# FURTHER OBSERVATIONS ON THE DIAGNOSIS, ETIOLOGY, AND TREATMENT OF ENDOPHTHALMITIS*

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INFECTIOUS ENDOPHTHALMITIS IS A CATASTROPHIC COMPLICATION OF INTRAOCULAR surgery and penetrating injuries of the eye. Determination of etiology and treatment success has been confused in the literature because of failure to obtain cultures from the intraocular contents. Rational therapy necessitates determining if the inflammation is infectious or sterile.[1-3]

The purpose of this report is to consider and emphasize the following:

1. A technique for obtaining cultures, utilization of specific media, and the importance of diagnostic vitreous aspiration.
2. The relative frequency of etiologic agents in specific types of infectious endophthalmitis.
3. The rationale and results of intraocular antibiotics augmenting conventional therapeutic routes.

## MATERIALS AND METHODS

One of the authors (RKF) has seen in consultation, for the purpose of diagnosis and treatment, 54 cases of suspected endophthalmitis in the period between July 1969 through March 1975.

### DIAGNOSTIC TECHNIQUE

Patients suspected of harboring endophthalmitis, whether recent post-

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operative, long-term postoperative, traumatic, or metastatic, were taken to the operating room, and after appropriate sedation and retrobulbar anesthesia the anterior chamber and vitreous were aspirated for culture. This was accomplished by the following technique: A limbal-corneal keratotomy was made with a razor blade, attempting to incise the cornea deeply, but not to enter the anterior chamber.[4] A 25-gauge needle attached to a 1 cc tuberculin syringe was used to enter the anterior chamber through this incision. The yield of 0.1 - 0.2 ml of fluid was then immediately inoculated onto media as described below and placed on slides for staining. In the aphakic patients a second tuberculin syringe fitted to a 22-gauge needle was passed through the keratotomy wound into the vitreous and manipulated until 0.2 - 0.3 ml of aspirate was obtained. In phakic patients suspected of endophthalmitis complicating filtering blebs, trauma, or metastatic infection, vitreous was aspirated through a sclerotomy in the pars plana with or without an anterior chamber paracentesis.

The specimens aspirated from the anterior chamber and vitreous were then transferred in aliquots to blood agar, thioglycolate liquid, and brain-heart infusion (BHI) to be maintained at 37° C, and to blood agar, Sabouraud agar, and brain-heart infusion (BHI) with gentamicin (50 mcgm/ml) to be maintained at 25° C for fungal isolation. Care was exercised to place the drops of aspirate away from the edge of the plates, and the mouths of the tubes containing liquid media were flamed before and after inoculation. Slides for Gram, Giemsa, and recently GMS (modified Gomori methenamine silver) staining were also prepared from each aspirate.

### INTERPRETATION OF CULTURES

The criteria for a positive culture consisted of growth of the same organism on two or more media, or semiconfluent growth on one or more solid media at the inoculation site. An equivocal culture was defined as growth in one liquid medium or scant growth on one solid medium only.

### INTRAOCULAR AND CONVENTIONAL ANTIBIOTIC THERAPY

In the operating room, after aspiration of anterior chamber and/or vitreous material and appropriate inoculation onto media and slides, antibiotics were slowly injected through the previously prepared site into the approximate center of the vitreous cavity and/or anterior chamber. The dosage of antibiotics in all treated cases included gentamicin 0.1 mgm (100 mcgm) in 0.1 or 0.25 ml into the vitreous and cephaloridine 0.25 mgm (250 mcgm) in 0.1 ml into the anterior chamber or vitreous.

TABLE I: CULTURE SITE RESULTS FROM 27 POSITIVE ISOLATES

| Culture Site | No. Samples | Culture Positive |
|---|---|---|
| Anterior chamber | 18 | 10 |
| Vitreous | 20 | 20 |
| Wound | 4 | 4 |

*7 cases — vitreous-positive, AC-negative; 0 cases — AC-positive, vitreous-negative.

TABLE II: ISOLATES FROM 27 CULTURE POSITIVE EYES

| | | Gram Positive | Gram Negative | Fungi |
|---|---|---|---|---|
| Recent postoperative* | (13) | 6 | 6 | 1 |
| Long-term postoperative† | (5) | 3 | 1 | 1 |
| Trauma | (6) | 5 | – | 1 |
| Metastatic | (3) | 1 | – | 2 |
| Total | (27) | 15 | 7 | 5 |

*Within 2 weeks of surgery, with 2 exceptions.
†Inadvertent or filtering blebs.

In selected cases amphotericin-B 0.005 mgm (5 mcgm) was injected into the vitreous.

This regimen was augmented at surgery and for several days by subconjunctival or periocular injections of gentamicin 20 mgm, and Kenalog (triamcinolone) 40 mgm. The patient then usually received cephaloridine 500 mgm every 6 hours I.V. or I.M. after a base line creatinine level was obtained. In addition, appropriate topical antibiotics and steroids were used.

## RESULTS

From the 54 cases of endophthalmitis, microorganisms were isolated in 27 cases, cultures were considered equivocal in 5 cases, and in 22 cases the cultures were negative.

### CULTURE SITE

Eighteen of the 27 eyes yielding positive cultures had an anterior chamber paracentesis and 10 of these were culture positive. Twenty of the 27 eyes had a vitreous aspiration and all 20 were culture positive (Table I). In addition, cultures from four dehiscent wounds or ruptured blebs were

TABLE III: 27 ENDOPHTHALMITIS ISOLATES

| | | | |
|---|---|---|---|
| Staphylococcus aureus | 4 | Proteus species | 3 |
| Staphylococcus epidermidis | 7 | Pseudomonas | 2 |
| Streptococci | 3 | Klebsiella | 1 |
| Propionibacterium acnes | 1 | Hemophilus influenza | 1 |

Fungi – Candida – 2
– Fusarium – 3

TABLE IV: TREATMENT WITH INTRAOCULAR ANTIBIOTICS

| Culture | No. Cases | Useful Vision | Vision Lost |
|---|---|---|---|
| Positive | 15 | 6 | 9 |
| Equivocal | 2 | 1 | 1 |
| Negative | 9 | 7 | 2 |
| Total | 26 | 14 | 12 |

all positive. In 7 cases the vitreous sample was culture positive while the anterior chamber had no growth. In 5 of these 7 cases the eyes were aphakic. In no case was the aqueous tap positive and the vitreous aspirate negative.

EITOLOGIC AGENTS

Of 27 eyes with positive cultures, Gram positive bacteria were identified in 15, Gram negative bacteria in 7, and fungi in 5 (Table II). Of 13 eyes having recent surgery, 6 yielded Gram positive bacteria, 6 Gram negative bacteria, and 1 a fungus. On the other hand, of 6 traumatic cases, 5 showed Gram positive bacteria, none Gram negative bacteria, and 1 a fungus. Table III lists the specific isolates.

INTRAOCULAR ANTIBIOTIC THERAPY

Visual acuity of 20/400 or better resulted in 7 of the 27 culture positive eyes, 2 of 5 culture equivocal eyes, and in 18 of 22 eyes with negative cultures for a total of 27 of 54 cases of suspected endophthalmitis.

Intraocular antibiotics, in the dosage stipulated, included both gentamicin and cephaloridine in 26 eyes (Table IV), of which 15 yielded positive cultures, 2 were "culture equivocal", and 9 culture negative. Useful vision of 20/400 or better was achieved in 6 of 15 culture positive cases, 1 of 2 equivocal cases, and 7 of 9 culture negative cases, for a total of 14 of 26 cases.

TABLE V: INTRAOCULAR ANTIBIOTICS-TREATMENT FAILURES

| Type | Culture | Organism | Final Vision |
|---|---|---|---|
| Postoperative | + | Proteus rettgeri | LP |
| Postoperative | + | Ps. aeruginosa | NLP |
| Postoperative | + | Proteus mirabilis | HM |
| Postoperative | + | Proteus mirabilis | NLP |
| Bleb | + | Hemophilus influenza | LP |
| Bleb | + | Staphylococcus aureus | NLP |
| Trauma | + | Alpha-streptococcus | LP |
| Trauma | + | Fusarium solani | LP |
| Trauma | + | Staphylococcus epidermidis | NLP |
| Trauma | ± | Bacillus sp. | LP |
| Trauma | − | — | NLP |
| Trauma | − | — | HM |

TABLE VI: INTRAOCULAR ANTIBIOTICS—TREATMENT SUCCESS

| Type | Culture | Organism | Final Vision |
|---|---|---|---|
| Postoperative | + | Staphylococcus epidermidis | 20/200 |
| Postoperative | + | Staphylococcus epidermidis | 20/60 |
| Postoperative | + | Staphylococcus epidermidis | 20/30 |
| Postoperative | + | Staphylococcus epidermidis | 20/30 |
| Postoperative | + | Propionibacterium acnes | 20/60 |
| Trauma | + | Staphylococcus epidermidis | LP* |
| Postoperative | ± | Streptococcus | 20/40 |
| Postoperative | − | — | 20/40 |
| Postoperative | − | — | 20/70 |
| Postoperative | − | — | LP† |
| Postoperative | − | — | 20/400 |
| Postoperative | − | — | 20/100 |
| Trauma | − | — | 20/60 |
| Metastatic | − | — | 20/200 |

*Mature cataract, good potential function by light projection and ERG.
†Vitreous opacity, normal ultrasound and ERG.

TABLE VII: ELECTRORETINOGRAM RESULTS—SUCCESSFUL INTRAOCULAR ANTIBIOTIC TREATMENT

| Culture | | Normal or Slightly Abnormal | Moderately Abnormal | Markedly Abnormal |
|---|---|---|---|---|
| Positive | (5) | 1 | 3* | 1 |
| Equivocal | (1) | – | 1 | – |
| Negative | (6) | 2 | 4* | – |
| Total | (12) | 3 | 8 | 1 |
| Decreased B-wave | | (1) | (6) | (1) |

*Reduction also in untreated, "normal" fellow eye (2 eyes).

From Table V it can be seen that the 12 eyes which failed to respond to intraocular antibiotics contained 8 virulent organisms and an equivocal *Bacillus sp.* Only 2 had negative cultures. However, trauma (6 of 12 cases) was judged to play a significant role in final visual function.

On the other hand, of the 14 eyes which retained some vision (Table VI), 5 yielded *Staphylococcus epidermidis,* and one *Propionibacterium acnes.* In two eyes, the visual deficit can be attributed to either a cataract or clearing vitreous reaction. These eyes are presumed to have the potential to regain useful sight.

Twelve of 14 treatment successes receiving intraocular antibiotics underwent subsequent electroretinography 1 to 4 months after treatment (Table VII). Normal or only slightly abnormal tracings were present in three eyes, and moderately abnormal in eight. A markedly abnormal electroretinogram was seen in one eye in which 20/60 vision was achieved after a subtotal vitrectomy with instillation of both gentamicin 0.1 mg and amphotericin-B 0.005 mgm. Although fungal endophthalmitis was suspected, *Propionibacterium acnes* was isolated. Of the 12 electroretinograms, 7 manifested primarily a decrease in the B-wave with a relatively normal A-wave.

## DISCUSSION

Although paracentesis of the anterior chamber is a rational and often rewarding diagnostic approach in suspected infectious endophthalmitis, in this series aspiration of the vitreous proved more specific. Cultures were positive in each instance of 20 positive cultures that included vitreous aspiration. In no case was the aqueous positive when the vitreous yielded no growth. Therefore, in aphakic eyes or phakic eyes with clouding of the vitreous an aspiration of the vitreous must be performed if the greatest return of positive cultures is the goal. In eyes that have had recent surgery, the keratotomy should be enlarged slightly before inserting a 22-gauge needle into the vitrous to prevent wound dehiscence.

Approximately one-half of recent postoperative endophthalmitis was caused by Gram positive bacteria, and half by Gram negative bacteria. On the other hand, 5 of 6 infections of traumatized eyes were caused by Gram positive bacteria. Such information if confirmed by future experience may influence the initial choice of antibiotics in these two types of intraocular infection.

Examination of smears in this series contributed little to selection of therapeutic agents.

*Staphylococcus epidermidis* may be a more common cause of bacterial endophthalmitis than previously known. Two cases reported by Valenton, Brubaker, and Allen[5] and our 7 isolates of *Staphylococcus epidermidis* emphasize the pathogenicity of this common conjunctival inhabitant for the interior of the eye. The eye containing *Propionibacterium acnes* may represent the first reported case of endophthalmitis due to this organism. *Propionibacterium acnes* may be recovered more often in the future, since in a recent study by Perkins and associates[6] approximately 44% of normal conjunctivae, when cultured with anaerobic media, grew *Propionibacterium acnes*. Although this organism grew easily on all media at 37° from the anterior chamber and vitreous, inoculation of specimens into an anaerobic medium should be routine.

The one case of *Hemophilus influenza* occurred in an aphakic eye with a corneal bleb following keratoplasty ten years previously. The initial growth was not readily evident on blood agar due to its requirement for special culture media and nutrition. Therefore, chocolate agar at an increased $CO_2$ tension should be considered in cases of endophthalmitis.

As previously reported,[7] with the exception of trauma, when the cultures are negative the visual prognosis is favorable suggesting that the endophthalmitis is indeed sterile, or was successfully treated prior to obtaining cultures.

Although results utilizing intraocular antibiotics are encouraging,[7,8] several aspects need to be examined. The 6 visually successful results occurred in 5 cases due to *Staphylococcus epidermidis* and 1 case due to *Propionibacterium acnes*, both organisms that perhaps could be managed by conventional routes; while on the other hand, no case with a recognized virulent pathogen retained any useful vision. The only eye with bacterial endophthalmitis not treated with intraocular antibiotics in which vision was salvaged, however also contained *Staphylococcus epidermidis*. This infection followed trauma and was treated by concomitant routes of topical, subconjunctival, and systemic antibiotics.[7]

Our laboratory studies of gentamicin toxicity by administration into the vitreous suggest that 0.1 - 0.2 mgm is the maximum safe dose in the rabbit eye, and it should be noted that this is in conflict with the dosage of 0.4 mgm reported by Peyman and associates.[9] The 12 electroretinograms performed in culture positive as well as culture negative cases suggest that combined therapy of 0.1 mgm gentamicin and 0.25 mgm cephaloridine can be tolerated by the retina and should be considered as an adjunct to the treatment of endophthalmitis. The combination of subtotal vitrectomy and intraocular antibiotics was utilized in 3 cases in

this study, one of which caused by *Propionibacterium acnes* achieved 20/60 vision.

SUMMARY

This report of 54 suspected cases of endophthalmitis emphasizes the following findings:

1. That vitreous aspiration is more sensitive in making a culture proven diagnosis than anterior chamber paracentesis.
2. That *Staphylococcus epidermidis* is a much more common cause of endophthalmitis than previously appreciated.
3. That intraocular antibiotics in the recommended dosage, are reasonably safe clinically and add a new dimension to the treatment of endophthalmitis.

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*DISCUSSION*

DR HENRY F. ALLEN. The scientific study of infectious endophthalmitis is hampered by the following factors:

1. the lack of a large series of cases in the hands of any one investigator or group of investigators,
2. the attendant difficulty of controlling variables in evaluating the results of treatment and,

3. the poor results obtained even when treatment can be shown afterward to have been specific.

The principal variables, in order of their importance, are as follows:

1. the virulence of the infecting organism
2. the size of the inoculum introduced intraocularly
3. the time before initiation of specific therapy
4. the extent of incidental trauma to intraocular tissue at the time of contamination
5. host factors relating to local and systemic defenses against infection.

In the present study, the authors have confirmed, either implicitly or explicitly, the above concepts. In addition, their results have given a firm basis to an impression held by students of endophthalmitis that cultures of the aqueous may be negative while infection of the vitreous is present. This may be the most definite and at the same time the most important conclusion which can be drawn from their study. Before accepting this on face value, however, one must ask whether one could ever spread an anterior chamber infection into an uninfected vitreous by aspiration of the latter.

The authors conclude that "intraocular antibiotics . . . are reasonably safe clinically and add a new dimension to the treatment of endophthalmitis." If one knew what this meant, it might be possible to make a critical comment about it. Unfortunately, I know of no evidence either in the present paper or elsewhere in the literature showing that intraocular antibiotics are either better or worse than the same antibiotics delivered by a combination of topical, episcleral, and parenteral routes. As indicated above, such information is difficult if not impossible to come by.

The authors are to be commended for their careful study of a sizeable series of cases and to be congratulated on adding at least one piece of new information to a subject in which such scraps must be cherished and exploited.

DR TAYLOR ASBURY. Congratulations to the authors for an excellent study. I am impressed by the results using the vitreous route for both diagnostic and therapeutic purposes.

DR CLEMENT MCCULLOCH. Drs Forster and Norton have given us a valuable overview of this problem. I would just ask two questions.

When you take a culture from the aqueous or vitreous, do you put in antibiotic directly, before getting the results of the culture?

You have indicated that intravitreal injection of antibiotic is possible and important. Do you do that but once — that is at the time of the initial culture and before the result of the culture is back? Would you give repeated injections of antibiotic into the vitreous once you did have the result of the culture?

DR RICHARD TROUTMAN. I would like to ask the authors about their use of steroids and what their feeling is in this area. I feel that steroids constitute a very valuable

adjunct in the routine treatment of endophthalmitis since either the therapeutic agents that we use or the sterile agents causing a sterile endophthalmitis or both are highly irritating to the inflamed eye and may result in its loss even when the infecting organism is eradicated.

DR RICHARD K. FORSTER. The subject of endophthalmitis and its difficult management has prompted many questions, some of which have been asked by Drs McCulloch and Troutman and raised in even more detail by Dr Allen's discussion of our paper. We did not compare conventional routes of treatment to intraocular antibiotic therapy alone in our cases, but such a comparison is being conducted at the present in a rabbit animal model of endophthalmitis. I did not want to give the impression that our utilization of intraocular antibiotics in the 26 cases reported was done at the exclusion of conventional treatment. Following anterior chamber and vitreous aspiration for diagnostic purposes antibodies were injected into the vitreous and anterior chamber at surgery, and the patients then received concomitant periocular and topical antibiotics and steroids as well as intravenous antibiotics.

We have not utilized intraocular corticosteroids although others experience suggest that this may be beneficial. Instead, we have augmented our antibiotic treatment, with topical and periocular steroids in the form of Kenalog and use this treatment prior to awaiting culture results. Another route that we have been exploring but have not utilized in the human is repeat intraocular injections. An animal study has been done attempting to evaluate the toxic levels of gentamicin with repeat injections into the vitreous utilizing the fundus appearance, electroretinogram, and histopathology as criteria for toxicity.

A most exciting avenue has been the evaluation of a combination of vitrectomy plus intraocular antibiotics in a rabbit model of infectious endophthalmitis. The rationale for this approach is an old surgical dictum that abscesses should be drained; therefore, there may be some benefit from removing the mass of infecting organisms, eliminating the destructive effects of enzyme products of polys, and allowing for greater mobility of intraocular antibiotics by removing formed vitreous. This is also consistent with the apparent superior ability of the anterior chamber to handle infection than that of the vitreous cavity. Utilizing such an animal model we have found that a combination of antibiotics (gentamicin) and vitrectomy has been statistically superior to intraocular antibiotics alone in eliminating the infection after inoculating a rabbit eye with *Staphylococcus aureus* 24 to 48 hours previously. I would hope that this approach will in the future give us an added advantage in treating this catastrophic complication of surgery and trauma.