**INTRAOCULAR DEXAMETHASONE PRODUCES
A HARMFUL EFFECT ON TREATMENT OF EXPERIMENTAL
STAPHYLOCOCCUS AUREUS ENDOPHTHALMITIS***

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ABSTRACT

Background: We created a standardized model of severe *Staphylococcus aureus* endophthalmitis in the aphakic rabbit eye to test various treatment strategies involving corticosteroid administration in addition to vitrectomy and antibiotic treatment.

Materials and Methods: In 71 aphakic New Zealand albino rabbit eyes, experimental endophthalmitis was created by injecting 10^5 colony-forming units of *Staphylococcal aureus*. The animals were divided into 5 groups. One control group was followed up without treatment, while 4 groups were treated with vitrectomy and intraocular cefazolin injection. Two groups were also treated with intramuscular methylprednisolone, 1 group beginning on the day of surgery and 1 group beginning on the following day. In the final group, dexamethasone, 400 µg, was injected into the vitreous cavity at the close of surgery. Culture results were compared on the first 2 days after surgery. Inflammatory scores, including development of total corneal opacity, were assessed over a 21-day follow-up period, and histopathologic grading was carried out at the conclusion of the clinical observations.

Results: Simultaneous administration of systemic corticosteroids beginning on the day of vitrectomy decreased inflammatory scores 1 week after institution of therapy but did not affect final scores. Delay of initiation of intramuscular corticosteroid until the first postoperative day negated the

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positive effects. Administration of intraocular corticosteroids was associated with an increase in inflammatory scores throughout the period of observation, an increase in percentage of eyes that developed opaque corneas, an increase in choroidal inflammation graded moderate or severe, and an increase in retinal necrosis compared with vitrectomy and cefazolin injection alone.

Conclusions: This data suggest caution in the use of intraocular corticosteroids in treatment of severe endophthalmitis.

INTRODUCTION

Intraocular infection and inflammation destroy vital ocular structures and often result in loss of functional vision. Outcome is determined by a number of factors, the most of important of which may be virulence in the infecting bacteria. Control of bacterial replication is important in successful treatment but is not necessarily sufficient to produce a good functional outcome.

Control of inflammation, in addition to eradication of bacteria, may be important in final visual outcome; corticosteroids have long been advocated as adjunctive therapy in the management of endophthalmitis.^{1,2} In studies of treatment of childhood meningitis (a closed-space infection with similarities to endophthalmitis in pathogenesis and treatment), simultaneous administration of systemic dexamethasone concomitant with the administration of parenteral antibiotic reduces the number of long-term neurologic sequelae.³⁻⁵ Corticosteroids have a number of potentially beneficial actions, including decreasing prostaglandin production and inhibition of cytokines such as tumor necrosis factor (TNF) and interleukin-1 (IL-1).⁶

Graham and Peyman² suggested that intraocular corticosteroids might improve visual results when used to treat endophthalmitis. In their study, intravitreal corticosteroid administration improved outcome only when administered within 8 hours of inoculation of bacteria into the vitreous cavity. The administration of corticosteroids and antibiotics concomitantly 24 hours after inoculation of bacteria did not improve outcome. In a previous model of *Staphylococcus epidermidis* endophthalmitis, we reported that the administration of intraocular corticosteroids or systemic corticosteroids was associated with improved inflammatory scores throughout the posttreatment course. The intraocular route had no significant advantage over the systemic route in this study, however.⁷ Recent studies⁸⁻¹⁰ have also suggested improvement in several outcome measures when eyes treated without vitrectomy were given intravitreal corticosteroids and intravitreal

antibiotics. Thus we studied the administration of corticosteroids in conjunction with vitrectomy and intravitreal antibiotic injection in a rabbit model of severe aphakic *S aureus* endophthalmitis. We have previously reported that vitrectomy and cefazolin provided a better outcome in this model when a number of parameters were compared with controls.¹¹ In this report, we compare three strategies of concomitant corticosteroid administration to try to further improve measures of outcome.

MATERIALS AND METHODS

To assess the role of corticosteroids as an adjunctive therapy to the basic strategy of vitrectomy and antibiotic injection, we created a model of bacterial endophthalmitis by injecting 10^5 colony-forming units of a laboratory strain of *S aureus* into aphakic rabbit eyes and evaluated 3 different strategies of corticosteroid administration. Seventy-one eyes of New Zealand rabbits weighing 2.5 to 3.0 kg were used in this study. The lens was removed by ultrasonic fragmentation by pars plans lensectomy.

Three weeks were allowed to pass for healing from the surgery, and the eyes were then examined before proceeding to create experimental infection. *S aureus* was then injected into the midvitreal cavity, and the eyes were reexamined 24 hours later and graded clinically. The eyes were assigned to 1 of 5 different groups: (1) untreated eyes, (2) vitrectomy plus intraocular cefazolin (15 eyes), (3) vitrectomy, intraocular cefazolin, and intramuscular methylprednisolone succinate, 25 mg per 0.2 mL administered for 5 days beginning on the day of surgery (13 eyes), (4) vitrectomy, intraocular cefazolin, and methylprednisolone succinate administered for 5 days beginning on the day following surgery (11 eyes), and (5) vitrectomy, intraocular cefazolin, and intraocular injection of dexamethasone, 400 µg (17 eyes). All treatment was initiated 24 hours after bacteria inoculation in eyes which demonstrated unequivocal and similar signs of clinical infection.

To perform vitrectomy, a 20-gauge needle was used for perfusion of balanced salt solution; with a suction cutting probe, the inflamed, abnormal material of the anterior chamber and the fibrin membrane was removed from the surface of the iris. Central and anterior vitrectomy were performed, taking care to remove vitreous from the undersurface of the iris. No attempt was made to remove vitreous from the retinal surface. For all surgery, rabbits were anesthetized with a 50/50 mixture of xylazine hydrochloride (20 mg/mL) and ketamine hydrochloride (100 mg/mL) by intramuscular injection. Phenylephrine hydrochloride 10% and cyclopentolate hydrochloride 1% were used to dilate the pupils. Animals were maintained in accordance with the resolution on animal use of the

Association for Vision and Research in Ophthalmology.

Cefazolin sodium, 2.25 mg per 0.1 mL balanced salt solution, was injected into the vitreous cavity in all eyes in the 4 treatment groups. Methylprednisolone sodium succinate, 25 mg per 0.2 mL, was injected intramuscularly for 5 days in groups 3 and 4. Dexamethasone, 400 µg, was injected in the midvitreous cavity at the close of the vitrectomy in group 5.

Clinical grading was carried out as previously described in all eyes prior to treatment, and 7, 14, and 21 days after treatment.¹¹ All animals were anesthetized on the first and second days after treatment, and vitreous was aspirated from the midvitreous cavity, removing 0.2 to 0.3 cc through a 23-gauge needle for quantitative culture. The vitreous samples were serially diluted and plated in triplicates onto tryptic soy agar (Difco) plates. After incubation of 24 to 36 hours at 37°C, lack of colonies on plates with the first tenfold dilution was considered a negative culture result. Eyes were included in the study only if they demonstrated clinical infection and had a positive culture either before treatment or at one of the two posttreatment cultures.

At the conclusion of 21 days of clinical observation, the majority of eyes were enucleated for histopathologic study. Sections were stained with hematoxylin-eosin and examined by an ocular pathologist who did not know the clinical management of the eye. Inflammation was classified as acute or chronic and a grading of mild, moderate, or severe was assigned for 6 areas of the eye: cornea, iris, ciliary body, choroid, retina, and vitreous. Notation of retinal necrosis was also made.

We evaluated culture results on days 1 and 2 after treatment; inflammatory scores 7, 14, and 21 days after surgery; the percentage of eyes developing corneal opacity 3 weeks after therapy; and histopathologic changes in the eyes 3 weeks after initiation of therapy.

We used the BMDP statistical software to analyze our data. Repeated measures analysis of variance (ANOVA) was used to compare the influence of treatment on inflammatory scores. Data on inflammation were also dichotomized. An inflammatory score of 24 or higher was possible only with an opaque cornea. The effect of treatment on the risk of opacity was examined with a Pearson's chi-square, and the impact of treatment modality on the rate at which opacities developed was examined using life table approach; a cornea was considered to remain opaque once the inflammatory score reached 24, regardless of any observed decrease in inflammatory score. Direct comparisons between subgroups was evaluated with Fisher's exact test.

Analysis of the impact of treatment on the occurrence of positive cultures was conducted in a similar manner to analysis of the risk of opacity.

RESULTS

We have previously reported that vitrectomy and intraocular cefazolin reduced the inflammatory scores and the percentage of eyes developing corneal opacity; the number of culture-positive results decreased compared with no treatment.¹¹ Treatment with intramuscular corticosteroids beginning on the day of surgery further reduced the inflammatory scores on day 7 (untreated, 24; vitrectomy plus cefazolin, 19; cefazolin plus intramuscular corticosteroid, 14.5). The inflammatory scores in the corticosteroid group remained stable at this level over the subsequent 14 days, while the eyes treated without corticosteroids showed an improvement in inflammatory scores by day 21, so there was not a final significant difference between the 2 groups (Table I). There was no significant difference in the culture-positive results at 48 hours between the 2 groups (Table II). The percentage of eyes with opaque corneas was essentially the same at 21 days in these 2 comparative groups (corticosteroid, 27%; no corticosteroid, 31%) (Table III). Histopathologic examination of the eyes treated with corticosteroids showed a significant increase in the percentage of eyes demonstrating retinal necrosis (72% versus 27%; $P=0.003$), but no other significant differences.

Delay of initiation of intramuscular corticosteroid by 1 day resulted in the group of eyes with corticosteroid treatment having essentially the same inflammatory scores on day 7 and throughout the period of observation as the eyes receiving vitrectomy and cefazolin treatment. The percentage of culture-positive results on posttreatment day 2 was equivalent (48% versus 43%), and the percentage of eyes with opaque corneas at day 21 was not statistically significantly different (27% versus 37%). On histopathologic evaluation, the delayed corticosteroid group showed decreased numbers of eyes with severe vitreous reaction (55% versus 22%), but an increase in retinal necrosis (56% versus 20%) and an increase in moderate or severe choroidal reaction (56% versus 18%), although none of these effects was statistically significant.

When corticosteroid was administered into the vitreous cavity at the close of the surgical procedure, the inflammatory scores remained stable and equivalent to the pretreatment scores, while the inflammatory scores in all other treatment groups decreased. Comparing the eyes treated with surgery and intraocular corticosteroid with those that received no corticosteroid, there was an increase of corneal opacity at the close of the period of evaluation (27% versus 69%; $P=0.03$). On histopathologic evaluation, the group treated with intraocular corticosteroids showed an increase in eyes demonstrating retinal necrosis (27% versus 100%; $P=0.0001$) and an increase in moderate to severe choroidal inflammatory reaction (18% versus 70%; $P=0.03$).

TABLE I: AVERAGE INFLAMMATORY SCORE BY TREATMENT MODALITY

GROUP	PRETREATMENT		POSTTREATMENT		
	NO.	(%)	DAY 7 (%)	DAY 14 (%)	DAY 21 (%)
Control	15	21.4	24.7	26.7	27.1
Cefazolin + vitrectomy	15	20.8	19.0	19.6	16.7
Cefazolin + vitrectomy + SCS1	13	20.8	14.5	14.7	15.5
Cefazolin + vitrectomy + SCS2	11	20.4	20.0*	20.8†	18.5†
Cefazolin + vitrectomy + IOCS	17	21.4	21.3‡	22‡	20.7‡

IOCS, intraocular corticosteroids; SCS1, systemic corticosteroids initiated on day of surgery; SCS2, systemic corticosteroids initiated on day after surgery.

*Two animals died

†Three animals died

‡One animal died.

TABLE II: PERCENTAGE OF CULTURE-POSITIVE EYES BY TREATMENT MODALITY

GROUP	PRETREATMENT		DAY 1		POSTTREATMENT		DAY 2	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Control	15	100	13	87	13	87	13	87
Cefazolin + vitrectomy	14	93	8	53	6	53	6	40
Cefazolin + vitrectomy + SCS1	13	100	13	100	9	100	9	69
Cefazolin + vitrectomy + SCS2	11	100	7	78°	6	78°	6	43†
Cefazolin + vitrectomy + IOCS	16	94	9	54	2	54	2	8

IOCS, intraocular corticosteroids; SCS1, systemic corticosteroids initiated on day of surgery; SCS2, systemic corticosteroids initiated on day after surgery.

°Two animals died

†Three animals died

#One animal died.

TABLE III: PERCENTAGE OF CORNEAS OPAQUE BY TREATMENT MODALITY

GROUP	PRETREATMENT		DAY 7		POSTTREATMENT DAY 14		DAY 21	
	NO.	(%)	NO.	(%)	NO.	(%)	NO.	(%)
Control	15	7	8	53	13	87	15	100
Cefazolin + vitrectomy	15	0	4	27	6	40	4	27
Cefazolin + vitrectomy + SCS1	13	0	2	15	4	31	4	31
Cefazolin + vitrectomy + SCS2	11	0	2*	22	4†	50	3†	37
Cefazolin + vitrectomy + IOCS	17	0	10‡	63	11‡	69	11‡	69

IOCS, intraocular corticosteroids; SCS1, systemic corticosteroids initiated on day of surgery; SCS2, systemic corticosteroids initiated on day after surgery.

*Two animals died

†Three animals died

‡One animal died.

TABLE IV: ASSOCIATION BETWEEN TREATMENT MODALITY AND HISTOPATHOLOGIC OUTCOME

GROUP	NO.	RETINAL NECROSIS		SEVERE VITREOUS REACTION		MODERATE OR SEVERE CHOROIDAL REACTION	
		NO.	(%)	NO.	(%)	NO.	(%)
Control	14	8	57	12	86	8	57
Cefazolin + vitrectomy	11	3	27	6	55	2	18
Cefazolin + vitrectomy + SCS1	12	11	92	3	25	4	33
Cefazolin + vitrectomy + SCS2	9	5	56	2	22	5	56
Cefazloin + vitrectomy + IOCS	10	10	100	5	50	7	70

IOCS, intraocular corticosteroids; SCS1, systemic corticosteroids initiated on day of surgery; SCS2, systemic corticosteroids initiated on day after surgery.

DISCUSSION

Reduction of inflammation remains an important part of management of endophthalmitis. In the Endophthalmitis Vitrectomy Study, all treated patients received systemic corticosteroids. In this *S aureus* model of severe endophthalmitis and our model of *S epidermidis* endophthalmitis,⁷ beneficial effects of early intramuscular administration in eyes treated with vitrectomy and intraocular antibiotics were demonstrated.

Several investigators have studied the effects of addition of intraocular corticosteroids to intravitreal antibiotic injection in experimental infections treated without surgery. Jett and coworkers¹⁰ demonstrated that treatment with intraocular corticosteroids and antibiotics produced a better outcome when evaluated by electroretinography and histopathology than antibiotic injection alone in a model of endophthalmitis produced by a toxin-producing strain of *Enterococcus faecalis*. This improvement, however, was strain-dependent and did not occur when infection was produced by a toxin-producing strain of *Enterococcus*. Park and associates⁹ also demonstrated a beneficial effect for intraocular corticosteroid injection in a model of pneumococcal endophthalmitis. Studies of *S epidermidis* endophthalmitis noted beneficial effects from intraocular corticosteroids;⁸ although our model of severe *S aureus* endophthalmitis failed to show such a benefit.¹¹ Clinical studies by Mao and coworkers¹² showed good treatment outcomes in patients infected with *S aureus* whose therapy included intraocular corticosteroids. Although this was not a randomized study, direct comparisons between intraocular and systemic administration demonstrated no advantage for the intraocular route.

In this model, we assessed addition of corticosteroids to the treatment strategy of vitrectomy and intraocular cefazolin injection in an experimental model of severe aphakic *S aureus* endophthalmitis. The most successful strategy was beginning intramuscular corticosteroid injection on the day of the surgical intervention. This produced a faster decrease in inflammatory scores but did not improve the final outcome measured by inflammatory scores or the percentage of eyes developing complete corneal opacity. More eyes demonstrated retinal necrosis. Interestingly, all eyes remained culture-positive on day 1, suggesting the possibility of continued toxin production as a cause for the intraocular inflammatory changes.

Delay of corticosteroid administration until the first postoperative day negated the positive effects of intramuscular corticosteroid administration. There were no measures of outcome that showed improvement compared with surgery and antibiotic injection alone.

Intraocular corticosteroids did not improve any measure of outcome and produced a worsening in several of these measures. The number of corneal opacities was doubled compared with the eyes without any corticosteroid administration, and inflammatory scores were increased throughout the period of observation. On posttreatment day 21, the score was 20.7 versus 16.7 in the group without corticosteroid treatment. Most strikingly, all eyes administered with intraocular corticosteroids demonstrated retinal necrosis.

The causes for these worsened results are not immediately obvious. Culture results 48 hours after surgery were actually the best in those eyes treated with intraocular corticosteroids. This implies, therefore, that some part of the inflammatory process was altered in a counterproductive manner and that the increased damage was not a result of continued bacterial replication. Intraocular dexamethasone alone would not be apparently the cause of the observed results. Injection of intraocular dexamethasone in the same dose in our model of *S epidermidis* endophthalmitis did not produce worsening of results, but in fact improved the main outcome variable of inflammatory scores.⁷ Dexamethasone has been demonstrated not to have toxicity in doses under 500 µg.¹³

Injection of corticosteroids into the eye is different from systemic steroid administration in a number of ways. The dose reaches the vitreous cavity at a much earlier stage in the inflammatory cycle. The intraocular concentration of medication is probably several hundred times higher than that achieved with systemic administration. Finally, the effects are directly on the intraocular inflammatory process, whereas administration of systemic steroids probably not only affects the intraocular process itself to some lesser degree but may reduce the recruitment of additional inflammatory cells into the eye. The half-life of injected dexamethasone is short (3.5 hours), and thus 5 days of systemic administration may actually provide a longer exposure to therapeutic level of corticosteroids than intraocular injection.

These results suggest caution in the use of intraocular corticosteroid in the treatment of endophthalmitis. On the basis of clinical findings and results of other investigators, intraocular corticosteroid administration is not incompatible with good outcomes in some eyes and may be better than no corticosteroid administration at all. However, these data suggest that for some infections, intraocular administration alone may produce a worse outcome. These results suggest that all cases of endophthalmitis should not necessarily be treated in the same fashion. More severe inflammatory processes may respond to a given treatment strategy in a different way from mild inflammatory processes. Therefore, a single treatment strategy

for the many varieties of endophthalmitis may not be appropriate for all cases. Further evaluation comparing intraocular administration and systemic dosing will be necessary in laboratory models and in clinical trials in order to ascertain the most effective strategy. Evaluation of a combination of intraocular and intramuscular administration, as well as intraocular injection of nonsteroidal anti-inflammatory agents, deserves study.

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DISCUSSION

DR RICHARD K. FORSTER. Dr Meredith and colleagues have studied the effects of corticosteroids in conjunction with vitrectomy and intravitreal antibiotic injection in a rabbit model of aphakic *Staphylococcus aureus* endophthalmitis. Experimental endophthalmitis was produced in aphakic albino rabbits by injection of 10^5 colony-forming units of *S aureus*, and the animals were divided into 5 groups, including a control group followed up

without treatment and 4 groups treated with vitrectomy and intraocular cefazolin. In addition, 2 groups were treated with intramuscular methylprednisolone, 1 group beginning on the day of surgery and the second group beginning on the following day. An additional group received dexamethasone, 400 µg, and the animals subsequently had cultures taken and were assigned inflammatory scores, including the development of corneal opacity; after a 21-day follow-up time, histopathologic grading was done.

The results of this study are frankly somewhat surprising and to date represent a unique observation. The authors observed that simultaneous administration of systemic corticosteroids in the rabbit beginning on the day of vitrectomy decreased inflammatory scores at 1 week but did not affect final scores at 21 days, and that a delay in the initiation of corticosteroid until the first postoperative day negated any positive anti-inflammatory effect. In addition, administration of intraocular corticosteroids was associated with an increase in the inflammatory scores throughout the period of observation, an increase in the percentage of eyes that developed opaque corneas, and an increase in choroidal inflammation as well as retinal necrosis when compared with vitrectomy and intraocular antibiotic injection alone.

These results can be contrasted with a 1990 report by Meredith and associates¹ in which, using a standardized rabbit model of endophthalmitis in the rabbit injected with 10^5 colony-forming units of a laboratory strain of *Staphylococcus epidermidis*, they compared the signs of inflammation in the control eyes with several different treatment modalities and observed that clinical inflammation and media clarity compared at 1, 2, and 3 weeks posttreatment were best achieved with combined vitrectomy, intraocular antibiotics, and corticosteroids. The ocular histopathology in a rabbit model of gentamicin-sensitive *S epidermidis* endophthalmitis was reported by Maxwell and associates² in 1991, in which the histologic and clinical effect of intravitreal dexamethasone was graded in experimentally induced endophthalmitis, with the conclusion that all eyes treated with dexamethasone, with or without vitrectomy, exhibited fewer clinical and histologic manifestations of inflammation.

In 1992, Kwak and D'Amico³ evaluated the retinal toxicity and pharmacokinetics of dexamethasone after intravitreal injection. They established the lack of retinal toxic effect of a single intravitreal injection of 440 µg of dexamethasone sodium phosphate, either as a pure solution or in the commercially supplied preparation, but did document increasing retinal toxicity with higher doses. Park and associates⁴ investigated the role of corticosteroid therapy in decreasing inflammation and tissue damage associated with experimental pneumococcal endophthalmitis and concluded

that intravitreal corticosteroid therapy may play an important role in minimizing the inflammation and tissue damage associated with pneumococcal endophthalmitis.

In a retrospective review of 52 patients with culture-proven gram-negative endophthalmitis, Irvine and associates⁵ reported retrospectively that 65% of vitrectomy-treated eyes compared with 37% of eyes treated with vitreous aspiration achieved 20/400 or better visual acuity, and observed that 7 of 10 eyes receiving intraocular dexamethasone in addition to intraocular antibiotics achieved 20/400 or better vision. In 1993, Mao and colleagues⁶ reviewed the medical records of 27 patients with culture-positive *S aureus* endophthalmitis and reported that in 13 eyes treated by initial vitrectomy and intraocular antibiotics, 10 achieved 20/400 or better acuity compared with 7 of 14 eyes in the vitreous tap and intraocular antibiotic injection group. Of 8 eyes treated initially with intraocular corticosteroids, 7 achieved 20/400 or better visual acuity, compared with 10 of 19 that did not receive intraocular corticosteroids. The investigators concluded that the use of vitrectomy and intraocular corticosteroids combined with intraocular antibiotics was associated with the best visual outcomes in this group of eyes with endophthalmitis caused by *S aureus*.

Therefore, not only is the expected short-term experimental histopathologic response thought to be sensitive to corticosteroids, but in clinical reports of human endophthalmitis due to *S aureus*, eyes seem to fare better with concomitant intraocular dexamethasone than with vitrectomy and intraocular antibiotics alone.

How, then, can we explain the results presented by Meredith and colleagues? I would submit that the reason histopathologic examination of eyes treated with corticosteroids, either systemically or intraocularly, shows a significantly increased percentage of eyes demonstrating retinal necrosis is that although the initial inflammation caused by *S aureus* may perhaps be somewhat modified by corticosteroids, at 21 days the overall inflammatory response is overwhelming and produces an increase in retinal necrosis and an increase in moderate and severe choroidal reaction. In my 1992 American Ophthalmological Society thesis, "Experimental Postoperative Endophthalmitis,"⁷ a semiquantitative grading system was developed to evaluate the inflammatory reaction and extent of involvement of ocular tissues and cavities. In the aphakic rabbit model of endophthalmitis, 4 different vancomycin-sensitive organisms were injected, including *S aureus* intravitreally inoculated, with and without vancomycin, and with and without vitrectomy. Bar charts were constructed from the mean histopathologic inflammatory grading to display cavitory results with noncavitory tissue results. *S epidermidis* tended to produce a mild non-

cavitary, inflammatory response with little tissue damage, probably accounting for the relatively good prognosis for salvaged vision. In contrast, the noncavitary inflammatory response in the cornea, iris, ciliary body, retina, choroid, optic nerve, and sclera, including retinal necrosis and panophthalmitis, was most severe in the natural history model of *S aureus* endophthalmitis.

Future studies may better delineate the specific role of corticosteroids and whether or not the rabbit model is a good one to simulate the response in human disease. In addition, I would suggest histopathologic evaluation be done in a semiquantitative masked fashion at different time intervals, such as 48 hours, 1 week, and 3 weeks. A less overwhelming infection using fewer colony-forming units of *S aureus* might also permit the demonstration of corticosteroid efficacy. Certainly, the role of other anti-inflammatory agents should be considered, as well as the effect of anti-inflammatory agents in the setting of different infecting organisms.

I wish to congratulate Dr Meredith and his colleagues in reporting this most provocative and stimulating investigation.

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DR. RONALD M. BURDE. Although the treatment protocol used in this experiment may appear to be scientifically valid it is only so from a superficial viewpoint. Let us look at the damage being done. First with retinal injury there is a major release of glutamate, an excitatory amino acid whose effect is modulated by at least 3 different types of receptors, e.g., NMDA; karmic acid which affect calcium channels. The continued presence of glutamate leads to a major increase in intracellular calcium activation of phospholiposis, membrane damage and cellular destruction. Obviously, the availability and use of glutamate specific receptor antagonists would provide direct protection to the cell against the calcium cas-

cade. There does not appear to be a family of non-toxic compounds that are effective in blocking the glutamate induced calcium cascade at the moment. We know from studying the actions of the currently used calcium channel blockers that there are idiosyncrasies to each, e.g., verapamil being more specific for supraventricular tachycardia while nimodipine appearing to have a greater central nervous system effect in reducing vasospasms. Thus, to attack such problems as the retinal response to "trauma" requires us to pause out the individual effects of various types of membrane receptors and their antagonists and attempt to intervene at a specific site rather than at a site removed.

An example of such diversity is the demonstration that in the central nervous system, dexamethasone is more effective in protecting synaptosomes whereas methylprednisolone is more effective in preserving axons. Thus, the model presented this morning is like a mixed metaphor and marks a past science still performed.

Furthermore, it is no longer acceptable to test a given drug or group of drugs at one concentration. Again, drawing from this neurological literature, it has been demonstrated that in the treatment of spinal cord trauma there is a "J" shaped response curve with 15 mg/kg methylprednisolone being insufficient, and 60 mg/kg being too much steroid. The most adequate recovery was achieved with 30 mg/kg.

The number of experiments necessary to determine the appropriate parameters necessary to maximize the effect of a compound in question will make it impossible for a single testing facility to use even such lower mammals as mice or rats.

A new world - better but tougher!

EDWARD RAAB, MD. I have a question for Dr. Meredith on this excellent work. Can you provide from your studies either a conclusion or an educated speculation that might be helpful to those of us who are called upon for consultation about perforations during muscle surgery or who even may encounter those ourselves. Would it be a wise idea, in addition to whatever else we do when confronted with that situation, to consider venous steroids. I do not think we would resort to intraocular steroids at that point. Intravenous would not seem to harm, and might even help.

TRAVIS MEREDITH, MD. I would like to thank Dr. Forster and Dr. Burde for their very helpful comments. I agree entirely with Dr. Forster that this is a model of very severe inflammation and it may be that the treatment administered was simply insufficient to deal with the problems. Yet it does give us pause that in this one model we had a worse outcome with intraoc-

ular steroids. Until we have models and studies that show us that there is a superiority of intraocular corticosteroids to systemic steroids I think we must use the intraocular medications with caution. Further studies probably need to compare intraocular corticosteroids and controls to systemic administration. As we have seen there is a short duration of action from the intraocular administration and another group which could have been included in this study is one receiving both intraocular corticosteroids for the immediate effect and the longer term effects of systemic administration. So a fourth group would have received corticosteroids by both routes.

Dr. Burde's comments are particularly helpful and we are trying to look at a variety of ways to protect the eye. Certainly, we have to protect the cell membranes but we do have to modulate the inflammatory cascade inside the eye which causes this damage. The inflammatory cycle is extremely complex and it is not clear at all exactly how to attenuate the harmful effects. So it would be worth trying to protect cell membranes but I think that simultaneously we have to deal with the inflammatory response itself.

Finally, in response to Dr. Raab's question as far as prophylaxis I am not sure that a steroid would be necessary in perforations in cases of muscle surgery. However, taking a lesson in prophylaxis from the general surgeons it might be wise to consider a dose of intravenous antibiotic if you wish to provide prophylaxis in that situation.

Thank you very much.