses are again needed. Pagenstehr (51) published a case of injury where the optic nerve had been torn off and still sympathetic affection followed. He concludes against transmission along the optic nerve. Snellen suggested the possibility, here, of regrowth of connective tissue and lymphatics, and so, the spread.
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To explain these, Deutschmann made a series of experiments on rabbits, removing pieces of optic nerve, and after varying times killing the rabbits and injecting the sheath of the optic nerve from the meninges with Indian ink. He came to the conclusion that a fibrous connection was formed between the nerve ends, and that through this the injected fluid and so presumably cocci, could pass. But his experiments were most carefully repeated by Velhagen, 1889, and Bach, 1896 who entirely failed to establish his results, and indeed showed plainly that after a period of from two to five weeks, the injected fluid could not pass the cicatrized end of the nerve. (50)

The difficulties of the migration theory increase when we wish to explain the clinical fact that the second eye may become affected three or four weeks after the enucleation of the first. The advocates of this theory have said that the agents had entered the optic tract before the enucleation was performed. In that case, the pathogenic agents that maintained a grave, plastic inflammation in the eye, must change their character essentially and suddenly in the lymph sheaths of the optic nerve.

Cases of sympathetic ophthalmia occur after non-perforating injuries. Bronner, 1894, (8) has recorded a case where sympathetic ophthalmia appeared in the right eye eighteen days after a kick on the left which had caused no external wound, and persisted two years in spite of enucleation. Donaldsen, 1897, has reported another case where a blow on the eye caused a subconjunctival rupture of the sclera without external wound. The eye was enucleated in twenty days, but twenty-seven days after the operation sympathetic ophthalmia appeared in the other eye. The enucleated eye showed a plastic cyclitis, which is the constant appearance of eyes
SYMPATHETIC OPHTHALMIA

which have caused sympathetic ophthalmia. Nieden, 1894, viewed a case of sarcoma of the choroid, causing irido-cyclitis in the same eye and followed by sympathetic ophthalmia in the other. The eye was enucleated, and submitted to Deutschmann for examination. He reported that both in the neighborhood of the tumor and in the optic nerve were numerous short, thick bacilli. (50) Alt, 1899, found sympathetic ophthalmia to be caused by glioma retinae. (3)

Deutschmann explains these cases without external wound of the eye by supposing that the micro-organisms are carried by the blood stream and settle in the eye already weakened by tumor or traumatism.

Panas, 1897, has brought forward a great array of evidence to prove the frequent occurrence of endo-infection of the eye, as in the metastatic panophthalmitis sometimes seen in puerperal fever, ocular tuberculosis, and gonorrheal iritis, and, no doubt, bacterial infection occurs in an eye without external wound. To this de Wecker very patiently objected that sympathetic ophthalmia is most frequently found in vigorous patients. (50)

A clinical fact, absolutely unexplainable by the migration theory, is that we never meet with clinical symptoms of a meningitis in the course of a sympathetic ophthalmia, although, according to this hypothesis, a lymphangitis must take place at the base of the brain, especially about the chiasma. Finley, 1872, (16) favored the migration theory but believed that no satisfactory reason had been given for the non-occurrence of a basilar meningitis. There is nothing in the theory to prevent the micro-organisms at the chiasma from wandering from the intervaginal space to the meninges and exciting there an inflammation. If such an inflammation
should be only half as severe as that in the first eye affected, the clinical symptoms of such a meningitis could not escape us, but clinical observation shows that this region must be regarded as healthy during the course of a sympathetic ophthalmia. To this objection, Butschmann answered that the cocci lost in virulence as they ascended the nerve from the wounded eye against the lymph stream, and that when they reached the chiasma they were at once swept away by the lymph stream down the other nerve to produce sympathetic ophthalmia in the other eye. This, however, is a very weak explanation, for even granting that it was so in some cases, one would expect the infection to be so severe in others that at least a slight meningitis would be produced, though this is never so. Such a vital change within the lymph channels does not take place, at least in staphylococci, for it is contrary to what is known of the pathogenicity of the pus agents that they should excite a severe inflammation in an eye, suddenly lose their power as excitants of inflammation in the lymph channels of the optic nerve and the base of the brain, and then regain unabated vigor in the other eye. It must not be forgotten that staphylococci are more infectious to man than to any animal used for experiment. If the slight rubbing of these agents into the skin suffice to produce a severe furunculous inflammation, what must be expected at the base of the human brain if virulent staphylococci wander by continuity from the eyes to the meninges.

It is therefore of interest for us to know how this portion of the brain appears in men who suffer from sympathetic ophthalmia. Several such cases in which the patient died of intercurrent disease have been examined by Roemer, 1903-1906. The important fact common to all was that
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as the distance from the eye increased, the inflammatory symptoms in the optic nerve decreased, and were absent at the chiasma. (47)

There is no doubt that the inflammatory changes in the first part of the optic nerve in sympathetic ophthalmia are distant effects of the intraocular inflammation. At any rate, we can in no way conclude from the condition of inflammatory infiltration of the retrobulbar portion of the second nerve, that inflammatory agents have passed along its lymph channels toward the eye ball. (47) The advocates of the migration theory have maintained that the fundamental principle of the parasitic inflammation, advancing in the continuity of the optic nerve in sympathetic ophthalmia, does not rest on the question whether the staphylococci first mentioned by Deutschmann are the agents or not, but this objection according to Roemer, (47) does not hold good, because the basis of the migration theory rests upon experiments on animals with staphylococci. We must deny, from the very beginning, that any conclusion can be drawn, as to the pathogenesis of human sympathetic ophthalmia, from experiments on animals with any pus agents, for sympathetic ophthalmia is not a purulent inflammation. Roemer, 1903-1906, believed that the migration theory can not be authorized to draw, from experiments on animals, conclusions as to the symptoms of sympathetic ophthalmia in man, or to explain the pathogenesis of the same through a migration of germs along the optic nerve, until a continuous growth of such pathogenic germs as are dangerous to the eye, but do not endanger the rest of the organism through a general infection, has been demonstrated along this tract from one eye to the other. This postulate has not been complied with by the migration hypothesis.

Finally, the migration theory does not explain why the sympathetic ophthalmia begins in the iris and ciliary body in the overwhelming majority
of cases. If it were a lymphangitis that extended from one eye to the
other, every sympathetic ophthalmia should begin as a papillitis, but it
does begin as a uveitis. It has been shown by Andogsky of St. Petersburgh
that if a culture of cocci is injected into the vitreous, a mass of leuco-
cytes go out from the nerve and protect the disc, but if the cocci are
injected into the posterior part of the vitreous, they succeed in entering
the nerve. This tells against the migratory theory, for it is not often
in wounds of the vitreous that we find sympathetic ophthalmia, but after
wounds of the ciliary region. Here again, the hypothesis must seek a way
of escape. Some have conjectured that trivial changes in the optic nerve
could have been present in such cases. While elsewhere, the migration
theory always speaks of a process that extends by continuity, here the
agents arrive at "Tenons space from the sheath of the optic nerve, with-
out causing inflammation, skip an intermediate space and reenters the
eye ball with the ciliary vessels. (47)

Roemer, (47) states that the migration theory is unacceptable
for all of the clinical and experimental reasons mentioned, and because he
believes experience has shown that intra-ocular infections, whatever they
may be and however produced, never excite a lymphangitis confined to the
optic nerve, and which creeps along from one eye to the other by way of the
optic chiasma. If virulent bacteria are employed, they enter the circu-
lation in a mass, and the animal dies of general infection. If less viru-
lent stocks or bacteria of a saprophytic nature are used, they do not
extend to the optic tract, certainly not alone, it from one eye to the
other.

According to Gifford, 1920 (20) however, the optic nerve route,
if we include the lymph vessels of the orbital tissue, has the most attrac-
tive anatomic basis. He believes that the direct connection and open
path afforded by the nerves and their lymph spaces, is the most striking fact. He explains that the main objection, the infrequency of meningitis and the comparatively slight changes in the nerves, as compared with the uvea, may be explained by the assumption of a germ that has a specific affinity for uveal tissue, either inherent or acquired, but which can exist in other tissues. He states that the strongest possible proof of this theory would be a large number of optic neurectomies to show that that the danger of sympathetic ophthalmia was not greater after this operation than after enucleation.

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SPECIFIC METASTASIS THEORIES

SPECIFIC METASTASIS THEORY: EXOGENOUS ORIGIN

The theory that sympathetic ophthalmia originates hematogenously and is due to a specific metastasis from the eye first diseased, was first suggested by Mackenzie. Berlin in 1881 (39) however, was the first to enunciate it clearly. Berlin contended that a position 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 good eye, they there find circumstances analogous to their mother soil, and they develop and give rise to inflammation.

H. Gifford (23)(20)(19)(21)(27) and R. O'Connor (40) have a theory similar to that of Berlin's. In their theory, organisms growing in
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the exciting eye, after a variable period, develop there a special affinity for uveal tissue. After another variable period they gain access to the blood stream and are carried to all parts of the body. The uveal tract, however, being the vascular tract of the eye, is extremely likely to have organisms deposited, or as believed by Rosenow, the cells of the tissue for which a given strain shows elective affinity, take the bacteria out of the circulation as if by a magnet adsorption. Such deposits having occurred, the organisms are immediately through their affinity, able to start the characteristic inflammation, even though there be no primary reduction in the vitality of the tissues. H. Gifford (24) believes that the anatomic argument of this theory is based on the fact that the sympathogenic inflammation is frequently seen to invade and destroy the walls of the blood vessels; and the occurrence of this inflammation is in the form of numerous nodes; each one of which might be supposed to indicate a separate metastatic focus. But as this nodular formation is occasionally found fully developed in the first eye, when the second is entirely healthy, and as it is very often found has advanced in eyes enucleated at the first sign of sympathetic ophthalmia in the other, we must in order to make any use of the nodes as an argument for metastasis, assume that the germ gets into the blood from the first eye and then is distributed back to the first eye alone, thence starting a second crop of metastases for the second eye.

This hypothesis of specific metastasis attracted but little attention at first, but Roemer 1903-1906 (47) brought it in to prominence by experimental research, and believes he can prove that it furnishes an adequate explanation of all the symptoms, and the pathogenesis, of sympathetic ophthalmia.
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Many of the objections against it by Leber, 1881, and others, have lost much of their force with the advent of bacteriology. The view that the condition of development of organisms in the eye are the same as elsewhere in the body is no longer tenable as a general law. Different tissues and organs of the body, undoubtedly, show specific characteristics which make them suitable for special organisms as the streptococcus, typhoid bacillus, etc.

Parson, 1904, states that most facts point to sympathetic ophthalmia as being a disease of bacterial origin, and if the virulence of the organisms and the varying conditions of resistance of the tissues are taken into account, the variations in latent periods and many other difficulties are abolished. It is probable that the organism is pathogenic only for the eye and is innocuous to other parts of the body, though the conditions are not so adverse as to prevent its propagation. It is characteristic of organisms which set up metastatic inflammation, e.g. tubercle bacillus, that the disease is subacute, or chronic, and not purulent. Even virulent organisms may be inactive when circulating in the blood stream. It is a striking fact that saprophytes can set up serious inflammations in the eye while they are innocuous in other parts of the body. The specific organism of sympathetic ophthalmia, then, is not an ordinary saprophyte, but it is one pathogenic for the eye while indifferent to the rest of the body, and it reaches the eye by way of the blood. (41)

Bacterial investigation has shown that in almost all bacterial diseases, some of the organisms escape into the circulation; otherwise, the facts of immunity, the development of active immunity, the production of specific antibodies, especially bacteriolysins, would be incomprehensible.
It is the presence of specific antibodies that often makes these circulating bacteria innocuous, e.g. the presence of antistaphylotoxin in normal plasma prevents metastasis in a staphylococci panophthalmitis.

It is difficult to explain by any other hypothesis why a minimum interval is necessary for the origin of the disease, but the fact that the onset of sympathetic ophthalmia takes place after a certain time of incubation is plausible from views concerning metastasis. Thus, the plastic uveitis begins after the lapse of days or weeks. Perhaps it is necessary that the causative agents shall have increased and have overcome the resistance of the living tissue, and also, to have taken enough time to gain affinity to uveal tissue, before they can force their way into the blood.

This theory also explains how it is that sympathetic ophthalmia can break out several weeks after the enucleation of the wounded eye. The affection may already have gained access to the blood before the operation and may have circulated therein, sometime before being deposited in the uvea of the second eye, and there increase in amount and activity.

Roemer believes that this theory is best fitted to explain those cases of sympathetic ophthalmia which have no prodromal symptoms of irritation. Just as sympathetic ophthalmia may develop in the first eye, after the minutest injury, without previous irritation by any other process, so the sympathetic ophthalmia may develop in the second eye without prodromal symptoms as soon as the specific infectious agents have been implanted in it by way of metastasis. (47)

This theory is also able to furnish an explanation of the absence of meningitic symptoms, and of the commencement of the inflammation in the iris or ciliary body. By the assumption that the infection is carried
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to the second eye by way of the blood, the absence of symptoms referable to the base of the brain is clear, at once, particularly if there is a particular microorganism dangerous only to the eye. The best opportunity for the agents to settle in the second eye would be afforded in all probability by the organ most abundantly supplied with blood, the uvea, in which the inflammation usually starts. (40)

For cases with melanoma, the explanation is not so simple. The necrotic tissue allows germs from some other focus to invade it, producing a focus which then may reach the other eye. (27) However, the theory fails here.

In cases occurring after subconjunctival scleral rupture without a penetrating wound, it is easy to believe that organisms may reach the inside of the eye through the intact conjunctiva, or through a microscopic lesion in it, as occurs in late infections after trephining; the metastatic process then taking its course. (22)

The question now arises whether this theory, even though it may harmonize with the clinical facts, receives experimental support. Such support, according to Roemer (47) needs the proof of three facts.

First, it must be proven that after an acute or chronic intraocular infection, a part of the pathogenic agents enter the blood. Roemer demonstrated this in a great variety of intraocular infections. A portion of the morbific agents enter the circulation from the interior of the eye and are deposited in the large glands, not only in infectious inflammations that lead to sepsis, but in all other intraocular infections as well.

Second, it must be proven that the agents that enter the blood after intraocular infections, invade each according to its nature, with a certain predilection, those organs which they excite only their character-
istic disease. Roemer has demonstrated this. For example, when the agents of the ophthae epizooticae are injected into the vitreous of suitable animals, they enter the blood, seek out their specific localization and produce a specific foot and mouth disease. Hence, he says, we are justified in believing that the agents of sympathetic ophthalmia may likewise find from the blood suitable quarters in the vascular regions of the eye alone.

Finally, it must be proven that the pathogenic agents which excite inflammations only, within the eye, and are indifferent to the other organs of the body, may not only be found in the internal organs after an intraocular infection, but can also be traced to the iris of the other eye. This may be demonstrated by the following experiment: if a dense culture of spores of the bacillus subtilis is injected into the vitreous of several rabbits through the cornea and lens so as not to injure the blood vessels, and if the animals are killed at different times, culturable demonstrable spores of the bacillus subtilis are to be found in the internal organs of all the rabbits and in the iris of the second eye of many of them.

The final condition, alone, to produce after an intraocular infection of the first eye, a similar inflammation of the second, the animal remaining, meanwhile, in perfect health, i.e., to produce a sympathetic ophthalmia cannot be complied with, because we do not know the agent of this disease.

An important point brought out by Fuchs is that the sympathogenic type of inflammation is rarely found in an enucleated eye with traumatic uveitis, unless the second eye has sympathetic ophthalmia. In other words, Fuchs thinks that the characteristic pathology tends to appear almost simultaneously in both eyes, and this is regarded by him as strong evidence
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of a metastatic origin of the disease. While Fuchs has seen the sympathogenic type of pathology limited to one side in only three or four cases, Gradle speaks of seeing it a number of times in eyes enucleated in the absence of sympathetic ophthalmia. According to H. Gifford, even if one sided sympathogenic pathology were as rare as Fuchs supposes, the numerous cases where it is found well advanced, in eyes enucleated at the very outset of sympathetic ophthalmia, show that the assumption of a simultaneous metastatic infection of both eyes cannot be maintained. (24)

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SPECIFIC METASTASIS THEORY:— ENDOGENOUS ORIGIN

The cases of sympathetic ophthalmia after intraocular sarcoma, where the eye was unopened, suggested to Meller, 1913, (37) that the infection cannot be exogenous in those cases and that it must arise from endogenous causes. There, the question comes up whether an endogenous infection should not also be considered in exciting ophthalmia after injury. Certainly, a number of facts in this disease, up till then unexplained, could be cleared up if the infection really were of endogenous causes. Thus, Meller believes that the germs enter the system not through the eye wound, but through a lesion of the skin or some nonocular mucous membrane, and reaches the eye from the blood. And to account for the connection between sympathetic ophthalmia and penetrating wounds, he assumes, that after entering the blood, it develops in the wounded eye on account of the disturbed nutrition, and after growing there for a certain length of time, it acquires an increase power of attacking healthy eye tissues, and then reenters the blood and is redistributed to both eyes. It is, as we know, very rare to find the characteristic histological conditions in eyes which have been
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removed, after injury, as dangerous for sympathetic ophthalmia. But such a finding was to be expected, if the germs had already entered at the time of injury. According to Meller, an endogenous origin of the infection solves the enigma in a simple manner. The germs of exciting ophthalmia find their way into the eye, only later through the blood stream. He states that one can now understand why the histological changes in the first eye are always found fresh, even if the outbreak of sympathetic ophthalmia happened many years after injury. He believes the distribution of the foci in the uvea also points to a dissemination by the blood stream. The same picture is found in both eyes, whilst the infection in the second eye is certainly caused endogenously. The noxa must have been carried into the eye through the ciliary vessel system. If the germs settle in the choroid alone the eye remains pale but, nevertheless, can cause sympathetic ophthalmia.

Harbridge, 1919, (30) believes that the noxious agent causing sympathetic ophthalmia pre-exists in the body. He believes, like Meller, that injury in the offending eye merely prepares a soil for these toxic elements and that the resulting toxines find conditions in the fellow eye favorable for their development. He sees in the frequent relapses of the inflammation in the sympathizing eye, long after enucleation of the offending eye, evidence that there are contributory foci of infection in the body.

According to H. Gifford, 1920, (24) why not assume that in rare cases the sympathetic ophthalmia germ may get into the system through some other part than the eye, as had already been suggested by Roemer (47) and cause a uveitis with sympathetic ophthalmia characteristics; while in the vast majority it enters the body through the eye wound as it would naturally be supposed to do. He believes that Meller's explanation of the almost
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invariable association of sympathetic ophthalmia with penetrating wounds, accords poorly with the extreme rarity of sympathetic ophthalmia in all kinds of injury and disease of the uvea, as long as there is no penetrating wound, and it is open to the objections which apply to all forms of the metastatic theory.

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INTERORBITAL THEORY

Scheffels, 1890, suggested the nosebridge lymphatics as a path of transmission. (24) Arnold, 1891, brought forward the theory that bacteria might pass backward into the cavernous sinus and then be carried to the opposite eye by the veins, owing to reverse current induced by coughing etc., i.e. disturbances in intra cranial pressure. (41) Motais, 1904, and Gilbert, also urged intra cranial pressure variations, as favoring the passage of germs from one eye to the other, by means of the veins that communicate with the two orbits over the bridge of the nose. The path would be by way of the ethmoidal veins, through the nasal septum and over the crista-galli, and through the circular sinus. Gilbert urges that with the venous engorgements that occur during inflammations of the eye, it might be that an extra amount of blood would follow one of these courses to the opposite orbit. The main objection to the theory is that even if germs could follow the course into the other orbit, they would in all probability be carried away from the second eye as soon as they reached the larger vessels. (22)
Ever since the eye had been first examined histologically, assertions have been made of the connection between sympathetic ophthalmia and tuberculous lesions of the uveal tract. In many cases the average pathologist is unable to tell whether a tubercular uveitis or the definite pathological picture of sympathetic ophthalmia, as declared by Fuchs, 1905, is present. The latest views, on its pathology are associated with much controversy. Woods, 1936, (68) and Samuels, 1936, (48) believe that the pathological picture of sympathetic ophthalmia closely resembles that of ocular tuberculosis, but that the following differential points may be stressed. (1) The infiltration about the emissary veins occurs characteristically early in sympathetic ophthalmia and occurs rarely in tuberculosis and only in its late stages. (2) The general tendency in sympathetic ophthalmia is to a general uniform infiltration of the whole uveal tract, while in tuberculosis the infiltration tends to be focal and nodular. (3) Sympathetic ophthalmia attacks the posterior layers of the iris, with the formation of complete annular synechiae. Tuberculosis tends to attack the anterior layers, and interferes little with the motility of the iris. (4) In sympathetic ophthalmia the characteristic infiltration spreads to the other ocular tissues only along the extension of the uveal tissue and, while it invades it shows no tendency to destroy the surrounding tissues by caseation and necrosis. (5) In sympathetic ophthalmia even in the early stages we find phagocytoses of the pigment granules by the epitheloid and giant cells. In tuberculosis we find this pigment phagocytoses only rarely, and then in the late stage of caseation and necrosis. But Meller and his school in Vienna believe that sympathetic ophthalmia is
caused by the tubercle bacillus. They report success in isolating the
tubercle bacillus from the exciting eye and from the blood of patients
afflicted with sympathetic ophthalmia. (See below)

The idea of tuberculosis as a factor in the causation of sympa-
thetic ophthalmia has, naturally, met with contradiction from most clini-
cians, since those suffering from the disease showed no striking sign of
tuberculosis, had formerly always been healthy, and especially sound of
eye. It was almost certain that they would never have been attacked by
iridocyclitis had there been no injury. Moreover, people suffering from
tuberculosis of the lungs, for example, were no more endangered by any
injury to an eye or an eye operation than other healthy persons. However,
several theories of this connection have been proposed.

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MELLER'S THEORY

According to Meller, (37) all studies on sympathetic ophthalmia
were done on the question of why the second eye is attacked, but not one
single author concerned himself with the question of why, in the first
eye, iridocyclitis set in. The iridocyclitis of the first eye was accepted
as such a fundamental condition that no one dreamed of giving a thought
to it. It was this question with which Meller began his studies. He
states that the view existing in general today is that the disease of the
second eye depends on the first. Under the pressure of practical necessity,
the conception of sympathetic ophthalmia became crystallized in the form
that two principles must exist without which danger to the second eye can-
not be regarded as present. The injury to the first eye must be penetrat-
ing and the following inflammation must be iridocyclitis. If the second
eye is affected by iridocyclitis too, then the sickening is characteristic
of sympathetic ophthalmia. This interdependence of the two eyes, from the occurrence in the first eye, was proven (of course only spoken of in the negative sense) through the prophylactic influence of the enucleation when promptly carried out.

It was understood that the outbreak of the disease in the second eye depended upon what happened in the first eye, but that the inflammatory process in the second eye took an independent course and could be more serious than in the first eye. It was soon known that the disease in the second eye was not influenced by the enucleation of the first, if the inflammation in the former eye had already set in.

Most of the observers tried to find out the process which had caused inflammation in an eye that had formerly been healthy, and would certainly not have become inflamed, if the other eye had not been injured, but very little was said about the real cause of the inflammation of the injured eye. It appeared to be superfluous. For since the advent of bacteriology it was considered by most as self evident that the cause of the inflammation in the first eye was bacteria which had entered the eye through the wound, and in those cases of sympathetic ophthalmia after intraocular sarcoma of the first eye, the endogenous theory of specific metastasis was believed a good explanation.

Meller (37) believes he has definite proof that sympathetic ophthalmia is due to a tubercular condition of the first affected eye which, in turn, causes the sympathy in the other eye. He bases his theory on the work he has done with (A) spontaneous and (B) post-traumatic uveitis, which he states are of definite tubercular origin. I shall present Meller's work on these two diseases (A and B) and his resulting opinion (C), in regard to sympathetic ophthalmia.
Meller's earliest idea that spontaneous uveitis is frequently of tubercular origin, even in the case of apparently healthy people, reaches far back. As so often happens, it was also single cases here which first led his diagnostic thoughts in this direction, cases which had previously undergone cures of all kinds and up till then had been treated without success. On observing that a tubercular treatment produced unexpectedly good results, he turned his researches in the direction of tuberculosis. It was this therapeutic fact in the specific treatment of uveitis, whether of chronic, acute, or subacute course, which convinced him of its tubercular nature. At that time he had no proof of the correctness of this opinion, since these patients usually presented the picture of perfect general health.

The diagnosis of any type of tuberculosis was difficult to make, since medicine was not yet so far advanced in this field. But gradually as diagnostic methods improved, many reports were made of tubercular foci in the eyes.

In regard to lung findings in tuberculosis, a positive finding is certainly no proof that the eye disease arises from this etiology. And the same holds true with regard to the result of the diagnostic tuberculin injection, since the majority of these patients react locally, but nothing can be proved, thereby, for the etiology of the uveitis.

However, he believed an entirely different importance had to be attributed to the focal reactions which, after subcutaneous tuberculin injections, appeared in the diseased eye. If, after a tuberculin injection applied, for example, to the arm, the inflammation of the eye flares
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up, it must be regarded as etiologically specific. In many cases the focal reaction is very pronounced; many appear very threatening, and there is often general body discomfort. But, in most cases, the reaction passes off very rapidly and does no harm. Sometimes the vitreous opacities clear up quickly within a few days, being a sign that the diagnostic injection has had a real specific influence on the eye disease. Because of the danger of reaction in some cases, he has substituted the Mantoux test. Here, the focal reactions were absent or very mild. But Meller's conviction that his ideas are correct started from his use of tuberculin, originally for treatment.

In regard to the clinical picture of recurrences of spontaneous iridocyclitis, Meller believes that it depends upon the fact that the disease is carried in the blood, as a bacillemia, to the eyes. E. Lowenstein has proven that bacillemia is not so rare in tuberculosis and is not always the result of virulent miliary tuberculosis. He has also shown by his investigations that bacilli can circulate in the blood vessels of clinically healthy people too, and that bacillemia may run its course without any symptoms or after effects. (37)

Meller states that his position, after these facts had become known, was that a positive bacillus finding, through culture of the germs out of the blood, could be no other than a verification of his opinion. The frequency of these findings, taken by Meller up to October 1933, was 14% of 132 blood examinations in spontaneous uveitis, as positive. He believes that at the outbreak, or fresh onset of the disease are the most favorable times for finding bacilli in the blood. In most cases, the bacilli did not seem to circulate long in the blood, at least not in a
condition favorable for being cultured. He does not believe, however, that a positive blood culture is a positive proof that the inflammation is of a tubercular nature. He also thinks that bacillemia may occur in people of apparently good health and, also, in those with healthy eyes.

Meller states that the definite proof that spontaneous uveitis can be of a bacillary nature is only to be verified by the cultivation of the germs from the eyes themselves, but there lies his difficulty; to obtain sufficiently great a number of examinations to enable one to draw definite conclusions. He has obtained from the end of 1931, when he began to examine by culture the tissue of enucleated eyes, until the end of October 1933, only three eyes suitable for this purpose.

Histological findings made it possible for him to distinguish two different kinds of inflammatory processes, a simple exudative purulent process, and a proliferative inflammation with nodules of epithelial cells. Still, both can only be caused by the tubercle bacillus. Therefore, he believes the conception must be given up that one can only speak of tuberculosis where tubercles are present in the tissue structure. He states that the apparently harmless lymphocytic foci, as well as suppurative inflammations, vitreous abscesses, hypopyoniritis, etc., can be caused by tubercular infection. The virulence of the germs and the allergic state of the body and the organs attacked determines the kind of tissue reaction. P. Shurmann, the well known tuberculosis research worker, in one of his latest publications, has said that the bacillosis, that is, the existence of tubercle bacilli in healthy tissue, in lymph, and in blood, must, on principle, be considered as proven. (37) And E. Lowenstein says, in the same vein, that the bacilli can even be dormant.
Meller, in 1915, (37) who was also in favor of the then current teachings, against the tubercular etiology of sympathetic ophthalmia, examined two cases of sympathetic ophthalmia after penetrating injury where the massive nodular growths in the injured eye contained extensive necrosis. The absence of necroses in the infiltration of exciting ophthalmia had always been regarded as the fundamental difference from tubercular granulomata. These cases, he firmly believed, had upset the last barriers against tuberculosis as the cause, but before coming to that conclusion, he attempted to keep to the old beliefs by means of detailed histological studies, but states that the histological differences in the diseased eyes did not justify the idea that the etiology of both diseases is different.

Meller's studies, on the periphlebitis retinalis in spontaneous chronic iridocyclitis, caused him to pay more attention to the retina in such cases of exciting ophthalmia. In 1921, he believed that there was no difference between exciting ophthalmia and spontaneous chronic iridocyclitis, and of the tubercular origin of the latter he was convinced. He at this time said that the propagation along the perivascular lymph channels of the retinal veins seems to be of great importance for the recognition of the character of exciting ophthalmia. Quite independent
of the question of what occurrences render possible the onset of the disease, he believed these findings were proof that the histological changes must be caused by a demonstrable noxious agent, and that the way which this agent takes under certain circumstances and conditions is exactly the same as that occasionally taken by other well known poisons under similar circumstances as, for example, the tubercle bacillus. Thus, the picture of periphlebitis retinalis tuberculosa returns again in exciting ophthalmia, at least in the anatomical relationship. He stated that it is really surprising how histologically similar are exciting ophthalmia and tuberculosis of the uvea.

Many years passed. The contributions of E. Lowenstein on the presence of tubercle bacilli in the blood of people showing but slight changes in the lungs, drew Meller's attention to this method. Lowenstein made it clear that the blood of patients should be systematically examined for bacilli.

In 1931, Meller, in a case of sympathetic ophthalmia after scleral rupture where the patient was positive clinically for tuberculosis, took a blood culture and this was found to be positive. At this time, he was convinced of its fundamental importance, and at the end of 1931 was concerned with the idea of completing the chain of proof by trying to culture the germs from the eye tissue itself.

On January 18, 1932, he reported that he had succeeded in cultivating bacilli from the tissue of an eye with spontaneous iridocyclitis. And in July 1932 he obtained a typical tubercle bacillus culture from an eye with exciting ophthalmia. Since then, he states, three more positive cases from exciting ophthalmia have been reported.
Meller, considering the close connection between post-traumatic iridocyclitis and sympathetic ophthalmia, states that it was a matter of course that the study of blood cultures was also taken up in patients suffering from post-traumatic iridocyclitis. He then made a blood culture study of forty cases, and bacillemia was present in 20% of them.

Since bacillemia was not absolute proof of the etiology, he believed that he had to go further into the tissue findings. Altogether, he obtained fourteen eyes, seven of which were enucleated on account of iridocyclitis post-traumatica, and seven on account of atrophy of the eye from injury. The blood, as well as the culture findings of the tissues, was negative in all cases, as were the histological findings concerning the question of a specific inflammatory process. There was hardly anything to be expected from the seven cases of old atrophy, so there remained only seven cases of active iridocyclitis. He believes that these negative blood results do not, however, as might be thought, prove that the etiology of post-traumatic iridocyclitis is not of bacillary nature. As previously mentioned, the bacillosis of a tissue is the presence of tubercle bacilli in it without reaction at this point, after the germs have once entered through the blood. Meller believes, then, that should an eye containing such germs meet with an accident leading to tissue destruction, as in the case of perforating injury or severe contusions as in the case of scleral rupture, the germs would find a suitable pabulum where they can rapidly multiply. Without the blood containing bacilli at the time of the injury or immediately afterwards, a specific inflammation may set in. Therefore, he claims that the negative blood in these cases cannot be used against the possibility of a specific inflammation.
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Since the cultural as well as the histological tissue examinations have been negative, proof is not given that the common, simple, post-traumatic iridocyclitis is in some cases founded on tubercular infection.

Meller states that the number of cases is too small to enable him to draw final conclusions, and also, experience is lacking as to whether the tissue culture would grow under all conditions, even if the inflammation had originally been caused by bacilli. He believes it depends on whether living bacilli are present, and if they can still breed. He states that the tubercular etiology of post-traumatic iridocyclitis must not be rejected because of these negative results. He claims this to be wrong by the following facts. He has had a few cases in which the cultural findings in the injured eye were positive. Of these eyes, three had already caused sympathetic ophthalmia in the other eye, and one was just on the point of doing so. In these eyes, the histologic findings were either typical for sympathetic inflammation, and the inflammation had, clinically in fact, already set in, or there existed histologically a great suspicion of sympathetic disease, and the sympathetic inflammation of the second eye had already either occurred or it had not yet set in, and the second eye remained healthy.

Meller believes it would be very tempting to draw the conclusion from these facts, that just those cases of post-traumatic iridocyclitis as are caused by the tubercle bacillus sicken sooner or later of sympathetic ophthalmia. He states that the importance of tuberculosis for sympathetic ophthalmia, is proclaimed anew from these researches, since there is proof of the tubercle bacillus in the blood and eye in cases of sympathetic ophthalmia, and only now that they have succeeded in explaining the
character of the inflammation of the injured eye can we take up the study on the nature of the participation of the second eye.

Thus, according to Meller, our knowledge that the sympathizing inflammation is a true tubercular uveitis which appears, if the patient be at one time or another before the injury or at the time of the injury or soon afterwards, a bacilli carrier in the blood or carrier of bacilli in the tissues of the eye at the time of the injury, but which may occur within any unlimited space of time afterwards, if the patient should ever become a carrier of bacilli in the blood. This knowledge does not entitle us to give up the idea of sympathy of the eyes with each other, and to declare the disease of the second eye, of which there cannot be any doubt of its being tubercular in nature, as independent of the injury or the inflammation of the first eye; it being a primary bacillary infection. Also, that we must not forget that the second eye becomes affected only if the bacillary infection of the first eye has led to the known type of sympathetic infiltration, viz. nodules of granulating tissue, but not if in the first eye, an anatomically uncharacteristic form of infiltration has developed. And, perhaps the reason for this may be that the growths of the epithelioid cells have the capacity of penetrating the veins of the choroid. Thus, germs which by growing in the uvea of the injured eye may have become specially uvea-pathogenic, are carried into the blood stream and settle down in the uvea of the second eye. Meller believes that such a view clears up the reason for the prophylactic action of the enucleation when promptly carried out - an exceedingly important point which shows us that bacillemia alone cannot cause the clinical picture of sympathetic ophthalmia. (37)
SYMPATHETIC OPHTHALMIA

TUBERCULO-ANAPHYLACTIC THEORY

According to Stark, 1923, (52) the great similarity of lesions in tuberculosis and sympathetic ophthalmia, the power of the tubercle bacillus to remain dormant in the body over long periods, seem to point to tuberculosis as the possible cause.

Stark reasons that of all the possible antigens developed through endogenous infection of the uveal tract by microorganisms which may remain in the host for many years, the most probable would be that from the tubercle bacillus, especially since syphilis has been conclusively proved not to be a causative factor. He believes the process might be described as a primary injury to the eye by trauma or intraocular tumor, followed by secondary invasion of tubercle bacilli, with their eventual destruction in the tissues; the development of an antigen taken up by the blood stream, with the sensitization and development of an allergy of the uvea of the secondary eye; possible disturbance of the relations existing between the complement and antibodies by an antigen from a general or focal infection, so that the result of the whole process is an anaphylactic reaction of the uveal tract of the secondary eye, producing the clinical picture recognized as sympathetic ophthalmia. He also believes that the following facts point to a tuberculous origin. (1) Two thirds of the cases of sympathetic ophthalmia develop early in life before the individual has acquired any immunity from tuberculosis. (2) The clinical picture is practically the same in the two diseases. (3) While Fuchs and his pupils have found a definite pathological picture in typical sympathetic ophthalmia, yet the average pathologist has some difficulty in differentiating it from tuberculosis of the eye - the two conditions are similar. (4) Gifford's treatment by salicylates corresponds with the treatment of scleritis which is
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now admittedly tuberculosis, in the majority of cases, and also there are to be found in the literature, cases of the successful treatment of sympathetic ophthalmia by tuberculin.

* * * * *

TUBERCULOTOXIC THEORY

Guillery, 1925, (66)(67) has endeavored to demonstrate by experimental procedures that sympathetic ophthalmia is in its essence a tuberculotoxic disease. Guillery inserted semipermeable capsules containing living tubercle bacilli in pouches, between the ciliary body and the sclera of the eyes of rabbits, and later directly into the vitreous chamber of rabbits' eyes. The tuberculous toxin diffusing out from these capsules produced disease, first in the inoculated eye, and later in the fellow eye, Guillery believed that these lesions were identical with those of sympathetic ophthalmia. On the basis of these experiments, he expressed the view that sympathetic ophthalmia is tuberculotoxic in origin.

This view was partially endorsed by Volen, who repeated the experiments with tubercle bacilli and obtained similar results, but with capsules containing staphylococci, he obtained negative results. He did not believe that the lesions produced in the inoculated eye were entirely characteristic of sympathetic ophthalmia, but that the proliferative choroiditis produced in the second eye was identical with the early stage of sympathetic disease. On the other hand, Meesmann and Volmer, 1927, inquiring into the cause of sympathetic ophthalmia, greatly doubted Guillery's conclusion, and Poos and Sartorius, while confirming Guillery's work, reached radically different conclusions. These authors believe that the picture produced in the experimental eyes was a toxic endophthalmitis in which no initial injury was necessary to the first eye, and that the
lesions produced in the eyes were the result of general toxic injury to the entire reticulo-endothelial system and had nothing to do with the process in human sympathetic ophthalmia. Marchesani, likewise, criticized Guillery's views, believing that the tubercle-like structures, seen in sympathetic ophthalmia occur in many chronic inflammatory reactions due to toxins, and were the expression of an immune biologic defense mechanism of the body. He called attention to the fact that the capsules used by Guillery could not be made entirely permeable to tubercle bacilli, and he sharply disagreed with Guillery's assumption that sympathetic ophthalmia is a tuberculotoxic disease.
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BACTERIOLOGY OF SYMPATHETIC OPHTHALMIA

The bacteriology of sympathetic ophthalmia is negative as far as the discovery of a pathogenic organism is concerned.

Ayres, (5)(4) and Alt, 1837, Schmidt-Rimpler, 1891, (49), Schimer, 1892, (41) Randolph, 1888, (45) Collins, 1895, (11) have failed to find any organism in the exciting eye by the most varied methods and the use of all kinds of culture media. Pyogenic organisms have been found; staphylococcus by Deutschmann, 1882, (later he found a gram negative diplococcus) (14) also by Finley, 1892, (16); streptococci by Limburg and Levy, 1890. (41) It is highly improbable that ordinary pyogenic organisms should be the cause; it is not surprising that they should be found in the injured eye, but their presence in the sympathizing eye required ample confirmation before it can be accepted as an established fact. Organisms, generally cocci, sometimes bacilli, have been more frequently described in microscopical sections by Abraham and Story, 1882, (1) Berger, 1877, (41) and others. No importance is to be attached to the presence of so-called cocci unless the author has carefully considered the possibility of having mistaken them for the granules of mast-cells. It is noteworthy that the organisms have often been found in parts of the eye least affected by the specific inflammation, i.e., not in the uveal tract but in the scar episcleral tissue, optic nerves, (Deutschmann, 1839) or vitreous. (Abraham and Story 1882) (1)

Implantations of portions of affected tissues in the eyes of animals have generally given negative results. Schimer, 1892, (41) has obtained positive results with portions of the ciliary body from an exciting and from a sympathizing eye in the anterior chamber of a rabbit. In both cases a chronic uveitis was set up leading to commencing phthisis bulbi in
four to five weeks, when the eyes were enucleated. The rabbits' other eyes remained normal. Schirmer regarded this experiment conclusive evidence of the presence of organisms in the sympathizing eye.

J. Meller and others believe that the tubercle bacillus is the agent and that we are dealing then with a tubercular condition. This belief is not accepted by many of our foremost ophthalmologists. They are neither satisfied with the proofs, nor that it can explain enough of the clinical facts of the disease.

Every possible germ has been accused of being the agent of sympathetic ophthalmia. There are only two hypotheses that can be drawn from clinical experience concerning its nature; it must be one of the morbicic agents that retain their vitality for a long time in the eye and in the organism, for otherwise, the long duration of the sympathetic inflammation, its tendency to recurrence, and the fact that it may appear many weeks after the commencement of the disease, in the first eye, cannot be explained. It must also be a germ that is not pathogenic to the same degree to other organs of the body, as to the eye; indeed, it is highly probable that it is not infectious to any other part of the body. Thus far we have obtained no evidence that sympathetic ophthalmia can occur in the lower animals, so we have to suppose that man alone is susceptible to this pathogenic agent. Much clinical experience has taught us that persons who are suffering from sympathetic ophthalmia exhibit no lesions in other organs, even approximately resembling those in the eye, or any signs of a general disease, also, no symptoms can be ascribed to a meningitis. (41)

There is no doubt that there are infectious agents which are specially adapted to and have a special affinity for the eye. Dunn, 1904,
was one of the early ophthalmologists to believe that there is a special germ which either passes, or whose toxin is conveyed, to the other eye. (15) Trachoma is an example. The diplo-bacillus discovered by Morax and Axenfield, also excites a specific infectious disease, which may lead to grave corneal ulcerations, on the human eye alone, but cannot infect other animals. No one, who will not acknowledge this special affinity of the agent of sympathetic ophthalmia for the tissue of the human eye can give a plausible explanation of the pathogenesis of this disease. Without this hypothesis, the phenomenon that the second eye along becomes diseased, while all the other organs of the body remain unaffected, cannot be explained. (24)
C. COMBINED THEORIES
SYMPATHETIC OPHTHALMIA

MODIFIED CILIARY NERVE THEORY

Schmidt-Rimpler, 1892, (49) proposed a modification of Berlin's Theory. He said that the microorganisms, after reaching the second eye by way of the general circulation, attacked its tissues, rather than those of other organs, because they had been rendered less resistant in consequence of the congestion produced, causing a metabolic disturbance in them by the vasomotor reflex from the exciting eye, a view which had previously been advanced by Gifford, in 1887, (20) von Rothmund, and Meyer. Meyer's theory is that ciliary nerve irritation only causes sympathetic ophthalmia if the second eye already contains pathogenic organisms. If the eye is normal, sympathetic irritation is set up. (41) Panas (47) added to this obscure conception the idea that general toxic influences such as alcoholism, menstrual troubles, and catarrhal disease of the nose and throat, were predisposing factors of sympathetic ophthalmia. This theory is likewise untenable, because it is at variance with clinical facts and is rapidly disproved by experiment. (24)(21)(41)(49)

In the first place, according to this theory, sympathetic ophthalmia can attack only persons who are already sick in whose blood bacteria circulate or have entered from some pathological condition, but if anything is clinically certain, it is the fact that perfectly healthy persons suffer from sympathetic ophthalmia.

In the second place, this hypothesis does not explain why a certain form of chronic plastic uveitis, the peculiar nature of which has been demonstrated by Fuchs, must always appear in the eye first diseased. Why cannot glaucoma and other conditions associated with marked ciliary irritation (21) likewise cause sympathetic inflammation, instead of a penetrating wound if it depends wholly on the excitation of ciliary
SYMPATHETIC OPHTHALMIA

irritation? Gifford believes this to be a fatal objection to the theory.

The hypothesis is, also, unable to explain the characteristic interval of time between the infection of the first eye and that of the second. Why must at least fourteen days elapse after the injury before the onset of inflammation?

Again, how can it explain the rare occurrence of sympathetic ophthalmia after panophthalmitis, in which extreme ciliary irritation is certainly not lacking?

It is, also, impossible to understand from the theory how sympathetic ophthalmia can appear several days, or even weeks, after the enucleation of the first eye, when there has been no ciliary irritation for a long time. Nettleship (38)(6), Woods-White, (70) and others have definitely shown this to occur.

How can this theory explain the clinical cases in which sympathetic inflammation begins without irritation, especially in serous uveitis, so that the first trouble noticed by the patient is the reduction of vision. The explanation of the pathogenesis of sympathetic ophthalmia cannot be based on a hypothesis which does not account for such a large number of characteristic signs.

In addition, the experimental foundation of this theory is a failure. Certain investigators decided from insufficient experiments that when the exposed iris of one eye was irritated, the amount of albumin and fibrin in the aqueous of the other eye was increased. Wessley, 1900, however, has shown with great exactitude that the amount of albumin in the aqueous of the second eye remains normal when the first eye is irritated.

Roemer, 1903-1906, has shown experimentally that no intraocular
inflammation in the first eye is able to influence by reflex action an increase of the albumin, or a change in the content of antibodies in the aqueous of the second eye. Therefore, the idea that the reflex transmission of irritation can excite disturbances in the circulation and nutrition, of the second eye, has not been proven and cannot be proven. According to Roemer, (47) Schmidt-Rimpler attempts to vindicate the theory by saying that the site of irritation is especially in the ciliary body; and that the investigation of the aqueous does not suffice, because the latter is not secreted by the ciliary body, according to modern views.

In the first place, this assumption that the hypothetical irritation is confined to the ciliary body and is not transmitted to the iris, is an improbability, for the ciliary nerves supply both the ciliary body and the iris. In the second place, Roemer has proven that the composition of the intraocular fluid behind the iris of the second eye, the secretion of which, by the ciliary body, is not contested by Schmidt-Rimpler, is not influenced, in the least, by an intraocular irritation of the first eye.

Moll, 1893, injected cultures of the pyocyaneous bacilli, intravenously, in rabbits and cauterized the cornea with the silver stick or introduced sterile copper into the anterior chamber. In 77.3% the bacillus was found in the aqueous of both eyes. When one eye was not irritated, the aqueous contained the bacillus in 23.1%. Such investigators, in which virulent septicemia is produced, are of little value as regards sympathetic ophthalmia. (41) The advocates of this theory have performed surprising evolutions in order to try to evade these facts. While they formerly relied on the experiments of Mooren and Rumpf, they now claim
that it is not necessary for any change in the composition of the aqueous
to be produced by the hypothetically transmitted irritation. By this
claim, they have so modified the theory that it may be abandoned, for such
irritation cannot be traced and tested. To maintain that irritation of
one eye induces a lacrimation of the other, does not touch upon the ques-
tion whether an infectious disease of the second eye is favored, much
less caused in this manner, and this is the question in sympathetic oph-
thalmia. The latest idea is the statement that animal experiments contra-
dict Schmidt-Rimpler's theory, but that in man a transmission of the
irritation to the other eye may still be able to act in loco. Animal
experiment is insufficient for demonstration because it is impossible to
produce in animals the nervous irritation of the second eye known as sym-
pathetic irritation. Many things are confused in such conclusions. In
the first place, the symptom complex of sympathetic irritation has hitherto
been considered as having nothing to do with sympathetic inflammation.
In the second place, it is not necessary that the symptom complex of the
so-called sympathetic irritation should appear in animals, for, according
to Roemer, this symptom complex does not form a true ophthalmological
picture, but pertains to traumatic hysteria. The question is whether a
purely reflex irritation in the first eye can influence the processes of
circulation and nutrition in the second so as to favor, or cause, a
settlement of microorganisms from the blood. There is no positive evi-
dence, then, of such a conception, even in man, and many are opposed to
the idea because it is too untenable and may lead to far reaching conse-
quences. (47) However, there is the possibility that the location of the
sympathetic ophthalmia germ may be favored, or its action reinforced by
reflex disturbance in the circulation of the second eye. (24)
H. I. Faier

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D. FILTRABLE VIRUS THEORIES
SYMPATHETIC OPHTHALMIA

FILTERABLE VIRUS THEORY

The most interesting of the recent contributions on the pathogenesis of sympathetic ophthalmia are the experiments with filterable viruses. Von Szily, 1924, was the first to investigate this question. In 1924 he reported a series of experiments. The material from a herpetic lesion on the human cornea was injected into rabbits' eyes. After the characteristic herpetic keratitis had developed, the superficial layers of the cornea were removed, and this material was inserted in ciliary pouches of the eyes of other animals. In these animals, uveitis of the injected eye developed, and in 10% similar uveitis developed in the second eye. The papilla and optic nerve showed similar infiltration with lymphocytes and epithelioid cells. Going on the theory that filterable viruses have a predilection for nerve tissue, he believed that the mode of transmission from eye to eye was by way of the optic nerve. This work was confirmed by Abe, 1926, Velhagen, 1927 and by Gifford and Lucic 1927, (25) in this country. Gifford and Lucic, 1929, (26) further extended these observations by showing that herpetic virus inoculated as far back as the chiasma in eyes of experimental rabbits, produced lesions that spread forward along the nerves and produced uveal disturbances in both eyes. Marchesani, 1926, however, repeated the experiments of von Szily with negative results. (66)

On the supposition that sympathetic ophthalmia might be due to an ultramicroscopic unculturable virus contained in the tissues of the eye, numerous observers have attempted to produce the disease in the eyes of rabbits by direct inoculation of material from active human sympathetic disease into the eyes. In 1927 Gifford and Lucic (25) inoculated ten rabbits with the contents of a sympathetic eye, with entirely negative
results, except in one instance. In this, they offered the explanation that secondary contamination might be responsible. Meesman and Volmer, 1927, using material from five cases of sympathetic ophthalmia, inoculated sixty rabbits by the ciliary pouch method. Material from one case produced a uveitis in the second eye of three rabbits. Two of these, however, on post mortem examination, were found to have tuberculosis, but the third showed no lesions at autopsy. They believed, however, that there was a possibility that the disease in the eye of the last rabbit was due to herpetic virus acquired at a stall infection. Lesser, 1928, Marchesani, 1925, and Undelt, 1926, did some similar experiments again with negative results. (66) Woods, 1930, (65) has been greatly struck by the similarity, both in the clinical and in the pathological picture, of periodic ophthalmia in horses and sympathetic disease in man. The essential clinical pictures are almost identical and there are some resemblances in the pathological pictures. In equine periodic ophthalmia the demonstration that the disease is due to a filterable virus appears to be conclusive. (65) Further, it must be remembered that not all species of animals are susceptible to the various filterable viruses, and that in susceptible species a certain number of individuals appear to be naturally immune. For this reason the negative inoculation experiments are inconclusive! In a criticism of this work the attractiveness of a filterable agent as the responsible etiological factor in sympathetic ophthalmia cannot be denied, and the negative results from animal inoculation, while disappointing, are certainly inconclusive.

What is necessary to prove, however, is whether or not a filterable virus can produce human sympathetic ophthalmia as the result of inoculation from human cases.
E. BIOCHEMICAL THEORIES
SYMPATHETIC OPHTHALMIA

TOXINIC THEORIES

The autointoxication theory was brought forward by von Rothmund and Eversbusch in 1882. This theory is based chiefly on the fact that microorganisms have rarely been found; it has, therefore, been concluded that the inflammation is caused by their metabolic products. (41) By this theory the products of metabolism in the first injured eye, are supposed to be carried to the sympathizing eye in one of the following ways: either the products of metabolism pass through the lymph stream into the second eye and cause inflammatory changes; or these products pass through the blood into the circulation and cause changes in the second eye; or the damage is caused by toxalbumins in the vasomotor centers and in the ganglion; or the products of metabolism may remain in the originally injured eye, setting of their chemical irritation, which is an analogue of mechanical irritation, and in a reflex way damages the other eye and causes inflammation. (71)

Bellarminoff and Selenkowsky, 1902, (24) believe that sympathetic ophthalmia is caused by the continuous carrying over of bacterial toxins from one eye to the other by way of the optic nerve and chiasma.

Guillery, 1910, (24) claims to have often caused the characteristic clinical and microscopical picture of sympathetic ophthalmia, by intravenous injections of various bacterial products. He believes that the disease is neither microbic nor anaphylactic but is caused by the action of ferments which probably are the result of some sort of autointoxication.

The strongest clinical argument against the theory is that the disease continues after removal of the exciting eye, and may even commence under these circumstances.
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CYTOTOXIC THEORIES

Strong as was the internal evidence in favor of the germ theory of sympathetic ophthalmia, the failure of the vast majority of the numerous attempts to discover any particular germ in the first eye, coupled with the increasing knowledge of the phlogistic affects of autotoxins, especially those caused by the splitting up of various proteins in the body, naturally led to theories of sympathetic ophthalmia from which microbes were eliminated. (24)

The first of these theories was that proposed by Pusey, 1903. He based his theory on the work of Castaigne and Rathery who had found that when the entire pedicle of one of the kidneys of a rabbit was ligated and the degenerating kidney left in place, well marked degenerative changes took place in the opposite kidney; while if the ligated kidney was immediately removed, no such changes occurred. Pusey, then, suggested that when a damaged eye degenerates in the orbit, the cells of the eye, probably the lining cells of the ciliary processes and the iris, can give rise to a specific cytotoxin which, circulating in the blood, picks out the cells of the fellow eye and may cause changes which are those of sympathetic ophthalmia. Pusey's attempt to prove his theory by the injection into dogs of goat serum from animals immunized with dogs' uveal tissue, gave a negative result. About a year later, 1905, Golowin proposed a similar theory which embraced the additional supposition that the eye, injured by the toxins, became more easily the prey of germs circulating in the blood. (24)(42)

Schirmer, 1909, showed a fact against this theory, calling attention that noxious elements anywhere in the body, after removal of the primary focus of infection, gradually diminished in toxicity; hence, he
saw in the cases of sympathetic ophthalmia which develop some time after removal of the injured eye, and those cases of recurrent exacerbations in the sympathizing eye for months after removal of the offending eye, marked evidence contradicting this hypothesis. (42)

*  *  *  *  *

ANAPHYLACTIC THEORY

The most prominent of the biochemic theories is that which assumes that sympathetic ophthalmia is an anaphylactic phenomenon. It was inevitable that anaphylaxis, the magic key to so many biologic mysteries, should be applied to sympathetic ophthalmia; and the suggestion came almost simultaneously from two pathologists, Bail and Heim, to Elschnig, 1910, and Kummell, 1910, respectively; as these investigators are careful to explain. It was followed by an immense amount of careful work by these men, and as the work of Elschnig was first published and more elaborate, the theory is rightly known as his. (22)(58)(59)(61) In this theory it was assumed that an injury to the exciting eye resulted in an absorption and general dissemination of the uveal pigment, which produced a hypersensitivity of the organism as a whole and especially of the homologous organ, the fellow eye. Continued absorption of this uveal pigment from the exciting eye resulted in allergic intoxication of the sensitized tissue of the second eye, manifested clinically as sympathetic ophthalmia. A mechanism somewhat similar to that supposed to underlie serum sickness was assumed.

In brief, Elsching (58)(59)(61) has found, after much careful and laborious investigation, that on repeated injections of heteroserum into the rabbit's eye, the latter shows an anaphylactic reaction in the
shape of an iridocyclitis of limited duration, the reaction being more pronounced when the animal has been previously immunized by injections of the same serum into the blood. Injections of uveal tissue emulsions, as well as of chemically pure eye pigments, sensitize the system, as shown by the complement fixation method, to eye pigment, not only of the same species, but to eye pigment of other animals. This sensitization can be produced with pigment of the same species of animal, but not of the same individual nor to so marked a degree as when the pigment of another species is used. The reaction is organ specific but not species specific.

Kummell has obtained similar results; and in rabbits' eyes in which anaphylaxis was produced by repeated injections of hetero-serum, has found a lymphocytic nodal infiltration of the uveal tract, quite similar to that observed in sympathetic ophthalmia. With homo-serum or homo-tissue, he obtained no anaphylaxis; and in testing the serum of patients with sympathetic ophthalmia, he was not able definitely to demonstrate a sensitivity to uveal emulsions. (58)

In support of his supposition of an organic anomaly as auto-intoxication, Elsching has repeatedly tested the urine of his patients for indican and believed that the results obtained showed an abnormal frequency of auto-intoxication in patients with uveal inflammation. (22)

With the establishment of the organ-specific properties of uveal pigment and antigenic power in the homologous animals, Elsching's theory did not appear to assume a totally impossible mechanism. From the first this theory had many adherents and many critics.

Shiek, 1913, opposes the anaphylactic theory on the ground that since anaphylactogen from the eye is communicated to the whole system
within three hours after the antigen has been injected into the anterior chamber; the second eye would then be at the mercy of the slightest disturbance of the uveal pigment for a period of months, years, or a lifetime. Under these circumstances the enucleation of the first eye could obviously be of little use; but as experience shows, it is of the greatest possible use. (27)

This theory was investigated at considerable length by Woods (66)(61)(62). After confirming Elschnig's original findings on the antigenic properties of uveal pigment, he investigated the possibility of producing ocular inflammation by sensitization and intoxication with uveal pigment. By intraocular sensitization of dogs with canine uveal pigment, and intoxication by intrapentoneal injection, a uveal disturbance was produced in the second eye in a small percentage of the attempts made. This uveal disturbance was in no way comparable to clinical sympathetic ophthalmia, yet represented an inflammation of one uvea following the insult to the uvea of the fellow eye, induced after the manner of an allergic reaction. Woods, 1921, (63) investigated the immune reaction to uveal pigment in patients who had suffered wounds of the uveal tract. The serums of patients, thus, examined in the complement fixation reaction against an antigen of uveal pigment fell into two general groups: (1) in patients who had normal healing without the occurrence of sympathetic ophthalmia, substances were found in the blood stream which were capable of combining with the pigment antigen and fixing complement; (2) in patients who had developed protracted inflammation or sympathetic ophthalmia, following the uveal wound, such substances were not present.

The complement fixation reaction was later further investigated
by Fodor, 1927. (67) This observer found the same complement-binding substances in the blood serum of patients, following wounds of the uveal tract. He found that they were gradually absent in patients with sympathetic ophthalmia, but confirmed, only partially, the observations that they were present in all cases where normal healing occurred.

Woods, 1925, (64) later used uveal pigment as an antigen in an intracutaneous test, and found patients with sympathetic ophthalmia showed a definite hypersensitivity to pigment. In numerous controls, normal individuals and patients with other types of ocular disease, the intracutaneous test with pigment was negative. The complement fixation reaction was believed to be impractical as a routine diagnostic procedure due to technical difficulties. The intracutaneous test, however, was believed to be of definite value in detecting pigment hypersensitivity.

In his first clinical studies he reported thirty patients with penetrating wounds of the eye involving the uveal tract, tested with pigment by the intracutaneous method. Negative results were observed in fourteen, and positive results in sixteen of these patients. Of the fourteen negative patients, eleven showed normal healing and three showed persistent inflammation which necessitated enucleation of the injured eye. In none of these patients did sympathetic ophthalmia occur. Of the sixteen patients with positive intracutaneous tests, none showed normal healing; twelve patients had definite sympathetic ophthalmia, and two had sympathetic irritation. The remaining two patients showed persistent inflammation of the injured eyes, so intense that enucleation was performed. There was, however, no evidence of sympathetic disturbance in the second eye. On the basis of these findings, Woods expressed the opinion that
there was a definite allergic phase in sympathetic ophthalmia, but it did not appear that this was the only cause of the disease, and other etiological factors might well figure in the condition.

Both the complement-binding reaction and the intracutaneous test with uveal pigment were used by Gifford, 1929, (27) in a few cases. In four patients, two with penetrating wounds of the eye without sympathetic disease, and two with sympathetic disease, the intracutaneous test was negative; and Gifford failed to find complement-binding antibodies in the serums of any of these patients. Verhoeff, 1927, (56) found the intracutaneous test negative in one case of sympathetic ophthalmia. Gill, 1930, (28) used the intracutaneous test extensively in sympathetic disease and found it uniformly positive in all cases of sympathetic ophthalmia and negative in other conditions.

The general idea that allergy plus some other exciting agent produces the characteristic pictures of sympathetic disease, was taken up by other investigators. In 1930 Marchesani (67)(66) reported an interesting experiment. He isolated the B. subtilis, by the antiformin method from the enucleated exciting eye of a case of sympathetic ophthalmia. Repeated injections of this bacillus into one eye of a number of rabbits finally resulted in choroiditis in the untouched eye. No changes were noted in the other eye tissues of the body. After the acute inflammation had subsided the histologic picture was found to be round cell infiltration of the uvea of the inoculated eye, and lymphocytic infiltration in the choroid of the sympathizing eye. Judging from anatomical changes along the nerves the transmission of the disease did not occur by the nervous pathway. Marchesani believed this was not a question of simple
metastasis, but the changes in the second eye were due to allergy produced by the specific organism, which made its localization in the second eye possible. In short, a paired organ sensitivity developed which explained the localization of the exciting organism in the fellow eye, while it was not found in other parts of the body. This work was repeated by Iga, 1929, (66)(67) who sharply criticized Marchesani's views, believing that bacterial metastasis in the second eye was responsible for the picture. He further emphasized that B. subtilis was by no means pathogenic for rabbits. This work was further investigated by Kiyosawa, 1930, (67) who confirmed the view expressed by Iga. In this connection, the early experiments of Guillery, 1915, (66)(67) and later of Woods, 1916, (67) are interesting, these authors having shown that such ferment-producing organisms as B. subtilis produced degenerative products in the mediums in which they are grown, and these degenerative products have a selective irritative effect on the ciliary body. Marchesani's conclusion that the lesions observed in the second eye were influenced by allergy, is further questioned by the recent work of Friedenwald and Rones, 1931. (18) These authors found lesions almost identical with those described by Marchesani in the eyes of patients who had died of general septicemia. Riehm, 1929, (66) in a series of interesting experiments, modeled along the earlier experiments of Wessley, reached the conclusion that a foreign protein absorbed from one eye produced an elective sensitivity in the fellow eye. This was true only in pigmented rabbits. In albinotic rabbits, no such elective sensitivity of the paired organ was produced. He believed that similar organs with a common trophonervous influence was a closed entity and had a common inflammatory reaction which should be
designated as elective sensitization rather than sympathetic disease. In sympathetic ophthalmia, he believed, etiological conditions might occur. In penetrating wounds an infectious agent is present which acts as an antigen only in human uveal tissue, and sensitizes the uvea of both eyes. Such sympathetic ophthalmia is thus an anaphylactic inflammatory reaction to a bacterial antigen. In sympathetic ophthalmia, such as might follow disintegrating choroidal sarcoma or subconjunctival scleral rupture, inflammation in the uvea of both eyes might be regarded as purely allergic processes; the inflammation of the second eye being due to the phenomenon of elective sensitivity. Various other authors, without reporting experimental work, have emphasized the idea that the outbreak of sympathetic ophthalmia in the second eye might be due to a modification of the uvea of the second eye through allergy or endogenous infection which thus renders it liable to the action of other noxious agents.

In a later paper, Woods, 1932 (66) reported more extensive clinical studies on pigment allergy in sympathetic ophthalmia. In this report 153 intracutaneous tests with pigment were done on patients with a variety of ocular conditions. The summary of these tests are as follows: in twenty-seven cases of uveitis due to constitutional causes all showed negative reactions; in eleven cases of contusions with traumatic uveitis and with no sympathetic disturbance, all showed negative reactions; in eight cases of operations involving the uveal tract and all eyes lost with no sympathetic disturbance, all showed negative reactions; in four cases of endophthalmitis phaco-anaphylactica, one showed a positive reaction and three showed negative reactions; in forty-one cases of penetrating wounds
involving the uveal tract with recovery without enucleation and with no sympathetic ophthalmia, three showed positive reactions and thirty-eight showed negative reactions; in twenty-six cases of penetrating wounds involving the uveal tract with enucleation of the injured eye and no sympathetic ophthalmia, five showed positive reactions, and twenty-one showed negative reactions; in five cases of delayed, non-infecting, post-operative uveitis, all five showed positive reactions; in twenty cases of sympathetic ophthalmia, eighteen showed positive reactions and two showed negative reactions.

Three patients who showed normal healing of the injured eye and did not develop sympathetic ophthalmia, gave positive intracutaneous tests to the pigment antigen. In two of the patients, the tests were doubtfully positive, while in the third patient it was strongly positive. This last patient was the only one observed who showed a frank pigment hypersensitivity associated with normal healing. Three patients with sympathetic ophthalmia had negative reactions to pigment when the tests were first done in the acute stages of the disease, the reactions becoming positive several weeks later, as the disease subsided somewhat. Two patients with sympathetic ophthalmia showed negative intracutaneous tests the only time they were examined. In one of these patients, the disease was in the acute stage; in the other patient the disease had been quiescent for fifteen years. In the last patient, any hypersensitivity before present, may reasonably be supposed to have subsided.

On the basis of these observations, the conclusion was advanced that while hypersensitivity to uveal pigment is rather uniformly found in sympathetic ophthalmia, there is a definite group of patients in whom the development of this pigment hypersensitivity is delayed, and in certain
acute stages of the disease there occurs a negative phase of pigment hyper-
sensitivity just as negative tuberculin reactions are found in certain
acute stages of tuberculosis.

Further studies of Friedenwald and Wood, 1933, (66) strengthened the evidence that allergy to uveal pigment is definitely concerned
in the causation of sympathetic ophthalmia. These observations were as
follows: the histologic picture of the excised skin, into which pigment
had been injected, was studied in several persons at various times after
the injection. In the injected skin, excised a few days after the pig-
ment test had been done, no essential histologic difference could be de-
tected between the positive and negative intracutaneous reactions; but
in the injected skin, excised two weeks after the intracutaneous injec-
tion had been made, very marked differences were noted. In the patients
with negative intracutaneous tests the excised skin showed a moderate
infiltration of monocytes and lymphocytes around the injected pigment,
and a large part of the pigment remained free in the tissues not ingested
by the phagocytic cells. There was moderate perivascular round cell in-
filtration in the tissue, but the reaction in the main consisted of
lymphocytes, occasionally monocytes, and very occasional epitheloid cells.
In the patients with positive intracutaneous tests, however, the picture
two weeks or more after the test was radically different. The pigment
deposits were deeply infiltrated with large numbers of epithelioid and
giant cells in which the granules phagocyted. No free extra-cellular
pigment was found. The surrounding tissues showed intense perivascular
round cell infiltration. The general picture in the skin, two weeks or
more after a positive intracutaneous test, thus presented a histologic
picture strikingly that of eyes with actual sympathetic ophthalmia.

As a result of his many studies, Woods in 1933 concluded that hypersensitivity to uveal pigment was observed only after penetrating wounds of the eye and the development of such hypersensitivity indicated a grave prognosis, only one patient with frank pigment hypersensitivity having shown normal healing. In sympathetic ophthalmia the occurrence of pigment hypersensitivity at one or another of the stages of the disease is a general rule, although patients with acute exacerbations of the disease may pass through phases in which the intracutaneous test is negative as hereafter noted, hypersensitivity to pigment was also observed in other recurrent forms of post-operative and post-traumatic uveitis where sympathetic ophthalmia did not occur. Woods, therefore, believed that in addition to this pigment allergy, some other unknown factor entered into the etiology of sympathetic ophthalmia. This conception that pigment hypersensitivity was a factor but not the sole cause of sympathetic ophthalmia, led Woods to alter the original conception of the allergic basis of sympathetic ophthalmia expressed by Elschnig. He expressed the opinion that a difference in the immune responses of different patients or the development of allergy to pigment itself, might alter the normal immune biologic defense mechanism of the eye to the extent that normal healing did not occur. In sympathetic ophthalmia, this impairment of the normal resistance by pigment allergy permits some unknown agent to act, thus producing the characteristic clinical and pathologic picture.

According to S. R. Gifford, 1929, (27) this theory offers an attractive explanation of the few cases of so-called spontaneous sympa-
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Sympathetic ophthalmia occurring without a penetrating wound most often in patients with melanomas of the choroid. There are many objections to it, however. It involves a very complicated sequence of events, the most important of which is sensitization to one's own uveal pigment with subsequent reaction in the second eye has never been demonstrated experimentally. On such a theory, sympathetic ophthalmia would be expected to occur fairly often following any chronic iridocyclitis, whereas it actually occurs almost exclusively following a penetrating wound, the spontaneous cases being the greatest rarities. Elschnig's assumption that a condition of lowered resistance is necessary, is opposed by the common occurrence of sympathetic ophthalmia in otherwise healthy individuals. Since sensitivity is assumed to be complete before the reaction in the second eye occurs, enucleation after this event would theoretically be of no benefit. The very frequent occurrence of optic neuritis in the second eye, sometimes as practically the only symptom, is hard to explain on Elschnig's theory, as reaction to uveal pigment would not be supposed to affect the nerve that is free of pigment. The histologic picture of sympathetic ophthalmia of the second eye is characterized by infiltration, chiefly of the posterior part of the choroid, while in Woods, 1925, (64) experimental animals, this part was free of inflammation. A. Fuchs (27) has examined all the sections of sympathetic ophthalmia in the Vienna collection to determine how far the nerves were involved. Of seventy-one cases with section of the nerve, fifty-four showed some signs of inflammation in the nerve or its sheaths. In twenty-four this inflammation was marked, usually affecting the pial sheath and adjacent nerve substance and consisting chiefly of round cell
infiltration. Fuchs believes that the infiltration reaches the nerve from the choroid, around the vessels of the circle of Zinn, and that occurs very commonly in sympathetic ophthalmia and could be more often found, if the nerves were examined far enough posteriorly.

Anaphylactic manifestations are generally sudden and explosive; differing entirely in this from the usual course of sympathetic ophthalmia.
SYMPATHETIC OPHTHALMIA

CONCLUSION
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The question involved is, then: which one of the theories is most tenable?

I am inclined to believe from the material which I have read and presented here, that bacterial theories of specific metastasis, exogenous and endogenous in origin, offer the most natural explanation. However, it must be recognized that until we have the sympathetic ophthalmia germ, and susceptible material for experimentation, these theories are uncapable of definite proof or refutation.
PATHOGENESIS OF SYMPATHETIC OPHTHALMIA

CONCERNING THE THEORIES OF TRANSMISSION

BIBLIOGRAPHY
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