ROLE OF FOCAL INFECTIONS IN SYMPATHETIC OPHTHALMIA.

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This paper sets forth an hypothesis of the connection of focal infections with sympathetic ophthalmia, cites the writings of others that seem to support this view, and reports in abstract five illustrative cases. Read before the Pacific Coast Oto-Ophthalmic Society, August 6th, 1919.

The object of this paper is to call your attention to a possible relation between certain cases of sympathetic ophthalmia and focal infection notably of the apices of the teeth, the so-called apical abscesses.

The resemblance of certain of these cases is so close to certain other cases of serous iridocyclitis with focal infections as an admitted etiologic factor, that I am unable to see any substantial difference between them except the history on the one hand of a perforating injury of one eye preceding by a certain interval of time the outbreak in the second eye, and on the other hand the absence of such history.

I desire to place before you a working hypothesis of the pathogenesis which is based upon the work of many ophthalmologists and which, while it recognizes the etiologic rôle of focal infections in the production of sympathetic ophthalmia, gives a different evaluation to anaphylaxis from any I have been able to find in the literature accessible to me.

I submit the following sequence of events as enabling us to understand and explain the occurrence and course of sympathetic ophthalmia. It is of course hypothesis, not a statement of settled pathology.

First. A focal infection.

Second. A trauma of the eye with microbic implantation in the uveal tract of bacteria similar to those in the focal infection, or of a variety which by change, in oxygen pressure for example, may by transmutation become similar.

Third. A time interval during which sensitization of the uveal tract occurs.

Sensitization by (a) Local specific defense by first a zymogen with specific ferment and a splitting of the bacterial protein in the exciting eye. (b) Predilection for the uveal tracts.

Fourth. Escape "in sufficient numbers" into the circulation of bacteria either from the first eye or from the focal infection.

Fifth. After sensitization a continuous or intermittent supply of bacterial protein of the same sort which has sensitized the second eye, causing an anaphylactic inflammation by a process somewhat analogous to Arthus's phenomenon, but not the same.

To those of us not familiar with Arthus's phenomenon this abridged description gives the principal points.

If a rabbit is sensitized by the subcutaneous injection of horse serum every six days, the first few injections will be absorbed in a number of hours. The fourth injection produces a soft infiltration which is not absorbed before two or three days. The fifth injection causes an edematous infiltration which is harder and is not absorbed before five or six days. The sixth injection produces a white solid compact subcutaneous mass which persists for weeks and the seventh causes the skin over the subcutaneous mass to become red then pale and begins to dry, a spot of gangrene develops which produces a refractory ulcer. These results remain the same when the injections are given in different localities or when all but the last are given in different localities or when all but the last are intraperitoneal.

Sixth. Sensitization of the second eye, having occurred thru and by reason of predilection the antigen, to use Ehrlich's term, could come conceivably either from the focal infection or from the exciting eye which would suggest the necessity for removal of both the exciting eye and the focal infection and which moreover would explain why removal of the exciting eye alone has failed so sadly to save the

sympathising eye once the uveitis has become established.

Taking this sequence of events seriatim: Billings defines a focal infection as a circumscribed area of tissue which is the seat of an infection of pathogenic microorganisms.

Such an area as you know may be located nearly anywhere in the body. If primary it usually communicates with a mucous or skin surface. It may spread by contiguity or become secondary thru the blood or lymph channels. The eyeball itself may become either a primary or secondary focus, as, for example, in a panophthalmitis following a wound or a metastatic choroiditis; and as such itself disseminate bacteria and toxins, having a perfect predilection for ocular tissues.

The effects of a focal infection depend upon whether or not the pyogenic or nonpyogenic bacteria are present, also upon the location and therefore upon the successful local defense set up by the contiguous tissues. If the degree of success in erecting a wall of exudate about the focus is small there will be leakage, either of toxins or of bacteria or of both, into the circulation with results of course dependent upon the virulence and number of the bacteria, as well as upon the particular affinities of the strain, if it be streptococcus or pneumococcus, etc.

Bearing these pathologic considerations in mind let us then assume for the present the presence of a focal infection; for example, an apical abscess with streptococcus viridans as the invader. We might substitute a tonsillar crypt with streptococcus mucosus capsulatus if we choose.

The patient says he is perfectly well, feels no pain or tenderness about the tooth. The toxins and the streptococci are nevertheless leaking into the circulation either continuously or intermittently and of course may reach the uveal tract.

Why does not the patient invariably develop an iridocyclitis? Because among other things both the streptococci and the toxins are insufficient in number and virulence to get by the nonspecific defenses of the blood.

Moreover the strain of streptococci may have no special affinity for uveal tissues, furthermore the bacteria may be insufficient in numbers to cause any local specific defense by the uveal tissues.

Assume now the implantation in the uveal tissue thru a wound in one eye of a sufficient number of streptococcus viridans to set up an inflammation. If not in sufficient number or of sufficient virulence suppuration will not occur, but a so-called traumatic inflammation of greater or less degree. This inflammatory reaction is accompanied by leucocytic infiltration and the well known histologic changes. This histologic picture is not that of sympathetic ophthalmia.

If this eye, having been infected with streptococci, is inflamed a specific defense *in loco* is set up with leucocytic infiltration, and formation of a specific proteolytic ferment which splits the protein of the streptococcus (and probably its toxins).

The fixed cells of the uvea participate. They are sensitized, being rich in the specific proteolytic zymogen, or to use the language of Billings, the streptococci have a "specific elective pathologic affinity for the tissue," or else no resistance would have been encountered. If they were in sufficient number, therefore, the invader "excited a characteristic reaction and sequential train of morbid anatomic lesions."

Rosenow has been able by varying the oxygen pressure of his cultures to cause transmutation from streptococcus hemolyticus to pneumococcus, to mucous capsulatus, to viridans, also to change the virulence and elective affinities almost if not quite at will.

I assume such change is possible in an eye, i. e., that a strain having predilection for uveal tissue may be produced in one eye which will affect the other. What determines the production of such a strain I do not know. However Vaughan says "each foreign protein has its predilection tissue where it is largely deposited, whose cells it especially sensitizes and where it is disrupted."

This requires *time*. After a time in-

terval, injection of more of the foreign protein into a sensitized tissue will set up an anaphylactic reaction. What an anaphylactic inflammation in the eye is like we shall see presently.

Streptococci, or other bacteria escaping into the circulation, having an elective pathologic affinity for uveal tissue, escaping from the first eye, find their mother tissue nowhere else but in the second eye; they are there deposited, having been found in sympathetic ophthalmia by Angelucci, Limbourg, Levi and others. They especially sensitize the uveal tissue of the second eye. If now the supply is augmented by a supply from a second similar focus elsewhere in the body the conditions are met for an anaphylactic reaction if the numbers, and virulence and predilection are only sufficient. Conditions which we might believe to be rather rarely all fulfilled at one time and that the proper time.

So far much has been assumed, possibly on good grounds. Now let us lay aside assumption for a time and use facts.

Wibaut (loc. cit.) has produced, by anaphylactic means a nodular choroiditis, with lymphocytes and giant cells resembling the deposits in sympathetic ophthalmia. The method used was to inject freshly sterile horse serum into the vitreous of rabbits, and this produced no especial reaction. After a time interval of some fourteen days he injected intravenously a second dose of horse serum. This second injection was always followed immediately by a severe iridocyclitis.

Enucleation of the eye, after from twenty-four hours to three days, showed the appearance just mentioned, epithelioid lymphocytes and giant cells.

Following are some clinical facts in the histories of five cases, two of which met the classic diagnostic requirements for sympathetic ophthalmia.

CASES.

CASE 1:—H. R., planerman in box factory, age 37, first seen March 16th, 1912. Complained of blurring of his right eye, worse by artificial light, past ten days.

History:—Penetrating injury of left eyeball with gradual change in left eye since. Often red of late. Right eye began to blur about ten days or two weeks ago, constant now, no attacks of transient blurring or asthenopia before. Is recovering from a "cold" in the head with "crick" in the back of the neck (i. e. muscular rheumatism), no intolerance of light, no pain about the eye, no headache.

Present condition:—Vision 8/10 and J 1 at 15 cm. *right eye*, pericorneal injection, violet color, perforating vessels tortuous, dilated, dark colored, slight swelling of both upper and lower eyelids due, he says, to the "cold." Anterior chamber hazy, keratitis punctata. Posterior synechia. Pupil horseshoe shaped after atropin. Pigment cells on anterior capsule. Anterior portion of vitreous full of small opacities, no fundus details, reflex only, eyeball tender to pressure.

Left eye:—Phthisis bulbi, injection of bulbus, left eyeball tender also.

Diagnosis:—Plastic iridocyclitis, probably sympathetic. He was given local 1% atropin sol., one drop every four hours with hot fomentations.

March 18th, second day, he returned with irregular dilated pupil, showing dust like opacities over entire pupillary area, vision=8/13, enucleation of left eye advised. March 29th he returned with a note from Dr. Stillson to whom I had referred him on the 16th, confirming the diagnosis of sympathetic ophthalmia and advising enucleation which was accepted and performed at Minor Hospital March 30th, 1912. The enucleated eyeball showed a plastic inflammation. Tenonitis of recent date. Was not examined histologically.

April 26th, vision = 8/10 with cycloplegic skiascopy +1.50 and +1.25 not improved. April 28th, vision=6/6, June 1, 1912, vision = 8/6, patient very happy. Returns to work. Pigment dots on capsule still visible. Dec. 16th, 1913, conjunctivitis, vision = 8/8-1, argyrol. February 27th, 1915, thinks he is luetic. Wassermann negative. Sept. 16th, 1915, has been under antiluetic treatment since Feb. 27th. Sight is good, vision = 6/5, some vitreous haze but papilla fairly

clear. Excavation of papilla —5.00 D.

April 4th, 1917, vision impaired past week, V = fingers at two meters, atropin and dionin, X-ray of alveoli shows abscesses and pyorrhea, three or four teeth extracted. His dentist confirmed X-ray findings, saying that granulomas were present in one or two pus sacs. June 4th, under vigorous treatment vision cleared, can see spots of fundus thru vitreous haze, vision = 6/20. December, 1918, another attack of pericorneal injection, vision = fingers about two meters, X-ray shows apical abscess, tooth extracted, eye cleared up, vision = 6/13, remains comfortable and looks so at present, April, 1919. July, 1919, fundus easily seen, vision = 6/5.

CASE 2:— D. V. McE. Right eye injured by flying piece of steel which penetrated the eyeball, passing thru the cornea and lens, and was extracted by Dr. Würdemann thru the original wound of entrance. Following this a severe uveitis supervened, great pain but no plus tension. On account of atropin conjunctivitis Dr. Würdemann changed to scopolamin, the pain becoming violent, according to Dr. Würdemann, because of the inert scopolamin.

The patient asked for consultation and was turned over to me by Dr. Würdemann. I suggested radiography of his teeth which was accepted. Two apical abscesses were found together, with much pyorrhea and alveolar abscesses. The teeth were extracted, whereupon the violence of the pain began at once to subside and the eye gradually cleared up.

Examination of the right eye showed a 4 mm. scar in the pupillary area of right cornea, adherent band of lens capsule extending back to the pupillary border of the iris. The anterior chamber was hazy, the iris markings obscured, pupil slightly dilated; there was some punctate keratitis, injection of the entire conjunctiva, all three sets of vessels. Tension —1, eyeball very tender and much laceration and pain in, above and behind eyeball.

Left eye:—Pupil contracted, some violent pericorneal injection, eye intolerant of light, not especially tender, no sat-

isfactory examination of the fundus could be made in either eye at this time, attempts at accommodation were painful and avoided by the patient, but when attempted caused left eye to become red and suffused with tears. No keratitis punctata or hazy anterior chamber in the left eye, tension normal to palpation. Eyeball not tender to touch. Diagnosis right eye, traumatic plastic uveitis. Left eye sympathetic irritation. This diagnosis was concurred in by Dr. Würdemann. Shortly afterward the patient was examined by a representative of an insurance company, who strongly advised enucleation of the exciting eye. This I declined to accede to until the results of treatment of the apical abscesses could be observed, these results being favorable. Local treatment was instituted by atropin, dionin and hot fomentations with alkalies internally. Fischer's solution by Murphy drip enema, also $ZnSO_4$ on account of Morax diplobacillary infection which was present, followed after a short interval with subconjunctival injections of .5% dionin solution. The eye cleared up, the left gradually ceased to water and the man returned to work.

Feb. 10th, 1919, vision right eye 6/20 with +10.00. Vision left eye 6/4 with +1.00 $\ominus$ —0.37 cy. ax. 45. September 1, 1919, V. = 6/4 with correction. Eyes clear and comfortable.

This case is reported because I believe it shows the sort of case which will develop sympathetic uveitis if the local infection is not removed. I believe with the insurance examiner that this patient's left eye would have developed sympathetic ophthalmia in the ordinary course of events. Of course I cannot prove it.

CASE 3:—Reported only to show presence of a severe type of focal infection running concurrently with sympathetic ophthalmia. L. D. H., age 35, penetrating injury of right eye, January, 1916, followed by severe uveitis. After three weeks the eye was enucleated to save the left eye which was already the seat of a rather severe inflammation. This inflammation did not subside entirely after enucleation of the exciting eye, but continued a low grade uveitis. In order possibly to put a stop to this an iridectomy

was done in November, 1917, by Dr. Mattice, after which the eye was very sore and much inflamed for two months.

During the absence of Dr. Mattice in France I saw this patient, who at that time, July 29th, 1918, had plastic uveitis, the coloboma was filled with a whitish inflammatory exudate, *occlusio pupillae* also, vision = light perception? Tension —3; His mouth was very septic with a virulent pyorrhea which he said had been getting gradually worse the past two or three years. I believe early attention to this man's mouth would have saved his eye with vision.

CASE 4:—March 31st, 1917, Mrs. R. H., age 50, ocular history negative until three years ago, when right eye began to be inflamed, diagnosed as tuberculosis of cornea by a general practitioner, and treated for two years by tuberculin injections O. T. The inflammation gradually disappeared leaving the eye useless; vision light perception. Careful search by a competent internist now fails to show any evidence of present active tuberculosis. The right eye became somewhat inflamed again but no pain in it or headache. This inflammation, she states, is now gone, but three weeks ago the left eye began to be red and the sight to fail; some intolerance of light but no pain or headache. Examination of right eye shows slight pericorneal violet haze. A massive leucoma covers the lower three-fourths of the cornea. Thru the fairly clear portion, above, the pupil can be seen to be secluded. It resists atropin dilation. Iris markings not clear, some tenderness of the globe. Tension —1.

Left eye, injection of bulbar conjunctiva, slight edema of eyelids. Posterior annular synechia, which resists atropin dilatation, anterior chamber hazy; keratitis punctata, tension —2.

April 2, Clover leaf pupil, anterior chamber slightly clearer. Examination of mouth shows much bridgework and gold crowns. X-ray advised, but not accepted until April 7th, when the accompanying radiographs were made. Because she had just paid a \$70.00 old dental bill she could not afford to have the teeth extracted she said, but after thinking it over she decided to do so. By June 5th,

under dionin and atropin her descemetitis was slowly clearing, all her upper and two lower teeth were extracted. Inunction of lanolin hydrarg. 50%, hot fomentations and a course of subconjunctival injections of 5% dionin, brought about a gradual recession of the inflammation with slight improvement in vision.

About this time she began to develop an increasingly bitter opposition to the war program of the United States which caused her to seek other medical advice than mine, so that I lost track of her. This case fulfills the classic diagnostic requirements for sympathetic ophthalmia without trauma yet I cannot bring myself unreservedly to such a diagnosis. I feel that it was simply a case of double iridocyclitis, first one eye and then the other, produced by her focal infections.

CASE 5:—Mrs. B. April 3, 1916. Practice of Dr. Geo. W. Swift. She began to develop cataract in both eyes in 1910. In Sept., 1915, her left eye was operated on by Dr. MacWhinnie, three months later an iridocyclitis developed which destroyed the left eye. Urine negative, pulse slightly irregular. She has an arthritis in several joints.

On May 8th, 1916, the cataract was extracted by Dr. Geo. W. Swift, Dr. MacWhinnie assisting. Combined extraction right lens, no accident. On the second day afterwards she developed a rapid heart which soon improved under digitalin treatment.

May 15th she was allowed to return home. Eye still red, some cortical substance left. Anterior chamber deep, coloboma correct.

June 2nd, vision with +10.00 $\odot$ +3.00 c. ax. 15° = 4/10, clear vitreous and cornea, no spots. August 1st, slight capsular opacity needed. Dec. 5th, 1916, vision 5/10, with +10.00 sph.

July 30th, 1917, eye became painful one week ago and now can hardly see, tho better than last week. Feels no irritation in the eye. She has a low grade uveitis with contracted pupil. The coloboma is hard to make out. A plastic exudate has drawn the pupil upwards.

March, 1919, very small pupil. Sees to get about only with difficulty. X-ray of teeth shows pyorrhea alveolaris and several apical abscesses. These teeth

were extracted and appropriate treatment given to her pyorrhea.

May 16th. Eye white, comfortable, sight improving, health much better. When the uveitis has subsided it is hoped an iridectomy will improve her vision.

Diagnosis: Endogenous uveitis from focal infection. Case reported to show association of a focal infection with plastic uveitis showing immediate improvement on removal of the focal infection. I see no need to call this a case of sympathetic ophthalmia. Only a histologic examination of the eye could say whether or not nodular choroiditis with epithelioid and giant cells was present. "Plastic uveitis is no part of the sympathetic process per se. (Fuchs.)

Presence of giant cells and epithelioid lymphocytes in characteristic arrangement and distribution may be found in sympathetic ophthalmia at a certain stage, but undoubtedly cases of the disease occur in which these cannot be found. (Parsons.)

A case, in which the classic diagnostic points were all present, except the *histologic* findings, recovered following the discovery and removal of a focal infection after failure to cure by removal of the exciting eye. If it be objected that this case was cured by removal of the exciting eye and that iridocyclitis later was an entirely new affection, I answer, "How then is one to know save by post-mortem histologic examination of the sympathizing eye whether one is dealing with sympathetic ophthalmia at all?"

The discovery and removal of a focal infection and the cure of an endogenous iridocyclitis thereby is so common an event that we must admit focal infection to be a possible etiologic factor of the highest importance. Wibaut's production of a characteristically grouped infiltrate of epithelioid and giant cells, by anaphylactic means, appears to the writer to solve the problem of the exciting eye.

The problem of the sympathizing eye is not far from solved when we grant the possibility of predilection. A split protein having predilection for uveal tissue, or a streptococcus having a predilection for uveal tissue can find its receptors, to use Ehrlich's term, nowhere else

but in the sympathizing eye. Parsons' remark that, "It should not excite surprise to find pyogenic germs in the eye" and that "We should not mistake the granules of mast cells for bacteria" gives indirect evidence that bacteria are frequently present in the uveal tract. (See Fuchs on this point.) If this is indeed true we have only to find similar bacteria in the eye, and a focal infection at the same time, to uncover a condition ripe for an anaphylactic inflammation of the second eye.

That a focal infection, of a streptococcus viridans for example, is often present as the exciting cause of an iridocyclitis I believe fully. It should excite no surprise if a patient having a focal infection of this germ, or any other, receive a trauma to an eye, or a perforating trauma, deliberate or accidental.

Sympathetic irritation can scarcely be held either to decrease the liability to iridocyclitis in the presence of a focal infection or to increase the defenses of the second eye.

The inference by many authors that because panophthalmitis or suppurative choroiditis does not supervene we should rule out the pyogenic bacteria, is an illogical inference. Likewise the statement that because a long incubation period exists we must infer the action of a germ similar to the tubercle bacillus or spirochete, leaves the anaphylactic reaction altogether out of consideration.

All toxic protein products are not ptomaines. A comparatively innocuous protein may become toxic by a parenteral digestive splitting; as Vaughan has shown, and as Wibaut also has demonstrated by producing anaphylactic inflammation by horse serum.

The exciting eye in other words may itself assume the role of a focal infection and become in fact a focus of infection where the bacteria having predilection for uveal tissue are incubated. Moreover transmutation may occur there.

To my mind an endogenous septic endophthalmitis may occur in any eye at any time, trauma or no trauma, whenever there is present in the body a focus of infection from which toxins or bacteria can escape into the circulation. In a case of sympathetic oph-

themia it is not a question of removing the exciting eye only. We should remove not only one-half or three-fourths or seven-eighths of the poison or source of poisoning, but all of it. Having a case of uveitis we should search all the possible locations for focal infections and not be content with the removal of the focus which is located in the exciting eye.

CONCLUSIONS.

Sympathetic ophthalmia is an anaphylactic inflammation of the sympathizing eye.

Elschnig is right in so considering it, altho I cannot believe that such anaphylaxis is *always* caused by proteins originating in the digestive tract.

A focal infection caused by an invader similar to that implanted in the exciting eye furnishes the larger dosage required to determine anaphylaxis. (The sensitizing dose being always less than the determining dose.)

Besides the size of the dosage other factors enter into the process, such as predilection, virulence, and affinity of the bacteria.

In every endogenous uveitis the proteins of the septic emboli have already been subjected to, and perhaps modified by, the nonspecific defenses of the blood, as well as the specific defenses of the focal area, from which they may have escaped. This suggests a possible reason why the processes of local immunization are ordinarily operative, and that immunity not sensitization is the usual outcome in loco.

With the implantation, however, of bacteria from without which have not been so subjected or modified, having certain affinities, the establishment of a local defense creates predilection for this same tissue and the second eye is thus sensitized rather than immunized.

The focal infection now supplies the increased dosage required to bring about an anaphylactic reaction and after the time necessary to sensitize has elapsed the reaction occurs.

This hypothesis gives us a working guide as to what we may do for the patient, namely, give him the most minute search for focal infections.

VISUAL DEFECTS OF THE WEST POINT CADETS.

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This is a study based on statistics of the past six classes of the Military Academy, presented in tabular form.

The West Pointer is trained to be as nearly physically perfect as possible. He is carefully selected, physically, before he is admitted; and almost the only defect he is allowed to have on entrance is one of vision. The visual requirements are as follows:

For the Hyperopic: Vision must be 20/30 correctible to 20/20.

For the Myopic: Vision must be 20/40 correctible to 20/20.

For the Astigmatic: Vision must be 20/30 correctible to 20/20.

In all cases there must be no disease of the fundus.

This, from the start, means that more myopes are admitted than hyperopes

(statistics show six to one). Myopia develops or becomes known during the course of the cadet more often than hyperopia (curiously enough the statistics show 6 to 1 here also). Hence the refraction problem is one dealing with myopia almost entirely, and probably, for this reason, the graduation requirements are 20/100 in each eye correctible to 20/20.

As the classes have increased in number it is interesting to note that the percentage of defects in vision, both at admission 10% and graduation 20%, have remained practically fixed. This shows that about the same relative number develop trouble in the cadet corps as were admitted with it.