the mites, a considerable number being apparently unaffected by the treatment, although almost all of them contained stain, and therefore presumably drug. There was no significant difference between the actions of benzyl benzoate and dimethylthianthrene on the eggs, both being inferior to tetraethylthiuram

TABLE II.—Comparative Effects on Eggs after Rubbing in the Drugs for 3 Minutes

Drug	24 Hours Afterwards			3 Days Afterwards		
	No. of Eggs	Degenerate	Stained	No. of Eggs	Degenerate	Stained
Dimethylthianthrene..	36	25%	69%	10	50%	90%
Benzyl benzoate	76	34%	99%	58	47%	100%
Tetraethylthiuram monosulphide	65	50%	98%	45	78%	98%

monosulphide, which was more lethal and more rapid in its action. The results show that a single application of any of the drugs was probably insufficient to produce a cure, and we suggest that in human scabies it would be a sound policy to make a second application of the drug after a week, by which time any viable eggs would have hatched.

We would emphasize that these results have been obtained in animal scabies caused by mites of the genus *Notoedres*; but we consider it is probable that they are applicable to human scabies caused by *Sarcoptes scabiei*. We are unable to say to what extent tetraethylthiuram monosulphide may produce dermatitis, but its superiority over benzyl benzoate and dimethylthianthrene suggests that it should be given a clinical trial.

Summary and Conclusions

The conclusions we have reached as a result of the experiments may be summarized as follows:

Preliminary washing and scrubbing of the skin facilitated the sarcoptocidal action of the drugs tested.

The vegetable oil used as a vehicle for the drugs allowed these to penetrate the skin to a satisfactory depth within 15 minutes of their application. Such a vehicle should prove more satisfactory than the semi-solid mineral substances commonly used as ointment bases.

A single application of any of the drugs tested produced degenerative changes in almost all the mites within 3 days, but a proportion of the eggs still remained apparently unaffected. It is suggested, therefore, that a second application of the drug should be made after an interval of a week, by which time any eggs which survived the first application would have hatched.

The results of our investigations of animal scabies supported the generally accepted view that the larval mites leave their burrows, wander on the surface of the skin and clothing, and can be transmitted by the garments. Until the frequency with which this occurs in human scabies has been determined it would be unwise to dispense with the disinfection of undergarments and bedclothes.

No significant difference was detected between the actions of benzyl benzoate and dimethylthianthrene (mitigal). Tetraethylthiuram monosulphide was more rapid and more lethal in its action than either of those drugs; its superiority was such that it is worthy of a trial in human scabies.

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PENETRATION AND DISTRIBUTION OF SODIUM SULPHACETAMIDE IN OCULAR TISSUES OF RABBITS

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Recent work has shown that the local application of sulphonamides may be of value in the prevention and treatment of septic conditions. Thus various investigators have used sulphonamides in the form of powders and pastes (Colebrook, 1941; Fraser, 1941; Buxton, 1940; Robson and Wallace, 1941; Hrad, 1941) for the local treatment of wounds and burns. A great advantage of such a method of administration is that much higher concentrations can be attained locally than can safely be produced by the oral or parenteral routes; moreover, the whole organism is not flooded with the drug, and toxic symptoms are thus avoided.

A number of sulphonamides have been used for this method of treatment. It is important that the substances should penetrate readily into the tissues without producing any injury. It appears likely that penetration will be favoured by a reasonable degree of solubility in water, and that injury will be kept to a minimum if the solution does not appreciably deviate from neutrality. The number of sulphonamides possessing these properties is limited. Among these, sodium sulphacetamide (albicid soluble) has proved of value when applied locally in the treatment of eye infections and burns, and there is, moreover, evidence that its application produces a beneficial effect on experimental infections of the cornea with *B. pyocyaneus* in rabbits (Robson and Scott, 1942). It seemed of interest, therefore, to determine how readily this substance penetrates into the tissues and how rapidly it diffuses through them and reaches the general circulation; this was the object of the present investigation.

Methods of Investigation

Experiments were performed on 75 mature rabbits of both sexes and various breeds. For the prolonged application of the solutions celluloid funnels were made (see Fig. 1). These

FIG. 1.—Showing the celluloid funnels in position in the eyes of a rabbit, in the method used for the prolonged application of solutions.

were placed into the conjunctival sac under ether anaesthesia and kept in position by means of purse-string sutures through the lids. The funnels were so designed that their apertures

had a diameter greater than that of the cornea. The flanges therefore lay against the conjunctiva overlying the sclera, and no part of the funnel was in contact with the cornea. The amount of solution put into the funnel (3 c.cm.) was such that the cornea was not subjected to any appreciable fluid pressure. Care was taken to remove air bubbles after filling up the funnels. The solutions (2.5% or 30%) were applied for various periods, at the end of which the funnels were removed and the eyes excised for analysis.

In the second series of experiments, designed to study the rate of removal of the drug introduced into the eye, the funnels were taken out after standard periods of exposure to a 2.5% or 30% solution, and the conjunctival sac thoroughly washed

methods, and were found to agree to within 5%. The analyses were completed on the day of the animal experiment.

Results

The concentrations of sodium sulphacetamide in mg./100 c.cm. produced in a number of ocular tissues after various periods of exposure to a 2.5% or 30% solution of the drug and at various periods after cessation of exposure are shown in Tables I and II: the extent of individual variation was large, and hence both the mean and the range are given.

In part 1 of each of these tables are shown the concentrations attained in the various tissues after 5, 15, and 30 minutes' exposure to a 2.5% or 30% solution. Part 2 of each table

TABLE I

	Times in Min.	Cornea			Conjunctiva			Aqueous			Iris			Sclera		
		Mean	Range	No. of Expts.	Mean	Range	No. of Expts.	Mean	Range	No. of Expts.	Mean	Range	No. of Expts.	Mean	Range	No. of Expts.
1. Period of exposure to a 30% solution	5	227	138-407	6	132	52-246	5	16	T-46.5	6	T	—	5	83	14-160	5
	15	966	354-1,490	9	787	39-1,725	5	192	32-415	9	118	63-258	9	137	49-905	8
	30	928	375-1,590	9	664	224-1,030	7	354	115-685	10	175	49-269	9	127	42-219	9
2. Period after cessation of exposure of 15 min. to a 30% solution	15	211	88-356	9	89	24-182	8	123	39-260	8	45	9-108	9	22	0-32	9
	60	77	26-134	9	15	0-46	9	45	12-112	6	33.5	2-118	9	10	0-49	9
	120	62	15-118	6	7.5	0-23	6	17	7.5-33	6	2.1	0-6.4	6	0	—	6

T = trace.

TABLE II

	Times in Min.	Cornea			Conjunctiva			Aqueous			Iris			Sclera		
		Mean	Range	No. of Expts.	Mean	Range	No. of Expts.	Mean	Range	No. of Expts.	Mean	Range	No. of Expts.	Mean	Range	No. of Expts.
1. Period of exposure to a 2.5% solution	5	23	11-30	5	31	11-63	5	0	—	5				T	—	3
	15	76	47-130	7	63	37-140	7	9	3-23	7				T	—	3
	30	117	51-254	8	89	26-154	8	15	8-44	8	5	T-25	8	17	0-45	9
2. Period after cessation of exposure of 30 min. to a 2.5% solution	15	32	17-62	10	10	1-23	6	6	3-13	10	6	3-9	6	8	7-10	3
	60	21	14-35	10	8	T-16	6	8	4-12	10	6	2-11	6	3	0.5-4	3
	120	13	10-17	8	9	0-20	8	6	5-7	8	5	1-10	8			

T = trace.

out with saline in order to prevent any further absorption of the drug. After various periods the eyes were then removed for analysis.

Under clinical conditions drugs are often applied to the eye in the form of drops. A third series of experiments was therefore devised in order to study the penetration of the drug when drops were instilled into the conjunctival sac. The animals were anaesthetized with ether and the lids were held open so that the conjunctival sac formed a pocket. Some drops (0.1 c.cm.) of the solution (2.5% or 30%) were placed on to the cornea and conjunctiva and distributed throughout the sac by opening and closing the lids several times in order to imitate the conditions prevailing in the unanaesthetized subject. After 15 or 60 minutes the eyes were excised for analysis.

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.

The chemical analysis was based on the revised method of Marshall and Litchfield (1938), using dimethyl- α -naphthylamine as coupling agent. The preparation of the tissue extracts was carried out by a method similar to the one described by Bellows and Chinn (1939). The weighed tissues were thoroughly ground with 1 g. of clean sand and 4 c.cm. of 15% trichloroacetic acid in small glass mortars. The suspension was then washed into centrifuge tubes calibrated at 8 c.cm. and made up to the mark with water. After centrifuging for 15 minutes, 2 c.cm. of each supernatant fluid was pipetted into wide test-tubes and diluted with 2 c.cm. of water. The perfectly clear solution was then diazotized and coupled. Instead of ammonium sulphamate, which is not at present commercially available, a 20% solution of urea was found satisfactory for destroying any excess of nitrite. Readings were taken after half an hour to ensure maximum development of colour. Comparison was made with freshly prepared sodium sulphacetamide standards of appropriate concentrations, using a visual colorimeter (Hellige's colorimeter) for the more intense colours and a Zeiss stapho-photometer for the lower concentrations of sodium sulphacetamide. Readings were occasionally made by both

gives the concentrations noted at various times after the end of a standard period of exposure—i.e., after the funnels had been removed and the conjunctival sacs washed out. The duration of the preliminary exposure was 30 minutes for the 2.5% solution. This long preliminary period was adopted in order to obtain high concentrations in the ocular tissues and thus to be able to follow the rate of removal of the drug over a wide range of concentrations. When the eye was exposed to a 30% solution of sodium sulphacetamide it was found that oedema of the cornea tended to develop when the period of exposure was greater than 15 minutes. This oedema might very well interfere with the removal of the drug. It was therefore deemed advisable, with the 30% solution, to restrict the standard preliminary period of exposure to 15 minutes.

A striking feature of the results is the rapid rate at which the drug diffuses into the cornea and conjunctiva. Even with a 2.5% solution, concentrations were obtained well above those produced in the blood and in the tissues when sulphonamides are given by mouth. Moreover, the diffusion of the drug into these tissues went on progressively, so that by the end of 30 minutes of exposure the concentrations were some ten times greater than are usually present in the blood stream following oral or parenteral administration (Figs. 2 and 3). The diffusion into the aqueous and iris lags well behind, and the concentrations reached were much smaller. Nevertheless, after 15 minutes the concentrations in the aqueous were of the order of those produced by oral administration of therapeutic doses of the drug. In the case of the iris appreciable concentrations were reached only after an exposure of 30 minutes, and the same applies to the sclera, into which the drug also diffused slowly.

The relative rates of diffusion following the application of a 30% solution were similar in type to those discussed above for the 2.5% solution, though the actual figures were of course much higher. The drug diffused very rapidly into the cornea and conjunctiva, and by the end of 5 minutes of exposure concentrations of the order of 100 mg. per 100 c.cm. were produced in these tissues. By the end of 15 minutes the figures obtained were exceedingly high (around 800 mg. per 100 c.cm.), and such concentrations presumably tended to produce damage to the tissues, since, with 30% solutions, oedema of the cornea

was frequently observed after periods of exposure of more than 15 minutes. It is to be supposed that the damage so produced in the tissues interferes with the further entry of the drug, since the concentrations did not rise after a further period of

FIG. 2.—Illustrating the rise in the sodium sulphacetamide content of ocular tissues with increasing periods of application of a 30% solution, and the fall at various times after cessation of exposure.

FIG. 3.—Illustrating the rise in the sodium sulphacetamide content of ocular tissues with increasing periods of application of a 2.5% solution, and the fall at various times after cessation of exposure.

exposure, and indeed appeared to fall. In view of the wide individual variation among different animals this observed fall in the mean values is, however, not statistically significant. The rate of diffusion into the aqueous and iris again lagged

lens, and even on exposure of the eye to a 30% solution for half an hour the highest concentration observed was 6.8 mg. per 100 c.cm. Rather higher concentrations were found in the vitreous. When the eye was exposed to a 30% solution the mean values after 5, 15, and 30 minutes were 5.2, 7.7, and 10.3 mg. respectively; with a 2.5% solution only traces of the drug were found in the vitreous and none in the lens.

In order to exclude completely the possibility that the drug reached the ocular tissues in any appreciable concentrations after absorption into the blood stream, the sulphonamide content of the blood was determined in a number of the above experiments. Blood samples were taken through a cannula inserted into the femoral artery before beginning the experiment. The highest blood concentration found when both eyes were exposed for half an hour to a 30% solution was 7 mg. per 100 c.cm., but in other experiments much lower values were obtained, ranging from 0.4 to 3.7 mg. for an exposure of both eyes to a 30% solution for 15 minutes.

When exposure of the eye to the drug ceased the concentrations in the conjunctiva and cornea fell very rapidly, and within 15 minutes the greater part of the drug had diffused out of these tissues. After this period, however, the rate of diffusion became very much slower, so that even after 2 hours quite appreciable amounts of the sulphonamide were still present, especially in the cornea. In the case of the other tissues the initial rate of fall was not so marked, and it became slower still in the subsequent period. An important feature of these results is that even 2 hours after cessation of exposure the cornea, conjunctiva, and aqueous still contained concentrations of the drug at or above the therapeutic level.

The concentrations of sodium sulphacetamide in mg. per 100 c.cm. produced in the various ocular tissues 15 and 60 minutes after the instillation of drops (2.5% and 30%) into the conjunctival sac are shown in Table III. Each value represents the mean of 6 experiments. As was to be expected, the values were very much lower than when the eye is subjected to the continued action of the solution, as in the experiments with the funnels. Nevertheless, therapeutically active concentrations were usually present in the cornea and conjunctiva one hour after the application of the drops of the 30% solution, though such was not the case for the aqueous, iris, and sclera. With the 2.5% drops the therapeutically active concentrations were found only in the conjunctiva 15 minutes after application. The cornea contained but small amounts, and not even a trace of the drug was detected in the aqueous, iris, and sclera 15 or 60 minutes after application. Experiments on the drug content of the rectus muscles were undertaken in order to determine whether these might represent a path of entry of the drug into the eye. Small pieces of the muscle a few millimetres in length were dissected off at their insertion into the sclera. The sodium sulphacetamide content of the muscle 15 minutes after the application of 30% drops was found to be unexpectedly high. It thus seems probable that the drug rapidly diffuses through the conjunctiva into the muscle, from which it may possibly pass into the tissues subjacent to its insertion.

TABLE III.—Showing the Concentrations of Sodium Sulphacetamide (in mg.%) in Various Ocular Tissues 15 and 60 mins. after the Instillation of Drops of a 2.5% and 30% Solution (Each figure represents the mean of 6 experiments)

Sod. Sulphacetamide	Time after Instillation (Min.)	Cornea		Conjunctiva		Aqueous		Iris		Sclera		Rectus Muscle	
		Mean	Range	Mean	Range	Mean	Range	Mean	Range	Mean	Range	Mean	Range
30%	15	9.1	5.2-15	28.4	7.1-63.0	1.1	0.4-2.9	3.4	0.7-7	5.1	1.5-10	23.7	6.1-36.7
	60	8.2	3.3-15	17.1	13-34.5	2.0	0.9-3.4	3.1	0-6.1	4.1	1.4-5.9	—	—
2.5%	15	4.5	3.2-5.6	16.3	3.7-33	0	—	0	—	0	—	0	—
	60	0	—	0	—	0	—	0	—	0	—	0	—

behind that observed for the outer tissues of the eye. This lag was not prolonged, and after 5 minutes the concentrations of the drug in the aqueous and iris rose quite rapidly to reach values of the order of 100 to 200 mg. per 100 c.cm. within the next 10 minutes.

In the sclera high values were also quickly attained with the 30% solution. A maximum was reached after 15 minutes of exposure, beyond which there was no further increase.

The lens and vitreous were examined in a number of experiments. There was very little penetration of the drug into the

Discussion

When sulphonamides are given orally in the treatment of various infective conditions the dosage is so adjusted as to produce in the blood and tissues concentrations of the drug of the order of 5 to 10 mg. per 100 c.cm., since it has been found that these concentrations are usually sufficient to ensure chemotherapeutic effects. The present experiments show that such concentrations can rapidly be obtained in the cornea, conjunctiva, and anterior chamber of the eye by the local

application of solutions of sodium sulphacetamide into the conjunctival sac. Moreover, under appropriate conditions of application much higher concentrations of the drug can be obtained than could safely be produced by oral or parenteral administration.

In view of these very high values experiments were made to determine the rate of diffusion of sodium sulphacetamide through gelatin gels. The diffusion coefficient found was such as to account fully for the concentrations of the drug obtained in the cornea and aqueous. Indeed, higher values could theoretically be possible if the calculation were based on the diffusion of the drug through a homogeneous medium. Hawking (1941) has already carried out experiments on the diffusion of various sulphonamides through gelatin and agar gels, and his results are in substantial agreement with those obtained for sodium sulphacetamide.

It is interesting to compare the present data with those obtained by P'an (1941a). This investigator applied sulphanilamide in the form of a powder to the conjunctival sac and found high concentrations of the drug in some ocular tissues after one hour of continued application. At the end of this period the concentrations of sulphanilamide found in the cornea, conjunctiva, and aqueous were 185 mg., 90 mg., and 55 mg. per 100 c.cm. respectively. In the case of sodium sulphacetamide we could produce higher concentrations in the cornea and conjunctiva by the application of a 30% solution for only 5 minutes, though the figures were rather lower when a 2.5% solution was applied for 30 minutes. In the aqueous the concentrations of sodium sulphacetamide obtained by applying a 30% solution for 5 minutes or a 2.5% solution for 30 minutes are several times lower than found by P'an in the case of sulphanilamide.

There is evidence that in the human subject, too, sulphanilamide diffuses readily into the ocular tissues. Thus Luo and P'an (1940) found concentrations up to 44 mg. per 100 c.cm. in the aqueous after the application of sulphanilamide powder for one hour. With drops of a 1% solution applied over a period of one hour much smaller concentrations (1 to 4 mg.) were obtained.

P'an (1941b) has also made observations on the penetration of sulphapyridine and its sodium salt, which were both applied in the form of a powder for one hour. As was to be expected from its low solubility, the penetration of sulphapyridine was much less than that of sulphanilamide, and especially low figures were observed for the aqueous. The diffusion of the sodium salt gives figures of the same order as those obtained with sulphanilamide, but the application of the highly alkaline sodium sulphapyridine caused marked congestion and chemosis of the conjunctiva.

The experiments on the rate of removal of the drug from the ocular tissues show that high concentrations are maintained for only short periods, but that, following the initial rapid fall, lower concentrations within the range of therapeutic activity may be maintained for some considerable time. When drops were applied to the eye, however, the high concentrations attained with prolonged applications in the funnel experiments were not seen, and it was necessary to apply drops of a 30% solution in order to produce in the cornea and conjunctiva therapeutically active concentrations for periods up to one hour.

The question now arises as to the significance of the present experiments in the clinical use of sulphonamides applied locally to the conjunctival sac. This is of importance, since evidence is accumulating that local application of these drugs may be of value in the treatment of various septic conditions of the eye (Panneton, 1941; Guyton, 1941; Traquair and Cameron, 1941).

Local administrations of the drug should, if possible, be so spaced as to maintain constantly a therapeutically active concentration in the infected tissues. Moreover, such a concentration should be present for a reasonable length of time, since it is known that the action of sulphonamides is essentially bacteriostatic rather than bactericidal. The actual concentration needed will vary with the infecting organism; recent work on sulphonamides seems to indicate that, though 5 to 10 mg. per 100 c.cm. may produce an effective bacteriostatic action against susceptible organisms like the haemolytic streptococcus, less susceptible organisms—e.g., the *Staphylococcus aureus*—

will be appreciably affected only by higher concentrations of the drug.

These considerations suggest that if the drug be applied to the eye in the form of a solution this should not be too dilute lest the concentration produced be ineffective. Thus, in the case of sodium sulphacetamide, solutions containing up to 30% of the drug have been used clinically (Traquair and Cameron, 1941) in the form of drops. Moreover, it seems desirable that the drops should be applied at frequent intervals, to ensure the maintenance of effective concentrations over prolonged periods. In special circumstances it may be necessary to apply the drops in the form of a constant drip in order to build up the necessary concentrations in the anterior ocular tissues. It is possible that this may also be achieved by the application of the drug in the form of an ointment, a method which has already been used in the treatment of burns.

Guyton (1941) has, indeed, made observations on the penetration of sulphanilamide applied in the form of ointments to the rabbit's eye, and has found concentrations up to 40 mg. per 100 c.cm. in the aqueous. He emphasizes the importance of a freely soluble sulphonamide for local use. It is possible that the optimum method of applying sodium sulphacetamide clinically may well be in the form of an ointment.

Summary

Solutions of sodium sulphacetamide were applied to the eyes of rabbits, contact was maintained for various periods of time, and the penetration of the drug into the various ocular tissues was determined. Very high concentrations were reached under certain experimental conditions.

The rate of disappearance of the drug introduced into the eye was also studied. The initial fall in concentration was rapid, but slowed down subsequently, so that chemotherapeutic levels were maintained in some tissues for two or more hours.

Drops of a 2.5% or 30% solution of sodium sulphacetamide were instilled into the conjunctival sac as under clinical conditions, and the concentrations of the drug in the ocular tissues at various periods following the instillation were determined. With the 2.5% solution chemotherapeutic levels were observed only in the conjunctiva.

The advantages of the local application of sulphonamides in the treatment of eye infections are discussed. The results are examined with regard to their bearing on the most suitable concentration and frequency of administration of sodium sulphacetamide under clinical conditions.

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The annual report of the Industrial Welfare Society (14, Hobart Place, S.W.1) briefly records a large and varied activity which has included conferences, courses of lectures, contacts with Government Departments, and replies to innumerable inquiries on welfare work. The society is responsible for recommending to a number of firms suitable candidates for welfare work, and considerable time is taken in interviewing applicants who look to the society for guidance. The issue of the Factories (Medical and Welfare Services) Order and the setting up by the British Medical Association of the Industrial Health Committee (which has lately reported) drew attention to the advantages of closer linkage between doctor and factory, and meetings were arranged in several provincial towns to which local employers and practitioners were invited with a view to fostering such association.