Summary

Two different kinds of aberrant nerve fibres of the optic nerve are described, they are found between retina and hexagonal cells. One type involves maldevelopment of the posterior retinal layers in front of the growth. This was a case of a pigmented tumour of the optic disc infiltrating into the neighbouring retina and choroid. It is assumed to be a malignant degeneration of a pigmented naevus of the optic disc. The second is a case of hypertensive retinopathy with oedematous swelling of the papilla and a big druse. The nerve fibre tissue found between retina and pigmented epithelium is ganglioform degenerated. The retina in front of this tissue is well developed. A mechanical pushing out of the optic nerve fibres due to the oedema and the pressure of the druse is assumed to be the cause.

LITERATURE

MANN, IDA.—Development of the human eye. Cambridge, 1928.
——— Developmental abnormalities of the human eye. Cambridge, 1937.
SCHEERER.—*Klin. Monatsbl. f. Augenheilk.*, Vol. LXXI, p. 674, 1923.
SNEED.—*Arch. f. Augenheilk.*, Vol. LXXVI, p. 117, 1914.
VON SZILY.—*Zeitschr. f. Anatomie*, Vol. LXXIV, p 1, 1924 (reprint).

THE EFFECT OF DETERGENT ON THE PENETRATION OF SODIUM SULPHACETAMIDE (ALBUCID SOLUBLE) INTO OCULAR TISSUES*

BY

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IT has been shown recently (Bellows and Gutman, 1943; Leopold and Scheie, 1943) that the penetration of sulphonamides applied locally to the eye can be increased by various wetting agents.

In a number of investigations (see Robson, 1944; Robson and Scott, 1944) it has been found that experimental infections of the cornea with various organisms can be treated successfully by the local application of a number of sulphonamides, the most satisfactory results being observed with sodium sulphacetamide. This substance penetrates readily into the cornea and does not produce any irritation. The present experiments were carried out to determine whether the penetration of sodium sulphacetamide can be

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increased still further by the use of a wetting agent. In addition investigations were performed to localise the site of action of the agent and if possible to obtain some information on its mode of action.

Methods

Experiments were performed on mature rabbits of various breeds and both sexes.

Ten per cent. solutions of sodium sulphacetamide in water and freshly made 0·1 per cent. solutions of duponal ME dry in water were used throughout. Duponal ME (minimum electrolyte) dry is a detergent derived from technical lauryl alcohol.

In the first series of experiments, the drug was applied by means of celluloid funnels, as described by Robson and Tebrich (1942). The solutions were applied to the anaesthetised animal for 6 minutes, 10 per cent. sodium sulphacetamide to one eye, and 10 per cent. sodium sulphacetamide + 0·1 per cent. duponal to the other eye of the same rabbit, after which the funnels were removed and the eyes excised and dissected for analysis. Similar experiments were also performed on eyes with denuded corneae, and on excised eyes. The cornea was denuded by removing all the epithelium with a fine knife, care being taken not to injure the substantia. In the experiments on excised eyes, the funnel was sewn in place in the dead animal (immediately after killing), and incisions were made through the lids so that the eye together with the lids could be excised, with the conjunctival sac intact and the funnel in position. The funnel was clamped vertically and the eye supported on a pad of cotton wool.

In the second series of experiments drops were instilled into the conjunctival sac. As the volume of the drops is smaller in the presence of the wetting agent, a definite volume of the solution was applied as follows:—0·1 ml. of one solution was instilled into the conjunctival sac of one eye, and the lids then gently closed and opened for 20 seconds. Two minutes later, 0·1 ml. of the other solution was instilled into the other eye under the same conditions. The rabbits were killed and the eyes excised and dissected for analysis 15 minutes, 1 hour and 3 hours after the application of the drug. The two solutions were alternately used first in different rabbits in order to cancel out any possible errors due to reduced circulation, caused by loss of blood in the removal of the first eye. (Subsequent experiments suggest that this is negligible.)

In all cases the eyes were washed in saline immediately after removal and dried on blotting paper. The various tissues were then dissected off, rapidly washed in saline, and dried on blotting paper.

In the third series of experiments the effect of duponal on the penetration of sodium sulphacetamide into excised parts of the eye was investigated. Throughout these experiments *in vitro*, the excised eye, or parts of the eye, were kept moist by bathing as much as possible in a solution similar to the anterior chamber fluid (see Duke-Elder, 1927) and containing the following substances in the following percentage concentrations: NaCl (0·71); KCl (0·038); $CaCl_2$ (0·017); glucose (0·1).

In these experiments, the eye was excised and cleared of muscle and conjunctiva. It was then opened at the posterior pole so that

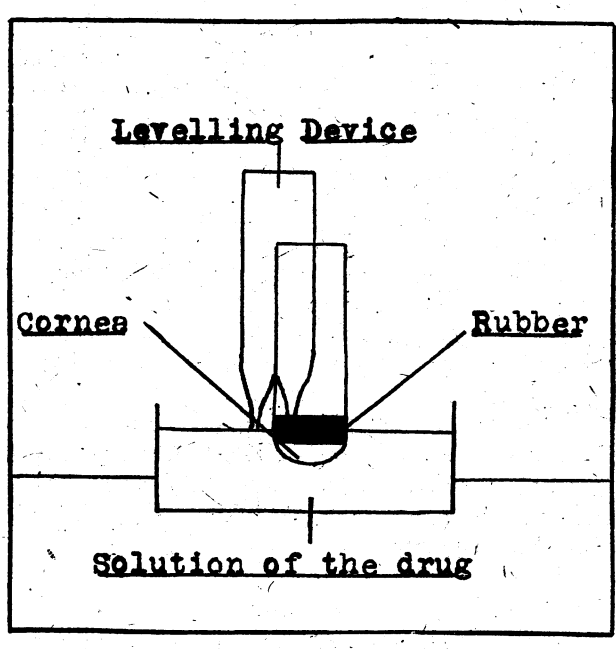

FIG. 1.

Method used for studying the permeability of tissues.

the cornea and sclera together formed a sac, from which the lens, iris, choroid, and retina were removed. The sac was drawn over the end of a small glass tube, of diameter slightly smaller than that of the cornea, so that the cornea, excluding the limbus, formed a membrane over the mouth of the tube (see Fig. 1). The membrane was secured in position by a loop of silk thread, which was covered with tightly bound layers of elastic insulating rubber. 0·8 ml. of the anterior chamber fluid was placed inside the tube which was lowered into a solution of the drug; the levels were adjusted by means of a small perspex slip, cut so that it had two equal legs and a slit so that it could move freely up and down the

side of the glass tube: the level of the solution inside the tube was the same as that outside, when both legs were just touching the solutions. After 5 and 15 minutes the contents of the tube were stirred by a stream of air from a syringe and 0·1 ml. of the fluid removed for analysis. The drug content of the tissue was also estimated after 15 minutes. This method was used for studying the penetration of sodium sulphacetamide through the cornea, the sclera, and the denuded cornea.

The chemical analysis was based on the method of Bratton and Marshall (1939), and the preparation of tissue extracts on the method described by Bellows and Chinn (1939). The weighed tissues were ground with washed silver sand and 4 ml. of 15 per cent. trichloroacetic acid. Each suspension was washed into a tube calibrated at 20 ml. After standing for at least 30 minutes it was filtered through a Whatman No. 2 filter paper and the residue washed with 5 ml. of distilled water. The filtrate was made up to a volume of 25 ml.; 10 ml. of the solution was diazotised and coupled. For concentrations greater than 0·1 mg. per cent. in the filtrate, readings were taken on a visual colorimeter; for smaller concentrations a Spekker photoelectric absorptiometer was used. The concentrations in the aqueous were usually too low to be estimated by this method, and the following method was adopted: 0·4 ml. of 15 per cent. trichloroacetic acid was added to the aqueous and the mixture transferred to a calibrated centrifuge tube and made up to 2 ml. After centrifuging for 10 minutes to sediment the small amount of protein precipitated, 1 ml. was transferred to a weighing bottle where it was diazotised and coupled, using 0·1 ml. of reagent; readings were taken using the micro cell of the Spekker absorptiometer.

Results

The results of six experiments in which 10 per cent. solutions of sulphacetamide were applied to one eye, and similar solutions containing 0·1 per cent. duponal to the other eye, are shown in Table I. The drugs were applied for 6 minutes by means of the funnels. The mean results for three similar experiments performed on excised eyes and for three experiments *in vivo* on eyes with denuded corneae are also shown. With solutions containing duponal, the amount of drug in all the tissues is greatly increased. There is no significant difference between the results for the experiments *in vivo* and *in vitro*, except in the case of the conjunctiva; in that tissue there is a higher concentration of the drug in the isolated eye. This difference is probably due to the fact that in the living animal appreciable amounts of the drug are taken by the blood passing through the vascular conjunctiva.

The results for eyes with denuded cornea show that removal of the epithelium leads to a great increase in the permeability of the cornea. The detergent has no effect on the permeability of the denuded cornea, but its effect on the penetration of the drug into the conjunctiva remains, of course, unchanged.

TABLE I

Concentrations of sulphacetamide in the ocular tissues (mg./100 gm.) after the application of 10 per cent. solutions of sodium sulphacetamide with or without detergent in the funnel for 6 minutes.

S + D = 10 per cent. sodium sulphacetamide + 0·1 per cent. Duponal M.E dry.
S = 10 per cent. sodium sulphacetamide alone.

Tissue	Funnel expt. *in vivo* Normal cornea		Funnel expt. *in vivo* Denuded cornea		Funnel expt. *in vitro* Normal cornea	
	S + D mg. %	S mg. %	S + D mg. %	S mg. %	S + D mg. %	S mg. %
Conjunctiva	391	127	531	353	1330	400
Cornea ...	349	191	1250	1190	370	145
Aqueous ...	29·1	6·4	336	422	16·3	4·8
Iris	20·7	14·0	184	238	42·9	18·5
Sclera ...	170	29·3	132	180	202	59·8

The results of the experiments with drops are shown in Fig. 2. The concentration of the drug, in mg./100 gm. of tissue, is plotted against the time elapsing between the instillation of the drops and the removal of the eye for analysis; each point represents the mean of five experiments. In all cases the presence of duponal leads to an increased penetration of the drug into the tissues; the concentrations in these cases then gradually fall to the control values. The aqueous differs from the tissues in that the drug content reaches a maximum after 1 hour as compared with 15 minutes in the tissues; this is probably due to the time taken for the drug to diffuse through the tissues into the aqueous. As might be expected, the external tissues, *i.e.*, the conjunctiva and the cornea, contain more of the drug than the iris and the sclera; the lowest concentrations were found in the aqueous.

Table II shows the results for the *in vitro* experiments with the individual tissues; these results are shown in Fig. 3, in which the uptake of the drug by the tissues in the various experiments are compared. In the intact cornea there is, in the presence of

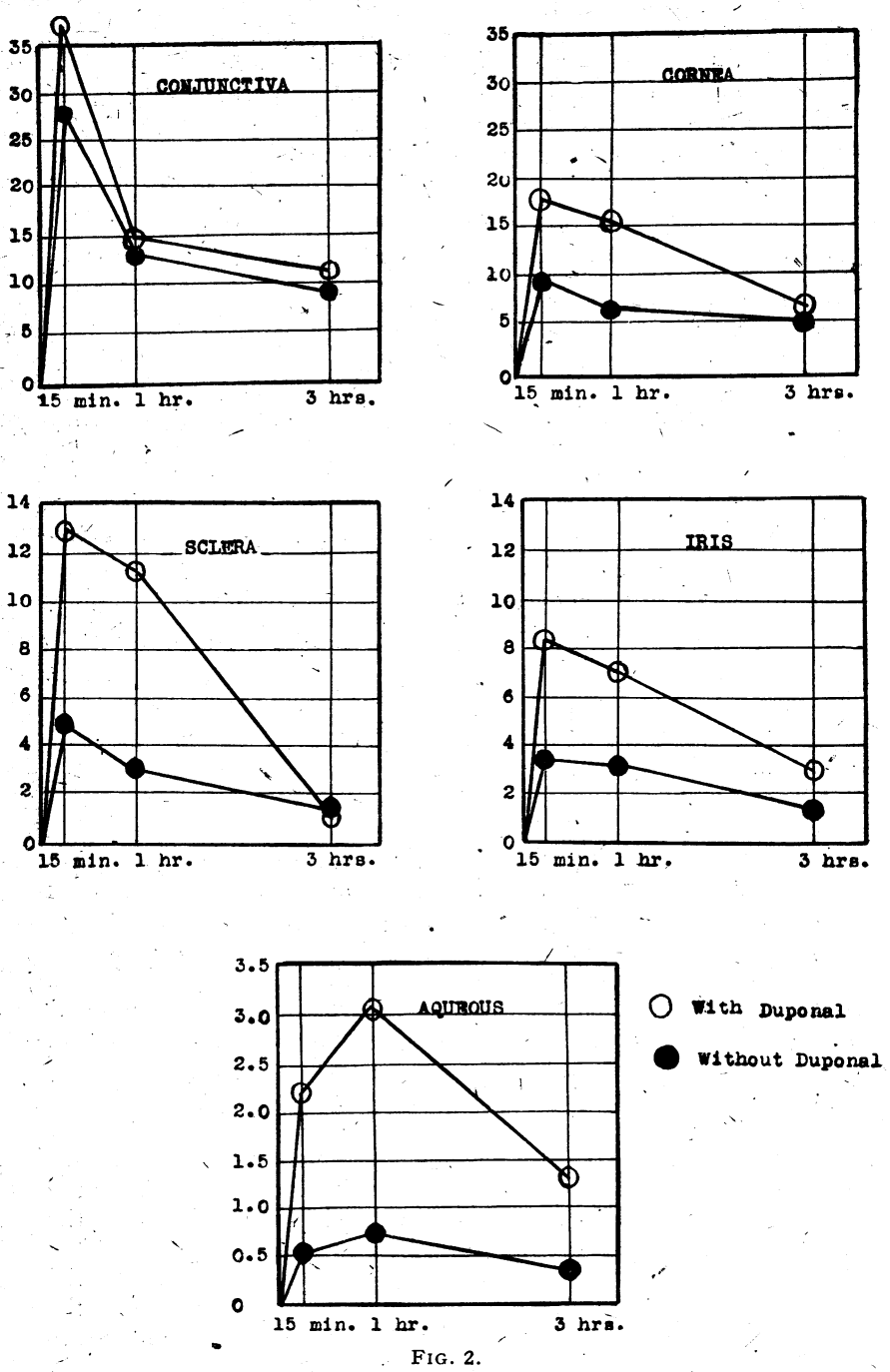

FIG. 2.

Concentration of sulphonamide (in mg. per cent.) in the ocular tissues, 15 mins., 1 hour and 3 hours after the application of 0·1 ml. of a 10 per cent. solution of sodium sulphacetamide alone, and with 0·1 per cent. Duponal.

TABLE II

Showing the effect of Duponal on the passage of sodium sulphacetamide through the cornea *in vitro*. The second and third columns show the concentrations attained in the cornea with and without Duponal, while the fourth and fifth columns show the corresponding concentrations in the artificial a.c. fluid. Each figure is the mean of three results.

Tissue	Concentration of sodium sulphacetamide in mg./100 gm.			
	Tissue after 15 minutes		A.C. Fluid after 15 minutes	
	With Duponal mg. per cent.	Without Duponal mg. per cent.	With Duponal mg. per cent.	Without Duponal mg. per cent.
Intact cornea	803	357	29·5	8·3
Denuded cornea	3440	3620	200	210
Sclera ...	3240	3660	152	218

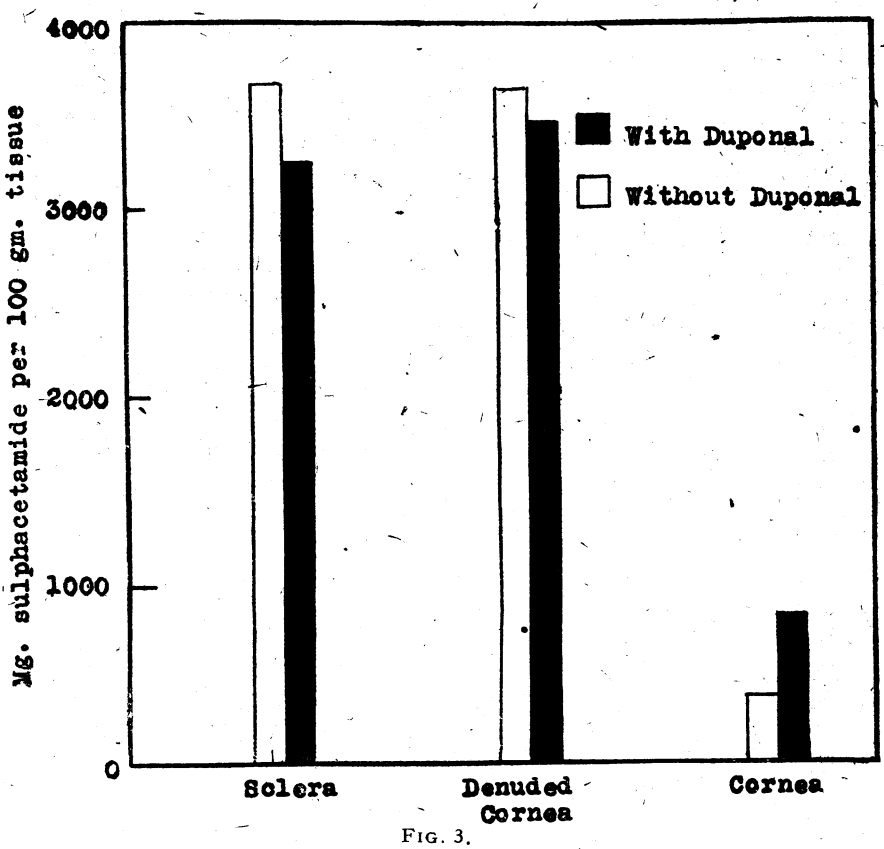

FIG. 3.

Concentrations of sulphacetamide in the sclera, denuded cornea, and the intact cornea, after 15 mins. in a 10 per cent. solution of sodium sulphacetamide, with or without Duponal. Experiments *in vitro*.

duponal, a marked increase both in the amount of drug which is taken up by the tissue, and the amount which passes through it. In the case of the sclera and the denuded cornea (both of which differ from the cornea in that they do not possess an epithelium), there is no increase either in the uptake by the tissue or in the amount passing through, in the presence of duponal. In these experiments the concentrations of the drug reached in the tissue and the anterior fluid were much greater than in those carried out with the intact cornea. It can thus be concluded that the epithelium acts as a barrier to the passage of the drug into the cornea, and the wetting agent may increase the rate of penetration of the drug by overcoming this barrier.

Discussion

These experiments show that by the use of a detergent, the penetration of sodium sulphacetamide into the ocular tissues can be appreciably increased, a result in agreement with those reported by Bellows and Gutman (1943) and Leopold and Scheie (1943) for other sulphonamides. An analysis of the data strongly suggests that the action of the detergent is exerted essentially on surface epithelium. This seems to be the most important barrier to the passage of drugs into and through the cornea and when the epithelium is removed the amount of drug which passes through the cornea is markedly increased. The detergent does not increase the passage of the sulphonamide through the substantia propria or through the sclera, and it is of interest that other experiments have shown that it does not affect the passage of the drug through gelatine gels.

It is evident that by the use of a detergent it is possible not only to increase the concentration of sodium sulphacetamide in the anterior ocular tissues, but also to prolong the period during which an effective chemotherapeutic concentration is maintained. This is clearly brought out in the experiments with drops and the curves in Fig. 2 show how appreciable these effects are in the case of the cornea, iris and aqueous.

These results suggest that a combination of sulphonamide and detergent might be of value in the local treatment of infections of the anterior part of the eye, especially when these involve the cornea and possibly the iris; the combination should also be of value in cases of injuries of the anterior part of the eye. It has been shown that the addition of duponal to sodium sulphacetamide increases its effectiveness in the treatment of experimental corneal ulcers produced by streptococcus haemolyticus (Robson and Scott, 1944). Clinical trials are now in progress.

Summary

1. The penetration of sodium sulphacetamide into the ocular tissues has been studied, both in living rabbits and in isolated ocular tissues.

2. Application of the drug with a wetting agent, Duponal ME dry, increases the penetration of sodium sulphacetamide into and through the cornea.

3. Removal of the corneal epithelium causes a great increase in the penetration of the sulphonamide into and through the cornea, *i.e.*, the epithelium acts as a barrier to the passage of the drug.

4. The wetting agent does not increase the passage of the drug into the denuded cornea (*i.e.*, the cornea with the epithelium removed). It may be concluded that the wetting agent acts by overcoming the epithelial barrier.

5. The results suggest that addition of a wetting agent to sodium sulphacetamide would be of most value in infections of the cornea and iris.

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REFERENCES

BELLOWS, J. G. and CHINN, M. (1939).—*Jl. Amer. Med. Assoc.*, Vol. CXII, p. 2023.
BELLOWS, J. G. and GUTMAN, M. (1943).—*Arch. Ophthal.*, Vol. XXX, p. 352.
BRATTON, A. C. and MARSHALL, E. K. (1939).—*Jl. Biol. Chem.*, Vol. CXXVIII, p. 537.
DUKE-ELDER, S. (1927).—*Biochem. Jl.*, Vol. XXI, p. 66.
LEOPOLD, I. H. and SCHEIE M. G. (1943).—*Arch. Ophthal.*, Vol. XXIX, p. 811.
ROBSON, J. M. (1944).—*Brit. Jl. Ophthal.*, Vol. XXVIII, p. 15.
ROBSON, J. M. and SCOTT, A. A. B. (1944).—*Brit. Jl. Exp. Path.*, Vol. XXV, p. 81.
ROBSON, J. M. and TEBRICH, W. (1942).—*Brit. Med. Jl.*, i, 687.

A MODIFICATION AND EXTENSION OF THE McREYNOLDS' OPERATION FOR PTERYGIUM*

BY

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M.E.F.

THE operation for the removal of pterygium is probably one of the commonest ophthalmic operations performed in South Africa and the Middle East. The condition occurs more commonly in male adults, but is not uncommon in females and it is seen at all ages from puberty to old age.