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Endotoxin-Induced Uveitis in the Rat*

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Abstract. Experimental studies of ocular inflammation induced by endotoxin have been performed almost exclusively in rabbits. Although the rat has been considered refractory to both the systemic and local effects of endotoxin, the present study has shown that intravitreal injection of endotoxin evoked a characteristic acute inflammatory response which was reproducible and dose-dependent. In addition, a consensual ocular response in the control eye occurred which was less severe but also dose-dependent. Preliminary investigations support the view that consensual responses of this nature may be mediated by a nervous reflex arc mechanism. Sequential histological analysis revealed a marked polymorphonuclear cell infiltration of most ocular tissues in the early stages, while mononuclear cells predominated after 3 days. Widespread intravascular microthrombi were also observed, particularly in the ciliary vessels. Recovery, however, was usually complete by 7 days.

Introduction

Bacterial endotoxin (ET) has been used extensively in the study of nonimmunogenic ocular inflammation because the response is reproducible, finite, and dose-dependent (Levene, 1959). The frequent participation of the eye in local and generalized Shwartzman reactions in which there is an enhanced response to a second IV injection of ET in animals which have been 'primed' with either a local or parenteral injection 24 h previously (Rietschel, 1975; Nowotny, 1969), is well-established. In addition ocular inflammation may be induced after a single IV injection of ET (Ayo, 1943). This has been described as a specific toxic ocular reaction, but it is probably similar to the response in other organs (Chien et al., 1964), since the pathological appearances consist essentially of

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microthrombi and capillary leakage (Levene and Breinin, 1959). According to Ayo (1948) the ocular response to a single IV injection of ET showed marked species variability. Ocular inflammation was readily induced in the rabbit, cat, and dog, but monkeys and guinea pigs were less susceptible. Frogs, roosters, pigeons, rats, and mice showed no response to IV ET.

A single intraocular injection of ET will also produce a marked inflammation within a few hours (Segawa and Smelser, 1969) and the pathological changes are similar to those occurring in the skin after a local injection (Taichman et al., 1966). Studies of locally induced endotoxin uveitis, however, have been carried out almost exclusively on the rabbit. During our studies on ocular inflammation, we found it necessary to develop an experimental model of uveitis in a smaller laboratory animal, namely, the rat. Although the rat has been used previously for the study of immunogenic uveitis in conditions such as Freund's adjuvant arthritis (Waksman and Bullington, 1960; Tilgner et al., 1972a, b) and phacoanaphylactic uveitis (Behrens and Manski, 1973), endotoxin-induced uveitis in the rat has not been described previously. In this study the clinical and histological changes induced in the rat eye by the intravitreal injection of Shigella ET are described. The response to intraocular ET was dose-dependent, and highly reproducible. In addition, a consensual response occurred in the control eye which was also dose-dependent.

Materials and Methods

Animal Models. Columbia-Sherman male rats (300–350 g) were used. Anesthesia was achieved with IP buffered pentobarbital sedation and ether. A total of 78 rats was used for this study. A minimum of three rats was used for the clinical and histological studies at each time interval. For clinical evaluation, the numbers were often considerably greater.

Injection Technique. Intravitreal injections of endotoxin were performed in the following manner: An airtight system consisting of a Hamilton microliter syringe, fine (PE-10) polythene tubing, and a 30 gauge needle (without hub) was used to deliver precise 1 µl volumes of fluid. The eye was grasped with forceps behind the limbus and the needle inserted into the vitreous, avoiding contact with the lens (Fig. 1). The tip of the needle was visible through the pupil. One microliter of *Shigella flexneri* endotoxin (Difco) in Earle's Balanced Salt Solution (EBSS) was injected into the right eye of each animal. The needle was immediately withdrawn and no reflux of fluid occurred. Pilot experiments with colored dyes indicated that the entire volume of fluid was retained within the vitreous. The left eye was used as a control, receiving 1 µl EBSS intravitreally through a separate identical system.

Throughout the course of the study a few eyes showed evidence of traumatic cataract, typically seen as a pearly white posterior opacity, 2–3 days following the operation. These eyes were excluded from the experiments.

Clinical Examination. Biomicroscopic examination of the eyes was performed at 1, 3, 6, 9, 12, 18, and 24 h after injection and daily thereafter for 8 days. Uveitis was graded on a scale of 0–7 (Table 1). Animals were killed at 3, 6, 9, 12, 18, and 24 h, and 3, 5, and 7 days after injection of endotoxin.

Histology. The eyes were enucleated immediately after death and fixed for 12–24 h in Carnoy's solution (1:3, acetic acid: absolute ethanol). In order to facilitate fixation without the loss of vitreous a small window was made in the posterior sclera and the eye suspended from a cork with 6–0 black sutures (Ethicon). After fixation, a similar window was made in the cornea to

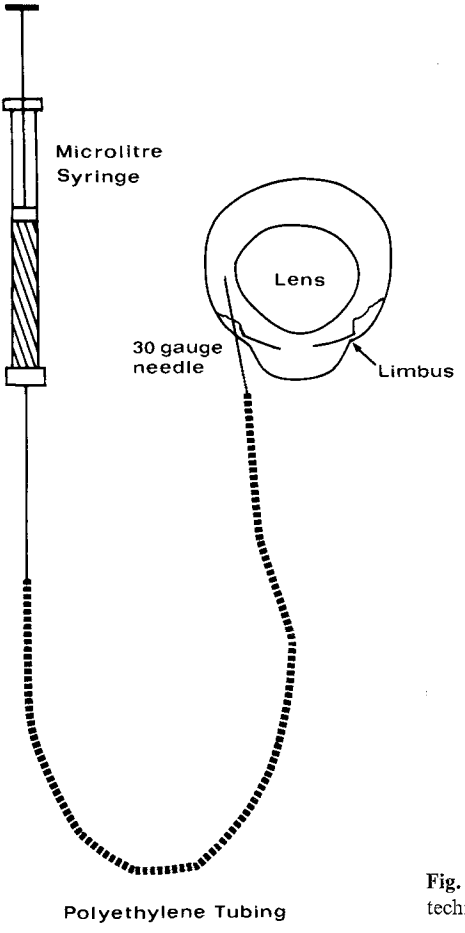

Fig. 1. Diagram of intravitreal injection technique

Table 1. Scoring system for clinical evaluation of uveitis by biomicroscopy

Clinical signs		Grade of uveitis (score)
Iridial hyperemia		1
Flare	Mild	1
	Moderate	2
	Severe	3
Cells	Occasional	1
	Moderate	2
	Marked	3
Maximum possible score		7

enhance paraffin infiltration. Conventional methods of dehydration were followed with a double embedding procedure in Paraplast Plus at 60° C. The globe was then serially sectioned at 4 μm and the sections stained with hematoxylin and eosin (H and E), periodic acid Schiff (PAS), Mallory's phosphotungstic acid hematoxylin (PTAH), Prussian Blue, and Alcian Blue/Acid Fuschin stains.

Results

Clinical Observations. The time course and dose-response curves to intravitreal injections of ET are shown in Figure 2. With a dose of 0.2 μg/μl endotoxin, the experimental eyes developed the first signs of uveitis after 1 h and a maximal response after 9 h. This was manifested by chemosis, marked iridial hyperemia with engorged iris vessels, a dense flare with fibrinous exudate in the anterior chamber, synechiae between lens capsule and iris often extending 360°, a pronounced cellular invasion of the aqueous, and the appearance of a retroiridial hypopyon which was visible through the translucent iris. This severe degree of uveitis persisted for at least 3–6 h but by 24 h there was less flare and fewer circulating cells in the anterior chamber. The retroiridial hypopyon, however, remained for 1–3 days. Signs of uveitis were observed for up to 5 days after injection of 0.2 and 2.0 μg endotoxin. A more prolonged uveitis was observed with doses of 20 and 66 μg/μl (Fig. 2).

Control eyes also developed a dose-related inflammatory response (Fig. 2), although the response to 0.002 μg/μl consisted mainly of iridial hyperemia. A peak response occurred generally 9–12 h after injection and there was no maximal response at any dose, although hypopyon was observed in the control eye when its fellow received the largest (66 μg/μl) dose. In addition the inflammation subsided more rapidly with lower doses, while higher doses produced a low-grade prolonged inflammation. There was a close correlation between test and control eyes at the various doses of endotoxin.

Clinical Effect of Contaminants on the Consensual Response to Endotoxin. Since it is well-established that commercial saline preparations contain trace amounts of endotoxin (Bito, 1977), it was possible that contaminants with the EBSS may have contributed to the consensual response. However, the injection of EBSS alone into one or both eyes produced only a transient grade 1–2 uveitis lasting a few hours. In addition, solutions of ET in minimum essential medium (MEM) had a consensual effect similar to ET in EBSS.

Clinical Effect of Trauma on the Consensual Response to Endotoxin. A reproducible consensual response was elicited when the needle was inserted into the control eye without injecting EBSS but not when the control eye was uninjected. However, insertion of the needle alone into the control eye in the absence of ET in the test eye, did not produce significant inflammation. Moreover, animals subjected to deliberate lens injury anteriorly by passing a 30 gauge needle through the center of the cornea, or posteriorly, by passing the needle through the limbus at such an angle as to rupture the posterior lens capsule, failed to develop typical consensual responses. These data are summarized in Table 2.

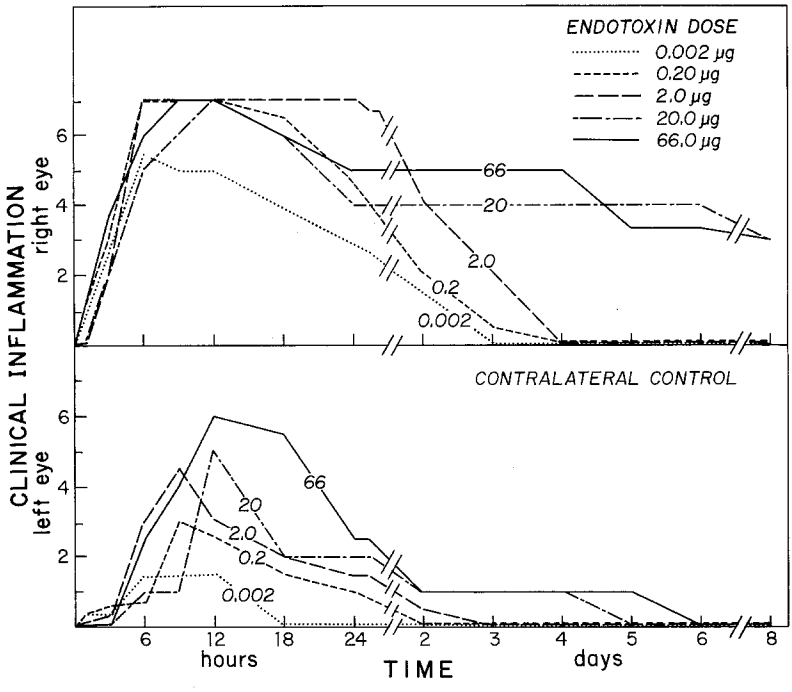

Fig. 2. Time course and dose-response curve of endotoxin-induced uveitis: Endotoxin-injected right eyes (top); EBSS-injected control eyes (bottom)

Table 2. Effect of various modifications of experimental systems on production of uveitis in test and control eyes

Test system	Right eye (test)		Left eye (control)	
	Maximum grade uveitis	Duration (h)	Maximum grade uveitis	Duration (h)
Right eye, ET Left eye, EBSS	7	> 72	6	> 72
Right eye, EBSS Left eye, EBSS	2	6–8	2	6–8
Right eye, ET Left eye, MEM	7	> 72	6	> 72
Right eye, ET Left eye, not injected	7	> 72	0	–
Right eye, ET Left eye, needle only inserted	7	> 72	3	48–72
Right eye, needle only Left eye, needle only	1	3–4	1	3–4
Right eye, needle only Left eye, deliberate lens injury	1	3–4	3	24–48
IV ET	3	3	3	3

Table 3. Effect of single dose of IV ET on the rat eye

ET (mg/kg)	Clinical grades of uveitis		
	Rat	Right eye	Left eye
0.8	1	0	0
	2	0	0
80	1	0	0
	2	0	0
800	1	2	2
	2	0	2
2,400	1	3[a]	2[a]
	2	3[a]	3[a]
800+saline infusion	1	3	3[a]
	2	3[a]	3[a]

[a] Chemosis

Clinical Effect of Circulating Endotoxin on the Consensual Ocular Response to Endotoxin. The possibility that high doses of endotoxin injected into the vitreous might produce a consensual response via the circulation was explored. Intravitreal injections were performed as before and IV injections were adminstered by way of the penile vein. Table 3 shows the ocular response of the rat eye 1 h after the IV injection of various doses of endotoxin in 0.1 ml EBSS. Iridial hyperemia and aqueous flare were elicited with doses greater than 80 mg/kg body weight and this response could be enhanced by the infusion of IV saline (Theiss et al., 1975). In addition, extremely high doses produced chemosis and corneal oedema suggesting the presence of severe ocular hypertension. However, the ocular response to IV endotoxin differed from that of intravitreal endotoxin since there was no evidence of fibrinous exudate, aqueous cells, synechiae, or hypopyon. In addition, the response to IV endotoxin rapidly subsided (< 3 h) unlike the prolonged response to intravitreal endotoxin. A similar response was observed after IV ET in eyes which had also received intravitreal EBSS, but a typical cellular consensual response was not elicited. It was, therefore, considered unlikely that circulating endotoxin had a significant role in the production of the consensual response to endotoxin.

Histology. The following observations describe the histopathological changes which occurred in the rat eyes after an intravitreal injection of 0.2 μg ET. Pathological changes were also noted in the control eyes after injection of EBSS which were similar to those in the experimental eyes after various doses of ET. Although there was considerable variation in the severity of the changes, there was close-correlation with the clinical findings.

The typical features of an acute inflammatory response characterized the ocular response to endotoxin in the rat. Polymorphonuclear leukocytes (PMN) infiltrated the anterior chamber, the iris and ciliary body, and the superficial

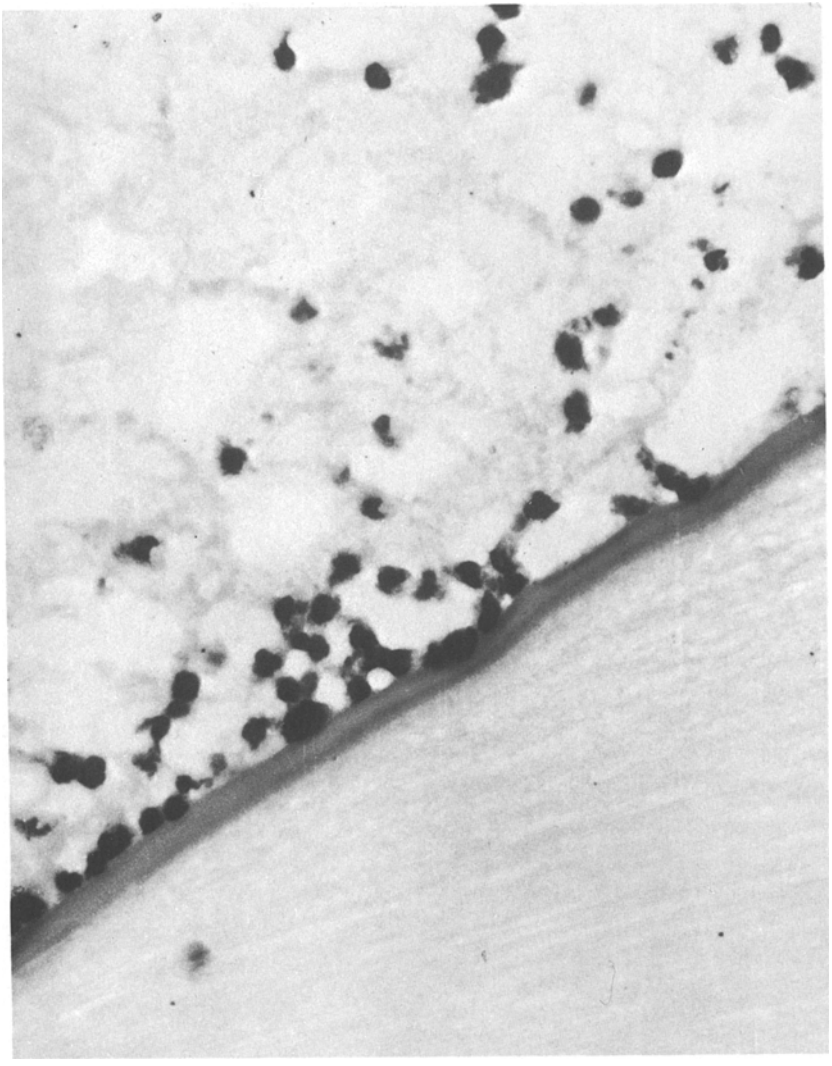

Fig. 3. Infiltration of vitreous cavity with PMN 9 h after injection of endotoxin. Note aggregation of cells along posterior lens capsule and vitreous fibrils (× 450)

layers of the conjunctiva after 3 h. Many of the PMN contained PAS-positive intracellular granules. Between hours 6–9, fibrin deposits increased rapidly to fill the anterior chamber. In addition, PMN had invaded the vitreous (Fig. 3), the gnaglion cell layer of the retina, and the deepter layers of the conjunctiva. A large aggregate of PMN in the posterior chamber corresponded to the clinically observed retroiridial hypopyon (Fig. 4B and montage). Mononuclear cells became more numerous between nine and twelve h and were closely associated with fibrin deposits on the iris surface (Figs. 4B and C). The synechiae seen

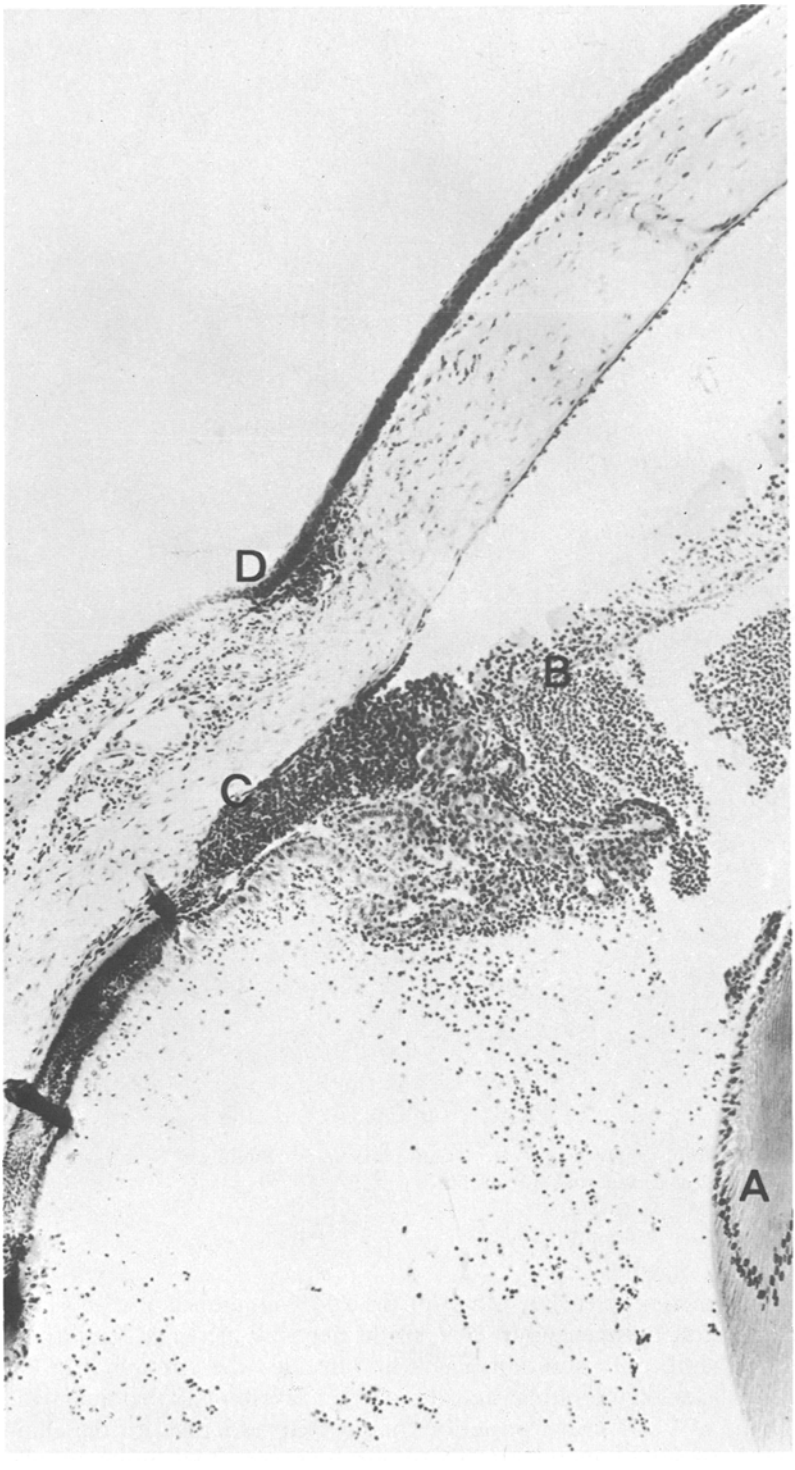

Fig. 4. Montage. Changes in anterior segment of rat eye 12 h after an intravitreal injection of 0.2 μg endotoxin (×27): **A** Transitional zone of lens epithelium, PMN and mononuclear cells adherent to zonular fibers; **B** large PMN aggregate in retoiridial position, (clinical hypopyon), fibrin deposit on anterior iris surface, PMN infiltrated in iris stroma; **C** iris root and outflow channels, heavy infiltration of these structures with PMN and mononuclear cells; **D** Limbus, (note PMN infiltrate)

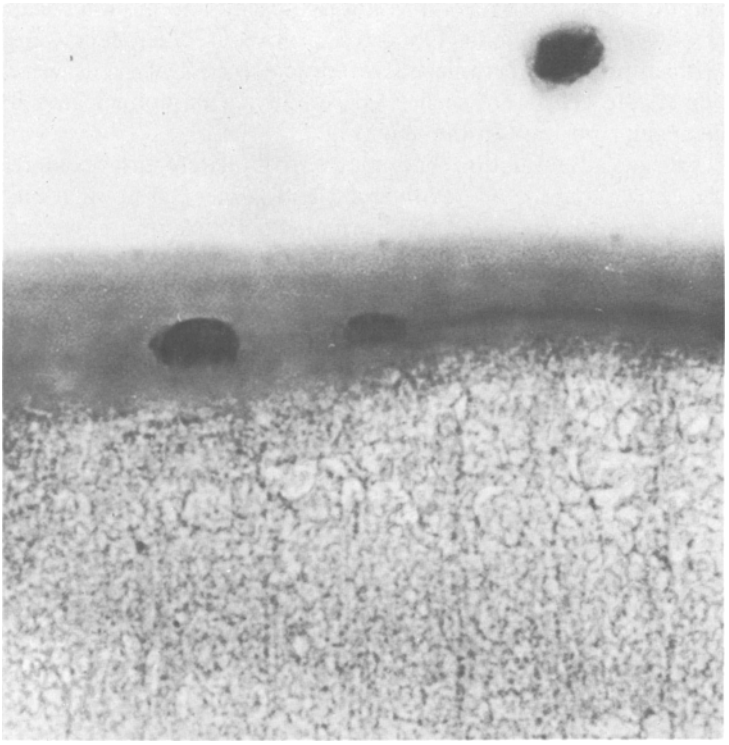

Fig. 5. Endotoxin-treated eye 5 days after injection. Field shows two mononuclear cells, one of which appears to have adopted a subcapsular position, and may have caused some thickening or swelling of the capsule (×850)

clinically were composed of PMN/fibrin aggregates connecting the iris to the anterior lens surface.

Structural changes were observed in a number of ocular tissues at this stage. In the lens, the epithelial cells of the transitional zone and the fibers of the bow region appeared oedematous (Fig. 4A). PMN were also observed in close apposition to the lens surface and on occasion appeared to lie within the capsule. A heavy infiltration of PMN persisted in all layers of the conjunctiva (Fig. 4D) and in some places the conjunctival epithelium was reduced to two layers, with thinning and disappearance of the basement membrane. The corneal epithelium, however, was unaffected in spite of some PMN infiltration of the anterior stromal layers at this stage. Increasing oedema of the ciliary body produced large cystic spaces in the stroma and fibrin microthrombi were visible in almost all vessels.

After 24 h, many PMN had apparently undergone lysis with release of their PAS positive granules and the mononuclear cell population had increased. By 3 days, the total cellular infiltrate was much reduced and was predominantly mononuclear. In the vitreous, mononuclear cells were consistently observed in close association with collagen fibrils, suggesting an adhesive interaction

between the cells and the fibrils. By 5 days, PMN were absent, and mononuclear cells were observed only in the iris, ciliary body, and vitreous. Such cells were moderately sized with appreciable cytoplasm. Infrequent binucleate cells were noted but no multinucleate cells were seen. Occasionally, a mononuclear cell was found in a subcapsular position in the lens (Fig. 5).

After 7 days, signs of inflammation had almost completely disappeared. In particular, the lens bow, conjunctival epithelium, and goblet cell population, and the iris and ciliary body stroma appeared normal. Microthrombi, however, persisted in the ciliary vessels. Occasional mononuclear cells were seen in the anterior chamber angle and the vitreous, particularly on the posterior lens surface.

Discussion

The present report describes the evolution of locally induced endotoxin uveitis in the rat. The acute inflammatory response to intravitreal ET was highly reproducible, and its intensity and duration were dose-dependent. The ET effects in the rat closely paralleled a similar uveitis in rabbits produced by the local injection of ET (Pappas and Smelser, 1959). Indeed, the ocular response to the intravitreal injection of ET in both the rabbit and the rat was very similar to the acute inflammatory response which occurred in the skin after intradermal injection of ET (Taichman et al., 1966). In each case there was capillary dilation, endothelial damage, fibrin deposition, and microthrombi in the vessels, and PMN cell invasion at an early stage followed by mononuclear cell predominance. The response, however, was of much shorter duration in the skin than the eye, which may have been a reflection of local sequestration of ET in the eye.

During the course of endotoxic uveitis in the rat, several significant alterations occurred to particular ocular tissues. Dilation and microthrombi of all ocular vessels was prominent at some stage, but the ciliary vessels alone remained occluded after the inflammation had subsided. This is in agreement with the known long-term increase in capillary permeability which occurs in rabbit ciliary vessels after IV ET (Levene and Breinin, 1959; Howes and McKay, 1973). The effect of local ET-induced inflammation on the conjunctiva was marked by PMN accumulation in the stroma and thinning of the epithelium which recovered after the inflammation had subsided. Although stromal PMN infiltration occurred in the cornea, there was no similar reduction in corneal epithelialization.

Changes to the lens included adherence to, and possible infiltration of the lens capsule by PMN and mononuclear cells. Vascular changes and cellular infiltration of the retina and vitreous were also prominent, and in particular it was interesting to observe the persistence of mononuclear cells in the vitreous compared to the aqueous or angle. It is possible that the adherence of such cells to vitreous collagen may initiate the process of vitreous detachment in inflammatory eye disease.

In addition to the local effects of ET, the rat eye was apparently subject

to vascular changes after a single IV dose of ET. In earlier reports, the rat was considered refractory to IV ET because of the failure to produce the generalized Shwartzman reaction (Apitz, 1935) or an ocular response (Ayo, 1943). However, the generalized Shwartzman reaction can be produced in pregnant rats in the third trimester (Kaley et al., 1962) and in nonpregnant rats if the injection of ET is followed by an IV infusion of saline (Theiss et al., 1975). This study has shown that an ocular response can be elicited in the rat eye if the IV dose of ET is sufficiently high, or if it is accompanied by an infusion of saline. However, the absence of a marked cellular response and the considerably shorter duration distinguished this form of ET ocular inflammation from that induced by local injection.

Of greater clinical interest, perhaps, was the observation of a dose-dependent consensual response in the control EBSS-treated eye. This response required both the presence of ET in the test eye and the insertion of a needle into the control eye. The severity of the response was also clearly related to the concentration of ET in the test eye. However, it was apparently unrelated to contaminants in the EBSS, to the trauma of injection, or to the presence of circulating endotoxin. Consensual responses in the untreated eye have been observed under several experimental conditions, including irradiation of the eye (Zygulska-Mach and Mach, 1975), local application of prostaglandins (Beitch and Eakins, 1969), stimulation of the contralateral fifth cranial nerve (Perkins, 1957), trauma to the fellow eye (Magitot, 1923; Le Plat, 1924), and anterior chamber paracentesis (Kottow and Seligman, 1978). A consensual ocular response has also been observed following the injection of bacterial filtrates (Guillery, 1911) which presumably contained high concentrations of ET. Perkins (1957) detected a consensual rise in intraocular pressure and an increase in aqueous protein and ocular temperature in the control eye after stimulation of the contralateral fifth nerve. Since these effects were abolished by cutting the fifth nerve to the consensually responding eye, he suggested that the effects were produced via a nervous reflex arc.

More recently the dependence of the ocular injury response on an intact axon reflex mechanism has been established (Butler et al., 1979) and it has been suggested that the common factor relating chemical mediators of ocular inflammation to the sensory nerve terminals may be the release of substance P (Butler, 1979). In our experiments the consensual response was unrelated to circulating ET, while the time course was sufficiently rapid to be compatible with a reflex arc mechanism, particularly since ET is known to release locally large quantities of intraocular prostaglandins (Bito, 1974). Studies by Beitch and Eakins (1969) have provided further support for a neuronal mechanism in prostaglandin-induced consensual responses.

ET, however, may produce ocular inflammation by several other mechanisms besides prostaglandin release. Activation of leukocytes (Horn, 1973) or platelets (Howes et al., 1973), release of catecholamines (Howes and McKay, 1972), and Hageman factor activation with vascular thrombosis and kinin formation (Morrison and Cochrane, 1974) are all induced by ET. Intraocular inflammatory responses produced by local and systemic injection of ET have different manifestations, at least in terms of the cellular response, which may be indicative

of different mechanisms. However, it is likely that the primary cellular mechanism is similar, since ET has a high affinity for binding to plasma cell membranes, particularly leukocytes (Chando, 1973). IV ET is rapidly removed from the circulation by PMN, and local ET produces a rapid PMN chemotactic response. Thus cellular mechanisms may be as important as the release of chemical mediators in the ocular response to ET.

The present study describes a simple, reliable, and reproducible method for the induction of nonimmunogenic uveitis in the rat eye using *Shigella* ET. The most significant observation however was the presence of a dose-dependent consensual ocular response. A relationship between experimental models of this nature and clinical sympathetic uveitis in which immunological mechanisms are of great importance is difficult to establish. However, it is possible that all consensual ocular responses are generated by a common mechanism whether the original injury be mechanical, chemical or immunological. The present study has, therefore, provided a further model for the study of the interocular transfer of inflammatory disease.

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