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COMMUNICATIONS

THE SULPHONAMIDES IN EXPERIMENTAL OCULAR INFECTIONS

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1.—General Considerations

EXPERIMENTAL studies on the value of the sulphonamides in ocular infections raise a series of distinct problems. In the first place the relative specificity of the sulphonamides against a limited group of organisms imposes the task of establishing the value of these drugs against the organisms commonly seen in ocular infections. *In vitro* experiments give some indication, but results obtained by this approach are not necessarily applicable clinically. *In vivo* experiments to extend these test-tube findings present the first difficulty that confronts the ophthalmologist, for most of the organisms commonly seen in ocular infections do not give clear-cut lesions in the experimental animal. In fact the only classical experimental corneal lesion that can be induced in the rabbit is from inoculation with *B. pyocyaneus*, though there is now evidence that certain strains of *staphylococcus aureus* introduced beneath the corneal epithelium may also be effective (Robson and Scott, 1943). There is less difficulty in inducing intra-ocular infection, for many organisms introduced into the anterior

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chamber or vitreous give a ready result. None the less, the experimental study of ocular infection, and especially corneal infection, is severely limited owing to the absence of suitable techniques for producing experimental lesions. It is for this reason that studies on the value of the sulphonamides in corneal infection are confined almost entirely to lesions produced by *Bacillus pyocyaneus*, though clinically this is a rare occurrence.

The other ophthalmological problems in studies on the value of the sulphonamides centre around the question of concentration reached in the eye by the administration of these drugs. Not all medications pass through the blood-aqueous barrier, as is well known from the failure of the arsphenamides to reach the eye. In determining the permeability of the eye to the sulphonamides in the bloodstream, comparative studies have therefore to be carried out with the various sulphonamides not only to establish their relative capacity to penetrate into the eye, but also their rate of excretion from the eye, for the maintenance of an adequate level of concentration of these drugs for a prolonged period is an essential therapeutic requirement. The possibility of reaching adequate therapeutic levels of concentration by the local application of these drugs also calls for attention. This involves in the first place a study of the relative tolerance of the eye to the various sulphonamides when applied locally and the relative capacity of the eye to absorb these drugs. Finally, *in vivo* experiments have to establish which of the various sulphonamides are most effective for such experimental lesions as can be produced, and whether the general or the local administration of such drugs is the more effective.

No systematic survey covering all these problems has as yet appeared, but valuable studies have been recorded by a number of observers on various aspects of these inter-related problems. By far the greatest number of these studies are concerned with the tolerance of the eye to the various sulphonamides and the relative concentrations that the different sulphonamides reach in the ocular tissues, when these drugs are administered locally or by mouth. Elsewhere (Sorsby, 1942) a survey of this literature has been given, and here it is only necessary to bring out the following salient features :—

(1) Sulphanilamide is well tolerated by the eye when instilled into the conjunctival sac or introduced into the anterior chamber in saturated solution (0.8 per cent.). Sulphanilamide ointment 5 per cent. is also well tolerated when introduced into the conjunctival sac, and insufflation of sulphanilamide powder does not appear to be deleterious.

(2) The various sulphonamides are not equally effective in penetrating into the eye from the bloodstream. Generally speaking

the aqueous level of sulphanilamide and sulphapyridine are about two-thirds of the blood level, that of sulphadiazine one half, and that of sulphathiazole one fifth.

(3) On local administration of sulphanilamide solution the levels of concentration in the aqueous are considerably lower than that obtainable by oral administration, and even such levels are not readily maintained owing to the great diffusibility of these drugs, but levels very much in excess of those reached by oral administration are obtained by the insufflation of sulphanilamide powder into the conjunctival sac. Sulphanilamide ointment (5 per cent.) in a suitable base and the soluble sulphanilamide preparation, sodium sulphacetamide, also gives a higher aqueous concentration than is obtainable by oral administration, whilst the corneal concentration level is exceptionally high. It is difficult to obtain high aqueous concentrations from a local administration of sulphapyridine, sulphathiazole and sulphadiazine. Such clinical data as are available show that the local absorption of sulphanilamide is rather bizarre.

It thus appears that higher aqueous levels and considerably higher corneal levels can be reached with various non-irritating local applications than by oral administration of the sulphonamides. If the level of concentration of the sulphonamides is the determining factor in the treatment of an infection, local treatment of corneal and intra-ocular infection is preferable—on *a priori* grounds—to general treatment, not only because of its avoidance of symptoms of drug intoxication, but also because of the opportunity it offers of reaching levels of concentrations locally that could not be obtained by general administration.

2.—Experimental Control of Corneal and Intra-ocular Infection

REVIEW OF LITERATURE

Only a few studies on the value of the sulphonamides in ocular infections are available. *In vitro* studies by Joy (1942) on four different strains of *B. pyocyaneus* showed both sulphanilamide and sulphapyridine ineffective against one particular strain; the two drugs were equally effective against one other strain; and for the two remaining strains sulphapyridine was superior to sulphonilamide.

1. EFFICACY OF GENERAL ADMINISTRATION.

(a) *Streptococcus haemolyticus*.—Streptococci (1:1000 dilution of a 24-hour culture in peptone and horse serum, the resulting suspension containing about 5 organisms in each high-power field) injected in quantities of 0.05 c.c. into the anterior chamber of [? three] rabbits produced an infection which in control animals

led to the loss of the eye, but in rabbits treated with sulphanilamide was readily overcome. Infection of the vitreous was not so well controlled. If sulphanilamide was given 24 hours before the inoculation experiments, the anterior chamber showed no reaction and the vitreous infection was milder. The vitreous reaction could be made to increase or decline by withholding or increasing the dose of sulphanilamide. When fully developed infection is present sulphanilamide has no effect (Rambo, 1938).

The time-factor in the administration of sulphanilamide and the quantity of infecting material are stressed by Venco (1939), who also found sulphanilamide protective in rabbit experiments.

(b) *B. pyocyaneus*.—Joy (1940 and 1942) carried out an extensive investigation on the value of sulphapyridine in *B. pyocyaneus* inoculation in the cornea of rabbits (the right cornea of 64 rabbits and both corneae of 110 rabbits were used). His results varied with the time when treatment was instituted. When sulphapyridine was given prophylactically (two doses in 24 hours) infection was not prevented, but its course was materially influenced. In such cases if treatment is continued for 24 hours inflammation rapidly subsides, though viable organisms still remain, as is seen from the fact that in 70 per cent. of cases relapse occurs, and this incidence is reduced to 7 per cent. if treatment is prolonged beyond 24 hours. Treatment instituted concurrently with inoculation was probably as effective as prophylactic treatment, whilst the results obtained with treatment instituted after six hours were distinctly better than those obtained with treatment begun after 18 hours, though these, too, compared favourably with the lesions seen in the untreated control eyes. Joy also noted that the concentration of the drug in the blood proved extremely variable both in different rabbits and in the same animal on different days; in general there was no relation between the concentration and the course and end result.

v. Sallmann (1942) administered sulphadiazine (0.2 g/K for 1-3 days) to 9 rabbits 18 hours after inoculation. In seven the infection was not controlled, and in the remaining two it was checked only temporarily; ultimately hypopyon developed.

2. EFFICACY OF LOCAL TREATMENT.

(a) *Streptococcus haemolyticus*.—Rambo (1938) studied the effect of sulphanilamide injected into the anterior chamber or vitreous simultaneously with a suspension of streptococci. In three out of four eyes in which 0.02 gm. of sulphanilamide in suspension was introduced into the anterior chamber the organisms produced no reaction; in the fourth eye infection was delayed for 5 days. In contrast no control of infection beyond delay in the development of the process could be obtained by the

simultaneous injection of infecting organisms and sulphanilamide into the vitreous. That the control of the anterior chamber infection was due to the local action of the sulphanilamide was shown by the fact that the fellow eye in the animals in which the process was controlled succumbed to infection within 48 hours, these eyes having been inoculated with streptococci in the anterior chamber, but having received no sulphanilamide.

(b) *Bacillus Pyocyaneus*.—Robson and Scott (1942) studied the effect of 30 per cent. sodium sulphacetamide solution on corneal inoculation of *B. pyocyaneus*, initiating treatment in one series of 17 eyes one hour after inoculation, and in two other series of 12 eyes, after 5 hours and 12 hours respectively. Corneal ulceration was completely prevented in 11 out of the 17 eyes in the first series, but only in 5 out of 12 and 2 out of 12 in the second and third series.

Boyd (1942) having shown that the concentration of sulphathiazole in the cornea and aqueous is increased by iontophoresis, v. Sallmann (1942) applied this technique to the treatment of experimental *B. pyocyaneus* infection of the cornea, using sulphadiazine since the highest local concentration could be obtained with this drug. In one series of 7 rabbits treated by sulphadiazine iontophoresis 8 to 18 hours after infection, keratitis was checked in more than half of the eyes; in the rest there was only a delay in the course of infection. In a second series of 9 rabbits results were more satisfactory; iontophoresis in one eye was initiated 18 hours after inoculation and was combined with feeding. Feeding was helpful, but not curative in itself, as the keratitis of the control eye showed. In a third series of 12 rabbits local treatment with sulphadiazine powder, though occasionally giving surprisingly good results, proved inferior to sulphadiazine iontophoresis alone, or combination with oral sulphadiazine. Three preliminary experiments also suggested a slight superiority of sulphadiazine iontophoresis to local application of 30 per cent. solution of sodium sulphacetamide in corneal lesions of 24 hours standing. The most favourable results in lesions 24 to 30 hours old was obtained from a combination of iontophoresis with powder locally or by mouth.

(c) *Staphylococcus aureus*.—Robson and Scott (1943), working with a particular strain of staphylococcus aureus, obtained characteristic corneal lesions in the rabbit when the organisms were introduced into the cornea beneath the epithelium. Though the lesions varied from animal to animal, the two eyes of the same animal showed remarkably similar pictures, thus enabling them to study the effect of local medications by applying these to one eye only and using the other eye as a control. They found that

10 per cent. of sodium sulphacetamide was as effective as 30 per cent. and $2\frac{1}{2}$ per cent. solution was ineffective. In 27 rabbits all control eyes were affected, 21 of these being more or less heavily involved, whilst in the 27 treated eyes three were completely controlled and 17 but slightly affected, 7 eyes only having the same degree of involvement as the 21 control eyes. These results applied to those rabbits in which treatment was instituted 1 hour after inoculation and continued hourly for at least 48 hours. In none of the 6 animals in whom treatment was begun 24 hours after inoculation was the infection controlled. A solution of solubilized sulphathiazole did not appear promising. One point of interest was that though 10 per cent. solution of sodium sulphacetamide was effective in controlling the corneal infection there was no appreciable reduction in the number of staphylococci in the conjunctival sac, whilst pencillin (which also controlled the corneal infection) rendered the conjunctival sac free from staphylococci.

3.—Present Investigations

The object of the studies recorded here was to determine in the first place the efficacy of the sulphonamides in the local treatment of ocular infections and to assess its relative value to general administration of these drugs. For reasons already indicated, the bulk of the work concerned corneal infection with *B. pyocyaneus* and inoculation of streptococci and pneumococci into the anterior chamber. Rabbits were used throughout.

METHODS OF INFECTION :—

(a) *Corneal infection with B. pyocyaneus.*—Rich green 24 hours cultures of the organism on agar were used. As many colonies as possible were removed with a platinum loop and transferred to 2 c.c. of sterile normal saline solution, with which they were thoroughly mixed. This formed the infecting material. The rabbits' corneae were prepared by applying 2 per cent. butyn drops or ointment, and after 3 minutes the epithelium of the centre of the cornea could easily be scraped off with a discission needle. The bared area was then treated with the prepared infecting material applied by means of a platinum loop.

(b) *Anterior chamber inoculation with streptococci and pneumococci.*—The infecting material used was a 24 hours broth culture, diluted to 1 in 10,000. The rabbits' corneae were anaesthetized as for corneal inoculation. The infecting material (1/10 or 1/20 c.c.) was introduced into the anterior chamber by means of a finely graduated 1 c.c. syringe with a fine, sharp needle. Puncture at the limbus proved unsatisfactory; the needle had to be introduced

subconjunctivally 1 cm. away from the limbus. With care the iris could be avoided and the inoculation performed painlessly.

It will be noted that these experiments are not completely controlled in technique. The amount of corneal damage done in scraping off the epithelium probably varied to some extent, whilst the number and virulence of the organisms were not established. For these reasons control animals were used liberally.

A. CORNEAL INFECTION WITH *B. PYOCYANEUS*. (Table I.)

1. *The effect of 30 per cent. sodium sulphacetamide solution.*

—(a) Six rabbits had both corneae infected with *B. pyocyaneus*. Treatment was instituted 24 hours later and consisted of the instillation of 30 per cent. sodium sulphacetamide drops three times a day for 7 days to the right eye only, the left being used for control. Though the reaction of the corneae varied to some extent—the lesion produced by the infection ranging from a mild corneal ulcer to destruction of the cornea leading to marked ectasia, but generally consisting of a massive infected ulcer—no tangible difference could be seen as between the treated and untreated eyes.

(b) A further 8 rabbits were similarly used, but treatment commenced immediately after infecting the cornea. The left (control) eyes were treated with saline drops. Again no tangible difference between the treated and untreated eyes could be established.

(c) Three rabbits were used, as in the previous experiment, but treatment applied 5 or 6 times a day for 3 days. Again no significant results were obtained.

A point of interest in these experiments is that some heavily infected eyes showed after some two months remarkably little scarring of the cornea. This applied to untreated eyes as well as to treated eyes.

2. *The effect of 30 per cent. sulphanilamide ointment.*—

(a) Three rabbits' corneae were infected with *B. pyocyaneus*. Treatment was applied immediately after the inoculations and consisted of the instillation of 30 per cent. sulphanilamide ointment (oil in water emulsion base*) into the right eye and of the ointment base only in the left. Treatment was continued three times daily for a week. No tangible effect of the sulphanilamide ointment could be seen; in fact, the three left (control) eyes appeared to be rather less involved than the right eyes.

(b) In four more rabbits these experiments were repeated with this additional measure: a suture was passed through each of

* Composition:—Petroleum jelly 25 per cent., castor oil 25 per cent., lanette wax S.X. 5 per cent., water 45 per cent.

the four lids and the upper and lower suture on each side were tied in a bow after each application of ointment (or ointment base), so that the lids were closed during the course of the treatment, thus approximating the application of a bandage in the human patient. The results did not encourage further exploration of this procedure.

(c) In seven rabbits the infected right cornea was treated with 30 per cent. sulphanilamide ointment placed inside a contact lens fitting fairly accurately to the eye. The infected left eye had a contact lens with the ointment base only. The lenses were changed daily for 7 days. The picture in these cases was complicated by the fact that in rabbits whose cornea was not infected the wearing of a contact lens with sulphanilamide ointment or the base produced an irritative corneal lesion of the ground glass variety. No definite conclusions could be drawn, but it appeared that the (left) infected eyes treated with contact lens and ointment base showed more active lesions than the right eyes treated with contact lens and sulphanilamide ointment; in three rabbits the infective lesion in the right eye was definitely more under control than the left, and in two more, though the right eye showed less active infection than the left, there was a suggestion of a greater irritative reaction of the ground glass type (? due to poorer fit of lens, ? due to irritative action of the sulphanilamide ointment).

3. *The effect of sulphapyridine insufflation combined with 5 per cent. sulphanilamide ointment.*—In six rabbits the infected right eye was treated with immediate insufflation of sulphapyridine powder and the application of 5 per cent. sulphanilamide ointment applied under a lid suture as in 2 (b) three times daily for seven days. The infected left eye was untreated. In three rabbits there was no appreciable difference between the course of the infection in the right and left eyes. In the remaining three though severe corneal lesions were present; the treatment appeared to influence the course of the infection favourably.

4. *The effect of 30 per cent. sodium sulphacetamide administered intra-muscularly.*—In 14 rabbits the cornea of one eye was infected with *B. pyocyaneus*, the other eye having streptococci, pneumococci or staphylococci introduced into the anterior chamber. The animals, all weighing about 2 kilos, received no local treatment, but were given 5 c.c. of 30 per cent. solution of sodium sulphacetamide (1.5 grm.) intramuscularly immediately before infection and 2-3 c.c. on the three or four subsequent days. In no case (with one possible exception) was the *B. pyocyaneus* infection controlled to any extent, and this failure stood out strikingly against the generally favourable result on the fellow eyes infected with streptococci and pneumococci. These latter

results are discussed below. Here attention is drawn to the negative results of general treatment on *B. pyocyaneus* infection.*

B. INOCULATION OF STREPTOCOCCUS, PNEUMOCOCCUS AND STAPHYLOCOCCUS INTO THE ANTERIOR CHAMBER, COMBINED WITH INTRAMUSCULAR INJECTION OF SODIUM SULPHACETAMIDE. (Table II.)

The method of inoculation has already been described, and the administration of 30 per cent. of sodium sulphacetamide indicated (0.75 grm. per kilo before infection and 0.3–0.45 grm. per kilo daily for 3 or 4 days subsequently).

1. *Streptococcus haemolyticus* in pure culture.—Three rabbits thus infected in both eyes with 1/10 c.c. and treated with sulphacetamide showed severe iritis and hypopyon. In one eye of two of the infected rabbits the infective process was considerably less severe than in the remaining four eyes of these animals, and in a control rabbit which was infected but not treated. The subsequent experiments were carried out with diluted cultures.

2. *Streptococcus haemolyticus*: broth culture diluted to 1/10,000.—(a) Three rabbits thus infected in both eyes with 1/10 c.c. and treated with sulphacetamide showed definite iritis and flocculi of pus in the anterior chamber 24 hours after inoculation. With continued treatment the flocculi disappeared; the infection was clearly under control and spontaneous resolution of the remaining flocculi occurred after treatment was suspended on the fifth day. Remarkably little evidence of the iritis remained to be seen. In a control animal the infection ran a severe course.

(b) In three more rabbits the same procedure was followed, except that the left anterior chamber received 0.05 c.c. of the infecting material against 0.1 c.c. in the right. One of these animals died on the third day with both anterior chambers heavily infected. The two remaining rabbits reacted well to treatment, all the four eyes showed complete control of the infection after an initial iritis and pus formation.

3. *Streptococcus haemolyticus* 1/10,000 in the anterior chamber of left eye and corneal infection with *B. pyocyaneus* of the right eye.—Nine rabbits had the anterior chamber of one eye infected with 0.1 c.c. of the diluted broth culture and the cornea of the other eye infected with *B. pyocyaneus*. Intramuscular administration of sodium sulphacetamide for four days gave

* Two rabbits with pyocyaneus infection of one cornea and streptococcus inoculation in the anterior chamber of the fellow eye were demonstrated before the Ophthalmological Society in May, 1942. The animals had received sodium sulphacetamide intramuscularly; the streptococcal infection was controlled, the pyocyaneus infection completely uncontrolled.

TABLE I.—CHEMOTHERAPY IN *B. PYOCYANEUS* INFECTION OF THE CORNEA

Method of Application	30% sodium sulphacetamide drops			30% sulphanilamide ointment		Sulphapyridine powder and 5% sulphanilamide ointment	Sodium sulphacetamide intramuscularly
	(a)	(b)	(c)	(a)	(b)	(c)	
	Right eye treated 24 hours after inoculation three times daily for seven days. Left untreated	As in (a) but treatment commenced immediately after infection	As in (b) except that drops were applied 5 to 6 times daily for 3 days	Right eye treated with ointment immediately after inoculation three times daily for 7 days. Left eye treated with ointment base only	As in (a) but lid sutures also used	Right eye treated with ointment applied immediately after inoculation three times daily for 7 days. Left eye sutured. Left eye untreated	(The right cornea was infected with <i>B. pyocyaneus</i> . Other organisms were introduced into the left anterior chamber). No local treatment. General treatment for 3-4 days
Number of rabbits used	6	8	3	3	4	6	14
Results	Infection not controlled			Infection not controlled		In three rabbits the infection was not controlled. In three others? favourably influenced	<i>B. pyocyaneus</i> infection not controlled (? controlled in one case)

TABLE II.—CHEMOTHERAPY IN INFECTIONS OF THE ANTERIOR CHAMBER

Organism	Streptococcus haemolyticus both eyes (a)	Streptococcus haemolyticus both eyes (b)	Streptococcus haemolyticus 1/10,000 dilution in left A. C.; B. pyocyaneus infection of right cornea	Pneumococcus 1/10,000 dilution left A. C. and B. pyocyaneus infection of right cornea	Staphylococcus aureus 1/10,000 dilution in left A. C. and B. pyocyaneus infection of right cornea	Streptococcus haemolyticus 1/10,000 dilution
Method of treatment	Undiluted culture	Culture diluted to 1/10,000	Sodium sulphacetamide (0.75 gm./kilo before infection and 0.3-0.4 gm./kilo daily for 3-4 days) intramuscularly			30% sulphanilamide ointment applied after inoculation and three times a day for 7 days. Lid sutures
Number of rabbits used	3	6	9	3	2	1
Results	In two out of 6 eyes infection partially controlled	One rabbit died on third day with heavy infection of both eyes. Infection well controlled in the others	Infection controlled in 7 out of 9 eyes infected with streptococcus. (B. pyocyaneus infection not controlled in 8 out of 9 eyes)	One pneumococcus eye uncontrolled; the two others partial control	Infection uncontrolled	Infection uncontrolled

uniformly poor results in eight of the nine eyes with pyocyaneus infection. In seven eyes the streptococcal infection was completely under control; in the remaining two, the eye was severely infected and became useless.

4. *Pneumococcus* on broth culture diluted 1/10,000 into the anterior chamber of left eye and pyocyaneus infection of the cornea of the right eye.—In three rabbits thus treated, the pyocyaneus infection was completely uncontrolled. The three eyes with pneumococcal infection did not give the same satisfying resolution as seen with streptococcal infection; one eye was completely lost from moderate panophthalmitis, and the two remaining eyes showed fairly severe iritis. A control animal showed a severe reaction in both eyes.

5. *Staphylococcus aureus* (broth culture diluted 1/10,000) in the anterior chamber of left eye and *B. pyocyaneus* on the cornea of the right.—Two rabbits thus infected and treated gave no response to either infection.

C. INOCULATION OF STREPTOCOCCI INTO THE ANTERIOR CHAMBER, COMBINED WITH 30 PER CENT. SULPHANILAMIDE OINTMENT IN THE CONJUNCTIVAL SAC AND LID SUTURE. (Table II.)

One rabbit thus infected in both eyes with 0.1 c.c. of 1/10,000 dilution of a broth culture of streptococcus haemolyticus and treated immediately for a week with 30 per cent. sulphanilamide ointment three times daily into the conjunctival sac, which was kept closed by lid sutures, showed extensive infection of both eyes.

4.—Discussion

The results recorded may briefly be summarised as showing that:—

(1) The general administration of sulphanilamide (in the form of sodium sulphacetamide) controls an intra-ocular inoculation of streptococcus haemolyticus, and possibly also of pneumococcus, but does not control corneal inoculation with *B. pyocyaneus*.

(2) The local application of sulphanilamide, sulphapyridine or sodium sulphacetamide appears to be largely ineffective against *B. pyocyaneus* infection of the cornea, and there is no reason for believing that it is effective against streptococci inoculated into the anterior chamber. There is some suggestion that sulphanilamide ointment applied under a contact lens might favourably influence the course of a *B. pyocyaneus* infection of the cornea, but all other methods of local application, including lid suture, which is an approach to the clinical procedure of bandaging the eye, appear ineffective.

These results confirm the findings of Rambo and Venco on the efficacy of the general administration of sulphanilamide on intra-ocular infection with streptococci, but they do not quite tally with the findings of Joy (1940 and 1942) and those of Robson and Scott (1942) for *B. pyocyaneus* of the cornea. The data recorded here are not strictly comparable with those of Joy, for this observer employed sulphapyridine. v. Sallmann, who administered sulphadiazine by mouth (18 hours after inoculation) could not control *B. pyocyaneus* infection of the cornea, and Joy's results remain as yet unconfirmed. It is, however, possible that the strain of *B. pyocyaneus* employed by Joy proved susceptible to the drug—and his *in vitro* experiments with different strains suggest this—whilst the strains employed by Sallmann were more resistant, and those used by ourselves were still more so. The same possibility arises in assessing the contrary results obtained by Robson and Scott and by ourselves in controlling *B. pyocyaneus* infection by local treatment. These conflicting results and uncertainty as to the capacity of some strains of *B. pyocyaneus* only emphasise that this organism—or rather group of organisms—*pseudomonas*—as they are now designated by bacteriologists—is not really a satisfactory agent for the study of the effect of chemotherapy in corneal lesions. In any case there is no full study available which compares the effects of general administration with local application. Granted the efficacy of the sulphonamides in *B. pyocyaneus*—or some strains of it—the question still remains whether local or general treatment is superior. On the experimental side this question is likely to remain until a suitable standard organism and a standard technique for corneal infection are available. The staphylococcus, which is known to be resistant to the sulphonamides and bizarre in its behaviour in the experimental animal, does not appear very promising.

In the meantime it is well to remember that clinical evidence in ophthalmology points to the vast superiority of general administration of the sulphonamides over the local application of these drugs. Easily the most striking results obtained with the sulphonamides in ophthalmology are those seen from the oral administration of sulphapyridine in ophthalmia neonatorum—a condition in which local therapy is useless, though the affection is essentially a superficial lesion and the local application of the sulphonamides should be ideally effective. Complex theoretical problems are involved here, and whilst it is gratifying that there is much intensive clinical exploration of the possibilities for the local use of the sulphonamides in ophthalmology it is well to remember that these clinical explorations are largely empirical and have not, as yet, firmly established experimental validity to support them.

Summary

1. The problems involved in the experimental study of ocular chemotherapy are indicated, stress being laid on the absence of a satisfactory technique for the organisms commonly met with in ocular infections and on the levels of concentration that different sulphonamides reach and maintain in ocular tissues by the general and local administration of these drugs.

2. A review of the literature on experimental chemotherapy by general and local administration of the sulphonamides is given.

3. Work is recorded which substantiates the claims for sulphanilamide in controlling experimental intra-ocular infection with streptococcus haemolyticus and possibly also pneumococcus (Table II). *B. pyocyaneus* infections of the cornea were not controlled either by the general administration of sodium sulphacetamide or by the use of this drug in a variety of ways as a local application (Table I).

4. In the absence of a more standard technique of inducing experimental infection of the cornea, the problem of the relative value of general and local use of the sulphonamides remains unsolved. The value of local therapy is still an open question.

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REFERENCES

- BOYD (1942).—*Arch. of Ophthalm.*, Vol. XXVIII, p. 205.
 JOY (1940).—*Proc. Soc. Exper. Biol. and Med.*, Vol. XLV, p. 709.
 — (1942).—*Arch. of Ophthalm.*, Vol. XXVII, p. 1135.
 RAMBO (1938).—*Amer. Jl. Ophthalm.*, Vol. XXI, p. 739.
 ROBSON AND SCOTT—(1942).—*Brit. Med. Jl.*, Vol. I, p. 5.
 — (1943).—*Lancet*, Vol. I, p. 100.
 V. SALLMANN (1942).—*Amer. Jl. Ophthalm.*, Vol. XXV, p. 1292.
 SORSBY (1942).—*Trans. Ophthalm. Soc. U.K.*, p. 62.
 VENCO (1939).—*Ann. Ottal. e Clin. Ocul.*, Vol. LXVII, p. 179.