15849 P

Streptomycin in Experimental Ocular Infections.*

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Leopold and Nichols[1] have demonstrated that streptomycin administered to rabbits in dosages of 10,000 μg per kg body weight appears in the conjunctiva, sclera, extraocular muscles and aqueous humor. Much larger doses were necessary to obtain detectable amounts in the posterior segment of the eye. The intact cornea is not penetrated. Following abrasion, or by means of iontophoresis, streptomycin is found in the aqueous humor.

In the experiments to be described, rabbits were anesthetized by intravenous injection of nembutal. The streptomycin† of desired strength was applied as a saline solution, except where noted as the dry powder.

This paper reports the following observations:

1. Factors increasing penetrability through the cornea: We confirmed Leopold and Nichols'[1] observation that streptomycin does not penetrate the normal cornea, but does following abrasion and upon iontophoresis.

In our experiments with the abraded cornea, 100 μg per ml aqueous were obtained when a constant corneal bath of 10,000 μg streptomycin was applied for 2 hours. Iontophoresis of the unabraded cornea (22 v., 2 ma., anode to solution cup) for 30 minutes with a solution of the same concentration gave 25 μg per ml aqueous.

Increased penetrability occurred in the inflamed cornea. Values of between 25 and 200 μg per ml aqueous were obtained in 15 to 60 minutes following application of a bath containing 10,000 μg streptomycin per ml. This variation is related more to the size of the lesion than to duration of application.

In the intact eye, the addition to the corneal bath of one drop of 0.5% Areosol O.T. per ml of streptomycin solution resulted in increased penetration simulating values obtained upon abrasion. With a solution containing 10,000 μg of streptomycin per ml, 25 μg per ml of aqueous were obtained in 2 hours; with a bath concentration of 50,000 μg, values of 25 to 50 μg were obtained in 30 to 60 minutes. If 10 drops Areosol solution were added per ml of streptomycin solution, values of over 100 μg were obtained, with definite damage resulting to the cornea.

2. Local toxic effect upon application to the eyeball: In the abraded corneas as established by fluorescein staining, 3 instillations per day of a streptomycin solution containing 10,000 μg per ml produced no delay in healing, whereas a solution containing 50,000 μg per ml, or the use of the dry powdered streptomycin caused a definite retardation of healing to at least twice the normal period. With the higher concentrations, scar formation and vascularization also occurred.

3. Effect of intraocular injection: Direct injection of 0.1 ml streptomycin saline solution in concentrations varying from 250 to 10,000 μg per ml into the center of the vitreous humor produced negligible opacities when observed by means of the ophthalmoscope and slit-lamp. Inoculation by injection of 0.1 ml of a 24-hour broth culture of a virulent strain of *Str. pyogenes* simultaneously with the streptomycin solution resulted in complete protection against infection. This was true if the streptomycin was administered intravitreally up to 6 to 8 hours following inoculation. The control infected eye progressed to eventual abscess formation.

* This research was done under a contract between the Navy Program for Basic Research and Northwestern University.

1 Leopold, I. H., and Nichols, A., *Arch. Ophth.*, 1946, **35**, 33.

† We are indebted to Dr. Donald Robertson, Associate Medical Director, Merck & Co., Inc., Rahway, N.J., for the streptomycin used in this investigation.

4. Treatment of experimental *B. pyocyaneus* infections of the cornea: Ulcers of uniform severity were produced by inoculation of the cornea with a 24-hour broth culture of a virulent strain of *B. pyocyaneus*. Treatment consisted of 3 applications (drops) at 2-hour intervals of streptomycin solution containing 10,000 μg per ml. This form of treatment afforded complete protection when commenced within 6 hours following inoculation. The infected control eyes uniformly progressed to complete destruction of the cornea.

Summary. 1. The penetrability of streptomycin through the cornea may be increased by abrasion, inflammation, ion-transfer and wetting agents. 2. No local toxic effects were noted when saline solutions of streptomycin containing up to 10,000 μg per ml were used. With concentrations of 50,000 μg or as a dry powder, delayed healing occurred. 3. Intraocular injection, in amounts up to 1,000 μg of streptomycin in 0.1 ml saline were well tolerated. Smaller amounts (25 to 300 μg) were therapeutically effective up to 6 to 8 hours against a virulent strain of *Str. pyogenes,* though transient or negligible vitreous opacities occurred with these concentrations. 4. Experimental corneal ulcers produced by injection of *B. pyocyaneus* were prevented when treatment was started within 6 hours after inoculation by 3 applications at 2-hour intervals of a saline solution of streptomycin containing 10,000 μg per ml.

15850

Further Studies on the Mechanism of Alloxan Diabetes, Pancreatectomy and Alloxan.*

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The experiments to be presented here were performed in an attempt to investigate further the significance of the initial blood sugar fluctuations after alloxan and the character of the ensuing diabetes. To be more specific, they concern the problems of the pancreatic origin of the alloxan hypoglycemia and the interrelationship of external and internal pancreatic secretion in the development of alloxan diabetes.

The typical triphasic fluctuation of the blood sugar after a diabetogenic dose of alloxan is well known. An initial hyperglycemia is followed within a few hours by a secondary hypoglycemic phase which may last from 6 to 10 hours and after which the final persistent hyperglycemia and glycosuria develops. It is important to emphasize that the 2 initial phases, especially the secondary hypoglycemia, vary in severity with different species. In the dog for instance these fluctuations are rather mild and asymptomatic, while the rabbit is thrown into severe hypoglycemic shock and convulsions which it survives only if large amounts of glucose are given repeatedly over several hours.

The hyperglycemic phase is absent in adrenalectomized rabbits[1] and depends to a certain degree on the nutritional state of the animals and the glycogen stores of the liver. It is absent, too, in hepatectomized animals.[2] The explanation that it is extrapancreatic in origin[1] has found general confirmation and acceptance.

The secondary hypoglycemia starts at about the same time when histological examination of the pancreas begins to discover degenerative changes in the beta cells as

* This work has been supported by grants from the Douglas Smith Foundation for Medical Research and from the Eli Lilly Research Laboratories, Indianapolis.

1 Goldner, M. G., and Gomori, G., *Endocrinology,* 1944, **35**, 241.

2 Houssay, B. A., Orias, O., and Sara, T., *Science,* 1945, **102**, 197.