

OCULAR REACTION TO LENS PROTEIN*† A PRELIMINARY STUDY

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EXAMINATION of the literature on the subject of intra-ocular inflammation, with or without tension, arising as a result of the liberation of lens matter into the anterior segment, reveals the need for a careful review of the subject. Often tacit assumptions are made which appear to demand justification; conclusions are drawn from histological studies which have not been subjected to the critical analysis they deserve and demand; and a body of suspect theory has grown around the subject, whose very existence is queried in some quarters. It is for this reason that the matter has been taken up; a further stimulus was the striking fact that no writing on the subject emanating from Great Britain could be found, which appeared to indicate a justification for drawing attention to it.

Case Reports

Two of these patients were recently in the writer's care, and four were supplied in a personal communication from R. C. Davenport.

(1) **Married female, aged 70.** A left extracapsular cataract extraction, with peripheral iridectomy and anterior chamber washout, was performed in February, 1951. Recovery was quite uneventful and the patient left hospital after 10 days. Three weeks after operation her corrected vision was 6/6: no subsequent trouble was experienced.

In May, 1952, a similar operation was done on the right eye; some soft lens matter remained. Nine days later the eye was still very injected, with a "reactionary iritis"; the eye settled very slowly, and cortisone drops were used continuously. There was gross post-corneal deposit, and 7 weeks after operation a hypopyon appeared, and she was readmitted. Keratic precipitates were observed in the left eye. The eye whitened slowly under treatment, but 3 weeks later she showed a completely occluded pupil, iris bombé, and raised tension (44 mm. Hg Schiötz). An iris puncture was done and the eye settled slowly with normal tension. The right eye was still injected 3 months after the cataract operation and keratic precipitates were present in both eyes; the left showed a fine vitreous haze. Five months after the right cataract operation there were still keratic precipitates in each eye, more in the right eye than the left; vision was 6/6 in the left eye, and hand movements in the right with good projection.

(2) **Married female, aged 69.** A left extracapsular cataract extraction was performed in September, 1950. The patient was a diabetic subject, not taking insulin. She complained of some discomfort in the eye in May, 1951; the eye was slightly injected, one pillar was up to the wound, tension was normal; corrected vision was 6/24, probably attributable to retinal changes.

A right extracapsular extraction with peripheral iridectomy was done on July 31, 1952,

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and on August 22 she showed bilateral injection, and heavy keratic precipitates in each eye with aqueous flare and cells ; the tension was full in the left eye. Corrected vision was 5/60 in the right eye and counting fingers in the left. She was admitted and treated with atropine, cortisone, and heat ; on discharge 12 days later there was slight residual injection of both eyes, post-corneal deposits, and a few cells in the aqueous. Corrected vision was 6/18 in the right eye and 6/36 in the left. Both eyes were white and quiet by September 23.

(3) Male, aged 68. A left extracapsular cataract extraction was performed on July 26, 1951, followed by an abscission of iris prolapse 3 days later. The patient was discharged on August 14 with a whitening eye, and in September his corrected vision was 6/18. A right extracapsular extraction followed in July, 1952, and he left hospital after 12 days. The tension was full (31 mm. Hg Schiötz) 6 weeks after the operation, with no flare. Two months after operation the right eye showed a heavy cellular deposit on the posterior corneal surface, with tension still full. The eye was settling slowly when last seen.

(4) Married female, aged 52, a high myope. She had a left extracapsular cataract extraction on August 29, 1946. Some iritis followed in October which necessitated re-admission for 2 weeks; atropine irritation was noted. The eye was white in December, and vision was subsequently 6/9.

A right extracapsular extraction followed on September 26, 1950, and the patient left hospital with an injected eye after 2 weeks. Heavy keratic precipitates were noted in December, 1950, the left eye being white. The tension then rose in the right eye, and she was admitted and a paracentesis was done on January 9, 1951. The eye was white in March, 1951. In November, 1952, she was awaiting right capsulotomy.

(5) Male, aged 69. A right extracapsular cataract extraction was performed on January 5, 1950, and the patient left hospital in 9 days with corrected vision 6/36. In March vision was 6/6₍₃₎ in the right eye, and a capsulotomy was performed. On January 4, 1951, a left extracapsular cataract extraction was done. This was followed shortly after discharge in 9 days by a violent reaction which necessitated readmission for 2 weeks on January 20. Hyphaema and cells were present on the anterior chamber. On February 17 pus and keratic precipitates were present, and he was once again admitted. He was discharged with iris bombé and keratic precipitates, cells, and flare. He was later readmitted and an iridectomy was performed on July 12. His vision is now hand movements with good projection, and a Wheeler's iridotomy will probably be done later. The right eye has remained white with 6/5 corrected vision.

(6) Married female, aged 52, a high myope. A right intracapsular cataract extraction was performed on June 5, 1951; the capsule ruptured late and a small piece remained on the iris at 10 o'clock. On discharge 9 days after operation, vision was 6/18. The eye quietened rather slowly, and a few fine post-corneal deposits, with flare, persisted. In September the eye became painful, with full tension, corneal oedema, and many keratic precipitates; the left eye was a little injected with a few keratic precipitates. In January 1952, following cortisone treatment, she complained of much right-sided pain; the right eye was injected, with keratic precipitates, flare, and vitreous haze; the left eye was white. She was admitted to hospital for 6 weeks, when subconjunctival cortisone injections were continued. Atropine irritation was noted. A further period of in-patient treatment was given in July and August ; on discharge the right eye was quiet (vision 6/36), while in the left eye vision was perception of light with inaccurate projection. The left eye was injected, and showed a small hypopyon, many keratic precipitates, and a marked flare, tension being low. It is still irritable, and excision is to be carried out.

What is the condition with which one is dealing in the above cases ? Is it one condition, or many, or variations of one condition ? What features

distinguish it from sympathetic ophthalmia? What is the proper line of treatment and what can be done to prevent it?

These are questions which demand answers, and in the answer to the third lies a means of avoiding an experience which, though it comes seldom, none the less is so worrying that it is not easily forgotten.

The approaches to the problem differ considerably. As has been said, some deny the occurrence of an iritis or anterior uveitis as a manifestation of sensitivity to lens protein; others assume its existence without comment and discuss its treatment from this aspect; others again regard it as a mild form of sympathetic ophthalmia, or as a precursor of sympathetic ophthalmia. Yet again others regard a "reactionary" inflammation following cataract extraction as infective, or as due to the toxic action of lens proteins on the intra-ocular structures. It is proposed to discuss some relevant opinions and experiences; there would appear, incidentally, to be little doubt that into one of the categories to be thus discussed fall those cases of post-operative uveitis which in the past have been labelled as "mild" and "non-malignant" sympathetic ophthalmia, the lesion not being sufficiently intense or characteristic to justify enucleation and thus permit histological examination.

Courtney (1942) discusses "endophthalmitis . . . accompanying absorption of the crystalline lens". A marked feature of the cases he describes is raised tension; all presented inflammatory reaction in the second eye following cataract extraction in the first eye after an interval varying from 3 months to 9 years; in some of these a spontaneous rupture of the lens capsule in the second eye was supposed to have occurred, or alternatively it is suggested that autolysed lens matter might have passed through the intact lens capsule. In one case *Courtney* concluded that the reaction in the second eye was caused by a sensitivity to lens proteins induced by the intradermal test. He concludes that, if one is satisfied that the endophthalmitis is due to absorption of lens proteins in the second eye after extra-capsular extraction of cataract in the first, the proper treatment, however intense the inflammation, is removal of all lens matter possible from the inflamed eye.

De Veer (1940) discusses endophthalmitis phaco-anaphylactica in its relation to sympathetic ophthalmia. He describes the three explanations of endophthalmitis after lens injury which have been given:

- (i) It was first thought that the cause was infective, the lens matter providing a good bacterial medium. The possible importance of the synergistic action of bacterial antigens on lens protein antigen has been mentioned by several writers, and this aspect was stressed in the investigations of *Cooper*, *Lakhani*, and *Javer* (1948.)
- (ii) The next suggestion was that of an inherent toxicity in retained lens matter.
- (iii) Lastly *Verhoeff* and *Lemoine* (1922) produced the "anaphylactic theory".

De Veer himself describes the histological characteristics of three eyes:

(a) One was excised 4 weeks after a preliminary iridectomy, when it was still acutely inflamed by iridocyclitis, and signs of sympathetic ophthalmia had appeared in the second eye. There was a mass of granulation tissue around the lens, and the capsule had been ruptured; the picture throughout the globe was characteristic of sympathetic ophthalmia.

(b) In the second case preliminary iridectomy on the right eye was accompanied by injury to the lens capsule. Extraction 2 months later was uneventful. A year later iridectomy was done on the left eye, and 2 months afterwards the cataract was extracted. Low-grade inflammation in this left eye followed; the eye was soft when excised 4 months later, and 2 months later still the right eye was soft, with faulty projection. Again the histological picture was typical of sympathetic ophthalmia.

(c) The third case suffered an accidental knife injury, with damage to the lens, which was extracted 26 days afterwards. Both eyes were inflamed 3 months later, and the injured eye was excised. Inflammation in the sympathizing eye subsided gradually; sections of the excised eye showed typical sympathetic ophthalmia.

De Veer concludes that endophthalmitis phaco-anaphylactica is to be regarded as a precursor of sympathetic ophthalmia, and cites these cases in proof, postulating a pre-existing sensitivity to lens protein. Criticism of these conclusions would appear to turn upon an agreed definition of the terms employed, and especially upon the histology of the anaphylactic condition. While the possibility of an allergic basis to the sympathetic phenomenon is generally admitted, it is difficult to see the justification for assuming that the lens protein reaction is to be regarded as the "precursor"—*i.e.* the cause—of a typical sympathetic ophthalmia as exemplified in those three cases.

Cooper, Lakhani, and Javer (1948) sought to investigate this type of inflammation by experiment with lens protein, paying regard to the possible activation of the antigen by staphylococcal or other toxin. They concluded that cases with a positive skin test before operation showed a benign post-operative course if they had been previously desensitized, and that desensitizing injections after inflammation had begun might have an adverse effect unless the dosage was very small. In a group of 132 cases, ninety were proved insensitive and developed no reaction after extracapsular extraction, and twenty-one were proved sensitive and developed post-operative inflammation; however, ten were insensitive and developed inflammation, and eleven were sensitive but remained quiet. There are so many variable factors in such a group that conclusions must be drawn with considerable reserve, and provision of controls is difficult. The writers have no doubt, however, of the existence of the condition of allergic inflammation due to lens protein sensitivity, nor of the value of pre-operative desensitization. They insist that such desensitization must be done with small non-increasing doses, and assert that increasing doses may actually sensitize a patient.

Irvine and Irvine (1952), reviewing the subject, produce cases which fit in to the three categories of response noted above, which they accept without comment. Much histological material is described, but the conclusions drawn from it are not always readily acceptable.

Present Investigations

In the hope that some aspects of this problem might be elucidated by further histological study it was decided to investigate sections of eyes removed on account of inflammation following extracapsular cataract extraction in all cases where the history suggested that they might provide relevant material. It was also hoped that some idea might be gained of the incidence

of this condition. The arbitrary period chosen was that during which the present writer was pathologist to Moorfields Hospital, *i.e.*, from October, 1933, to December, 1936.

Histological Material

During this period 1,402 specimens were sectioned and examined. Of these 416 were not eyes but portions of tissue, and there were thus 986 eyes to be considered; the history and pathological aspects of all these were reviewed, and twenty were found that might provide important material relevant to the subject under discussion.

Thirteen were specimens of eyes removed for inflammatory trouble after cataract extraction from the first eye of a patient; these are referred to as "first eyes".

Seven were specimens removed for similar reasons after cataract extraction in the second eye of a patient, following a similar previous extraction in the first eye; these are referred to as "second eyes".

All twenty specimens were re-examined under the microscope, numbered for reference purposes, and grouped according to the findings.

First Eyes (Nos 1 to 6).—These were all rejected on the grounds that they did not appear for various reasons on histological examination to fall into the category under consideration.

No. 1 was removed 2 months after extraction, and showed much inflammatory reaction and total detachment of the retina.

No. 2 showed panophthalmitis with vascularized granulation tissue occupying most of the anterior segment, and a degenerate, haemorrhagic, sloughing retina.

No. 3 showed a typical secondary glaucoma with little inflammatory reaction, the iris being adherent to the cornea.

No. 4 suffered an abscission of a prolapsed iris the day after extraction; an acute iridocyclitis supervened, tension was low, and there was retinal perivascular cuffing and choroidal infiltration, with no inflammatory reaction around the lens remnants—a probable early sympathetic ophthalmia.

No. 5 showed similarly low tension, with a total detachment of the retina.

No. 6, one year after a successful extraction with resulting 6/9 vision, showed high tension of a haemorrhagic type.

First Eyes (Nos 7 to 13).—These all appeared to provide material which would prove valuable in the consideration of this group.

No. 7 was a scoop extraction with vitreous loss; the capsule was separated from the wound 11 days after extraction. The eye was painful and showed keratic precipitates 5 months after operation: sections showed intense inflammatory reaction around the lens remnants.

No. 8. A large piece of nucleus was left lying on the ciliary body; inflammation with keratic precipitates followed and the eye was excised. A condition of endophthalmitis was present, the lens remnants being surrounded by inflammatory tissue.

No. 9 was excised a year after extraction; iritis and secondary glaucoma were present, the lens remnants being similarly surrounded and infiltrated by inflammatory cells.

No. 10. A similar interval passed between extraction and enucleation; post-inflammatory atrophy of the uvea was marked, and eosinophiles were present in the atrophic tissues.

No. 11. The reaction was mild only, though some inflammatory cells were present amongst the lens remnants.

Nos 12 and 13. Reaction was intense; excision was done 4 and 3 months respectively after extraction, and the lens remnants were copiously invaded by inflammatory cells.

Second Eyes (Nos 14 to 18).—These five specimens were rejected as irrelevant because of many complicating factors.

No. 14 was from a diabetic patient, whose second eye became painful, with cataract and secondary glaucoma, 9 years after cataract extraction from the first. Paracentesis failed to relieve the tension, and the iris prolapsed through the operation wound.

No. 15 showed a right detachment and left macular degeneration as well as lamellar cataracts. Left preliminary iridectomy was followed by extraction in 1929, and right extraction was done in 1930; pain led to right enucleation in 1935.

No. 16. Left extraction was followed a year later by pain in the right eye with keratic precipitates and raised tension; the interval was considered to be too long to allow inclusion in the series, though admittedly the histological picture differed little from that seen in many included cases.

No. 17. The history was too defective to permit inclusion.

No. 18 had had left extraction in April, 1925, followed by capsulotomy in August. In January 1926, the right eye was injected, with hypopyon, cataract, and high tension; there was no perception of light. On section, the anterior segment showed only mild inflammation; there were exudate and cells in the anterior chamber but no keratic precipitates. Retina and choroid showed no involvement; the cataract was Morgagnian, with an intact capsule, and was of course not invaded by cells.

In the light of later experience it may prove to be that it would have been more correct to include this last case.

Second Eyes (Nos 19 and 20).—These two specimens give histological evidence of the correctness of their inclusion in this group.

No. 19. A right cataract extraction was followed by iridocyclitis and the eye was "excised too late". The trouble in the left eye was diagnosed as sympathetic ophthalmia; the section showed a picture not suggestive of sympathetic, but the interesting feature was that the lens capsule was incomplete, and inflammatory cells had invaded the lens; an intense plastic iridocyclitis was present. This may well be a most important case in view of Courtney's theories.

No. 20. A right cataract extraction was followed 2 years later by a glaucoma iridectomy in the left; 2 years later the left eye was blind, with keratic precipitates and low tension, while vision in the right eye was 6/9. The section showed an iridocyclitis, with ruptured lens capsule and intense inflammatory invasion of the lens.

Discussion

No one is more conscious than the writer of the difficulty of drawing correct conclusions from the evidence contained in the foregoing—historical, clinical, and histological—nor indeed of the fatal ease with which unjustified or even frankly incorrect conclusions could be drawn.

The study of this condition would be simplified if it were restricted to the occurrence of inflammation in a second eye subjected to extracapsular extraction following a similar operation in the first. But such an approach would entail an unjustifiable over-simplification. One is compelled to consider the possibility that a given patient may be inherently sensitive to lens proteins, a state of affairs which leads to reactionary inflammation after release of the proteins in a first eye. Again, spontaneous rupture of the lens capsule is postulated, and it must be admitted that this theory receives some histological support in the series examined. Further, reference to the literature leads one to consider the possibility of the passage of autolysed lens matter through the intact capsule; this suggestion opens the door wider still.

While doubts of the occurrence of a phaco-anaphylactic response are still expressed in some quarters, it is clear that the majority of writers on this and allied subjects are convinced of its occurrence.

The clinical evidence submitted seems to go a long way towards supporting this view. At least one may say that the cases quoted may be satisfactorily and completely explained on the hypothesis suggested—that they "fit in" with the theory, and that no more attractive theory presents itself.

One might consider that the weightiest evidence might be derived from histological studies, but it is just here that the greatest difficulties of interpretation arise. It is by no means certain that the presence of inflammatory invasion of the lens remnants in an eye subjected to extracapsular extraction indicates that the inflammatory reaction which led to excision was caused by any abnormal sensitivity to lens proteins on the part of the patient. Eyes are undoubtedly lost through simple "post-operative inflammation"—most likely an exogenous invasion. Again, in every instance recorded here, the reaction found in a "first eye" following extracapsular extraction presupposes a natural or inherent sensitivity to such proteins; is this truly an in-dwelling sensitivity, or was it induced by previous transudation of the products of lens autolysis through an intact capsule—a process which set the stage for a violent reaction when the lens matter was liberated by operation?

Any error in sifting the histological evidence examined here has been in rejecting sections which might possibly have lent support to the hypothesis of lens sensitivity. There is no doubt that eyes which have been excised on the clinical suspicion of sympathetic ophthalmia have in many instances proved histologically innocent, and the very attractive alternative of phaco-anaphylaxis is difficult to reject.

It is clear that further research in this subject is urgently demanded. From the present study it is difficult to escape the conclusion that phaco-anaphylaxis is a real occurrence; what is needed is more knowledge of the clinical differentiation between this and a mild or early sympathetic ophthalmia, for upon this depends the fate of the inflamed eye. The problem is infinitely more difficult if, as de Veer suggests, a sensitivity to lens protein is to be regarded as a precursor and primary cause of sympathetic ophthalmia. It is intended to follow this preliminary study by further investigation especially on the histological side. It is essential to discover what support there is for the separation of the phenomena of the ocular response to lens proteins into three categories: phaco-anaphylactic, toxic, and phacogenetic (it must be admitted that this last title stands condemned at the outset on etymological grounds). If one is satisfied of the existence of an allergic response, a decision must be made on the question whether patients are to be subdivided into four types:

- (i) those inherently sensitive to liberated lens protein;
- (ii) those not so sensitive;
- (iii) those in whom liberation of lens protein in one eye brings about a sensitization which causes a violent reaction to the subsequent liberation of lens protein in the second eye;
- (iv) those in whom it does not.

Spontaneous rupture of the lens capsule, "microscopic dehiscences" of the capsule (Irvine and Irvine 1952), and transudation of autolysed lens matter through an intact capsule, are all conceptions complicating the issue and increasing the difficulty of classification. An attempt will be made to correlate clinical findings with histological appearances, and in particular

to investigate the general significance of the invasion of lens matter by inflammatory cells and the special significance of the specific nature of these cells.

The most productive line of clinical research would seem to be an extension of the work of Cooper and others (1948), by attempting to discover whether a patient is sensitive to lens protein injection, with a careful subsequent study of the effect of extracapsular extraction. The result of such an investigation should show whether a pre-operative sensitivity test is justifiable or valuable, and whether, if the results are positive, pre-operative desensitization should be undertaken.

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