pallor increased. The needle was removed and the head of the couch lowered. Two minutes later he was still pale: B.P. 85/55, P. 40. Five minutes later his colour was a little better. Twenty minutes later he was still rather pale, but feeling well: B.P. 95/60.

Case 41.—Female aged 28. She was nervous beforehand, but had neither fainted nor been bled before: B.P. 165/95, P. 136. During bleeding she felt throbbing in the left arm, sick, "peculiar," and faint. She covered up her eyes and said she felt warm. Bleeding was stopped after 4 minutes, when 250 c.cm. had been taken. Two minutes later the donor was very cold and clammy: B.P. 80/55, P. 60. Eight minutes later she was still pale but not sweating; she said she felt better, and walked into the recovery room. After 33 minutes she said she felt quite well, but while the blood pressure was being taken she felt faint and lay down: B.P. 65/35, P. 60. After 43 minutes she was still pale; she walked across the room and sat down. At 56 minutes she was still pale, but felt well: B.P. 140/85, P. 96.

Case 42.—Female aged 28. Initial B.P. 115/75, P. 84. She was quite well during bleeding, but 3 minutes later felt sick and dizzy, but was not pale: she was sweating slightly. The head of the couch was lowered; 5 minutes later she walked to the recovery room, where she "flopped down on a bed." After two minutes, B.P. 115/75, P. 80; 20 minutes later, B.P. 100/70, P. 136; 38 minutes after bleeding she felt and looked normal.

Case 47.—Male aged 26. This donor was very nervous and had often fainted before, but had not previously been bled. After bleeding for one minute, when only 100 c.cm. had been taken, he became pale; the pulse slowed and became impalpable. The needle was removed and the head of the couch lowered. He suddenly developed a typical convulsive attack, during the course of which he was pale, cold, and clammy; towards the end he flushed and then became pale again, recovering consciousness in 4 minutes. After 25 minutes he stood up; he was very pale and sat down again. Five minutes later he was still pale and feeling faint. Fifty-six minutes from the onset he was still faint and pale. Discharged and sent home by car. Before bleeding, B.P. 165/100, P. 80; at end of attack, B.P. 165/85, P. 60; after 8 minutes, B.P. 145/85, P. 72; after 13 minutes, B.P. 135/75, P. 80; after 22 minutes, B.P. 125/75, P. 60; after 30 minutes, B.P. 135/85, P. 72; after 56 minutes, B.P. 120/75, P. 64.

Summary

Observations have been made on a group of donors who fainted as a result of blood withdrawal, and the incidence of the different signs and symptoms has been analysed. Illustrative cases are given.

The majority of donors show a fall in pulse rate and blood pressure, but this is not invariable.

The faint in donors has so many points in common with the syncopal attacks described by Lewis in soldiers with effort syndrome, and by Ferris, Capps, Weiss, and Baker in individuals with hyperactive carotid sinuses, that it appears possible that the underlying mechanism of their production is the same. Modifications of the picture are probably due to the fact that the donor is in a recumbent position.

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C. P. Ward (*Arch. Pediat.*, 1941, **58**, 83), who records a personal case, illustrates the rarity of encephalomyelitis in measles by the fact that there were only five examples of this complication among 11,747 cases of measles. His patient was a girl aged 6 years, who developed severe encephalitis at the height of measles. For several days the prognosis appeared hopeless, but the encephalitis subsided and was followed shortly afterwards by transverse myelitis with flaccid paralysis and incontinence of urine. After nine days of complete paralysis recovery began and became complete, except for spastic paresis of the legs noted two months later.

LOCAL EFFECTIVENESS OF SODIUM SULPHACETAMIDE (ALBUCID SOLUBLE) IN TREATMENT OF EXPERIMENTAL ULCERS OF THE CORNEA

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There has been considerable discussion recently as to whether sulphonamides are capable of exerting their chemotherapeutic action when applied locally. Extensive trials have been made of the value of these drugs in the treatment of infected wounds and burns (see Colebrook, 1941; Buxton, 1940). While no general agreement has yet been reached, the consensus of opinion, based on clinical evidence, would seem to be that they are effective for some types of infections provided they are applied prophylactically or in the early stages of the infection.

There is, however, little experimental evidence concerning the value of locally applied sulphonamides in the treatment of infected wounds. A number of investigators have shown that some sulphonamides will prevent the development of gas gangrene when given locally together with the infecting organism. A delay of a few hours, however, greatly decreases the effectiveness of the drugs, and most, if not all, of the infected animals rapidly die (Legroux, 1940; Hawking, 1941; Gordon and McLeod, 1941). Nitti (1939) showed that the local application of sulphanilamide to wounds infected with streptococci in rabbits would prevent death of the animals.

The Investigation

It appeared to us that the eye would provide a very satisfactory medium for the study of the action of locally applied drugs on infection. The course of the infection can be followed accurately, and observations can be made as often as desired without unduly disturbing the animals. Moreover, each experiment can be very satisfactorily controlled, since one eye in each animal can be used for comparison. Rambo (1938) performed a few such experiments on rabbits, and the results suggested that the injection of sulphanilamide together with haemolytic streptococci into the anterior chamber of the eye would prevent the occurrence of a destructive infection.

Progressive septic lesions of the eye can easily be produced experimentally by infecting the cornea with *B. pyocyaneus* (see Axenfeld, 1908). It has, moreover, been shown (Joy, 1940) that the course of such lesions in rabbits can be favourably influenced by the oral administration of sodium sulphapyridine. We therefore decided to determine whether the local application of a sulphonamide would affect the course of such an actively progressive and destructive lesion.

In deciding which sulphonamide to use in these experiments we considered that the following properties were desirable: (i) it should have a high solubility in order to produce a reasonably high local concentration; (ii) it should be non-irritant; (iii) it should form a solution which does not deviate a great deal from neutrality; and (iv) it should readily penetrate into tissues.

Few of the known sulphonamides possess the above properties. One compound which does, however, conform

to the above standards is sodium sulphacetamide.* Since we had used this compound previously, in as yet unpublished experiments, with very satisfactory results, and since it has also been used with satisfactory results in the form of a paste applied locally in the treatment of burns (Robson and Wallace, 1941), we decided to employ it in the present investigations.

Methods

All experiments were performed on mature rabbits, of both sexes and of several breeds. Following various preliminary experiments a technique was devised by which a standard lesion of the cornea could be produced. In all the experiments such lesions were made in both eyes of every rabbit, one eye being treated while the other was used as a control. Great care was taken to make sure that the lesions were equal in both eyes, and on the few occasions when there was a slight inequality the treatment was applied to the eye with the larger lesion.

The lesion was produced under ether anaesthesia by removing the corneal epithelium with a discission needle. The area denuded was carefully measured by means of callipers and was usually about 4×4 mm. in extent. Accurate observation was assisted by the wearing of a Bishop Harman binocular loupe. In order to make quite certain that equal lesions were being produced the denuded areas in both eyes were, in preliminary experiments, stained with 2% fluorescein and were found not only to be equal in area but also to stain with equal intensity.

The lesions were inoculated with a culture of *B. pyocyaneus* by means of a metal loop. For each experiment a fresh twenty-four-hour culture on agar slope was prepared from a stock culture. (We are greatly indebted to Dr. Oag of the Bacteriology Department, University of Edinburgh, for the supply of these cultures.) After the application of the culture the lids were held apart for one minute and then allowed to close.

At periods of 1, 5, and 12 hours after application of the culture treatment with sodium sulphacetamide solution (30%) was begun. The lids were separated, and the lower lid pulled away from the eyeball, after which a few drops of the solution were placed on the cornea and into the lower conjunctival sac. This treatment was repeated four or five times daily. On each occasion a similar quantity of normal saline was applied by the same method to the control eye.

The eyes were examined daily during the first week, and thereafter at intervals of a few days. Detailed records were kept regarding the condition of the cornea, lids, and conjunctiva. After a note had been made of the amount of conjunctival discharge and the degree of corneal damage, a few drops of 2% fluorescein solution were instilled into both the treated and control eyes, and a note was made regarding the exact state of the corneal epithelium. Particular attention was paid to the degree of corneal oedema, the presence or absence of ulceration, abscess formation, or hypopyon. The eyes were usually photographed at 48 hours, towards the end of the first week, and towards the end of the period of observation, when the lesions in untreated eyes had either led to gross disorganization or become quiescent scars.

In the experiments in which treatment was started 12 hours after production of the lesion the eyes were carefully examined before the first treatment, by which time a definite, active, infective lesion was quite evident. In most cases the lesions were exactly equal in both eyes, although

in a few there was a very slight difference; in the latter cases the worst lesion was chosen for treatment.

The lesions in the control eyes developed along very definite lines although there were variations in severity. Twelve hours after inoculation the appearances were those of an infected abrasion. There was oedema at and around the site of the lesion; most of the lesion stained with fluorescein, although a certain amount of epithelization was occurring at the margins. There was also definite conjunctival and ciliary injection and some iritis. At 24 hours there was definite corneal ulceration, which then rapidly progressed until at 48 to 72 hours the ulceration was severe and fairly extensive, and in some cases ring abscess formation was evident, with or without hypopyon. At the beginning of the second week the ulceration or abscess formation had in most cases involved almost the whole of the cornea; some of the eyes perforated and ultimately shrank, while others developed gross vascularized scarring of the cornea, with staphylomatous changes in most cases. In a few animals scarring, although dense, was limited to an area involving about half of the cornea.

Conjunctival discharge had in most cases become fairly copious by the second day; but the conjunctivitis was not of long duration, and by the end of the first week there was, as a rule, little or no discharge.

Effects of Treatment

The effects of treatment, begun respectively at 1, 5, and 12 hours, on the corneal lesions are summarized in the table. It will be seen that when treatment was started

Table showing the Effect of Local Treatment with Sodium Sulphacetamide (30%), Begun at Various Periods after Inoculation with B. pyocyaneus, on the Development of Corneal Lesions

	Treatment begun after	No. of Eyes showing			
		No Ulcer	Moderate Ulcer	Severe Ulcer	Extensive Necrosis
Treated eyes ..	1 hour	11	4	2	0
Control eyes ..		0	4	4	9
Treated eyes ..	5 hours	5	0	2	5
Control eyes ..		0	0	3	9
Treated eyes ..	12 hours	2	1	8	1
Control eyes ..		0	0	2	10

1 hour after inoculation the effect was very pronounced. Ulceration was prevented in about two-thirds of the treated eyes, and in no case was there extensive necrosis; whereas in the control eyes ulceration occurred in all cases and extensive necrosis in more than half. By 24 hours the beneficial effect of treatment was usually evident, and the difference was considerable at 48 hours.

The treatment had also a beneficial action on the conjunctivitis: 10 out of the 17 treated eyes showed no conjunctival discharge, in 6 it was slight, and in 1 it was moderate. Of the control eyes 10 showed slight discharge; it was moderately severe in 6, and copious in 1. The condition of the treated and control eyes of a typical animal is shown in Fig. 1 (rabbit 322). It can be seen that, while the control eye had developed along the course described above, the lesion in the treated eye rapidly healed.

When treatment was started 5 hours after inoculation the effect was still quite pronounced, although not so striking as when treatment was instituted at the earlier stage; thus whilst ulceration was prevented in 5 out of 12 eyes, 5 of the treated eyes did develop extensive necrosis. The conjunctivitis was also beneficially influenced by treatment at this stage. Of the treated eyes, 7 showed no discharge, 4 slight discharge, and 1 moderate discharge; while in the control eyes discharge was evident in all cases, being slight in 4, moderate in 7, and severe in 1.

* This is the sodium salt of sulphacetamide, with which it must not be confused, since the latter has a low solubility and has to be administered orally.

When treatment was delayed until 12 hours after inoculation its value was very definitely lessened. Nevertheless even at this stage it exerted a beneficial effect in most instances. Ulceration was totally prevented in only 2 of the animals in this group, but on the other hand the lesions in the treated eyes were less severe than in the controls. The difference is well illustrated by the course of the lesions in rabbit 384 (Fig. 2). When examined at 12 hours, immediately before treatment, the lesion in the right eye was very slightly more severe than in the left, and the right eye was therefore chosen for treatment. Seventy-two hours after inoculation both eyes showed moderately severe corneal ulceration, which was slightly more extensive in the control eye. The ulcer in the treated eye gradually healed, leaving a fairly dense scar, which is clearly visible in the photograph. The ulcer in the control eye rapidly spread to form a ring abscess, and ultimately there was gross scarring which involved the greater part of the cornea.

Although conjunctivitis was again not a marked feature in the clinical picture, treatment had some beneficial effect; conjunctival discharge was present in all but one of the control eyes, whereas in 10 out of the 12 treated eyes no discharge was noted.

Discussion

This investigation has shown definitely that under the experimental conditions described a sulphonamide can produce its chemotherapeutic action when applied locally.

The problem of the period after infection at which local application of sulphonamides can still control such an infection is of great importance in connexion with the treatment of wounds, and especially of war wounds. It is therefore of particular interest to note that, in the present experiments, when the drug was applied for the first time 1 hour after inoculation with the organism the beneficial effect of the treatment was most pronounced; at 5 hours there was still a very definite effect; and even at 12 hours a certain degree of benefit was produced.

These results are in general agreement with the clinical experience that prophylactic treatment with sulphonamides must be instituted at the earliest possible moment in order to provide the maximum benefit. This point of view has been emphasized by Buttle (1940) in his discussion of the part played by chemotherapy in the treatment of wound infection.

Our results suggest that sodium sulphacetamide penetrates readily through the cornea, and experiments only recently reported by J. M. Robson and W. Tebrich show that this is the case. Indeed, under certain conditions it has been possible to produce, by the local application of a solution of the drug to the

conjunctival sac, concentrations in the cornea, aqueous, and iris which are much higher than can be produced when sulphonamides are administered orally or parenterally. Quite

FIG. 1.—(Rabbit 322.) Showing effect of treatment started one hour after inoculation. Right eye treated with 30% sodium sulphacetamide; left eye control. The treated eye showed an infected abrasion which was fully epithelized by the 5th day; the resultant scar was very faint and superficial, and cannot be seen on the photograph. The control eye showed an abscess involving two-thirds of the cornea by the fifth day. By the 17th day the cornea was markedly staphylomatous and had actually perforated; by the 32nd day the whole cornea was grossly scarred and the eye was shrinking.

FIG. 2.—(Rabbit 384.) Showing the effect of treatment begun at 12 hours. Photographs taken on 24th day after inoculation. The treated eye has a fairly dense central scar, slightly larger than the initial lesion. The control eye shows gross scarring of most of the cornea.

high concentrations are present in the cornea even within five minutes of the application of the drug. Of interest, too, is the fact that sulphanilamide has also been shown to penetrate readily through the cornea, especially when it is put in the conjunctival sac in the form of a powder (P'an, 1941); under these conditions high concentrations were found to be present at the end of one hour.

These experimental results suggest that the local application of certain sulphonamides might be of value in the treatment of infective conditions of the eye. The oral administration of sulphonamides has already been used in the treatment of trachoma (Lian, 1938; Loe, 1938; Thygeson, 1940), and although the drugs have not been proved to have any action on the trachoma virus itself, there appears to be general agreement regarding their value in controlling the secondary infection. There are, however, very few records regarding the value of locally applied sulphonamides in the treatment of eye conditions, although Johnstone (1941) has used various sulphonamides locally, in solution or as a powder, for the treatment of hypopyon ulcers.

During the past year sodium sulphacetamide has been used in the eye wards of the Royal Infirmary, Edinburgh (Traquair, Cameron, Paterson, Flint—personal communications) in the treatment of various infections of the eye, and especially of hypopyon ulcers of the cornea. The impression has been obtained that this treatment is of considerable value, although much further work will be necessary to assess this value accurately. Concentrations of the drug up to 30% have been used in this clinical work, and have produced no irritation or other ill effects, thus emphasizing the advantages of a substance which gives a neutral non-irritant solution.

Summary

Equal areas of corneal epithelium were removed from both eyes in a number of rabbits and the lesions infected with *B. pyocyaneus*. In all animals one eye was used as a control, the other eye being treated with a 30% solution of sodium sulphacetamide. All control eyes developed severe corneal ulceration.

When the first treatment was applied 1 hour after inoculation with the organism, ulceration was completely prevented in 11 out of 17 eyes; when it was applied 5 hours after inoculation, ulceration was completely prevented in 5 out of 12 eyes. When the first treatment was applied 12 hours after inoculation, ulceration was prevented in only 2 out of 12 eyes; the lesions in the 10 remaining eyes, however, were less severe than in the control eyes.

The relevance of these findings to the clinical use of the drug for the treatment of infective eye conditions by local application is discussed.

We are indebted to Mr. A. W. Edwards of British Schering Ltd. for the supply of the 30% sodium sulphacetamide solution. We should like to thank the W. H. Ross Foundation for the Prevention of Blindness, which defrayed the expenses of this investigation.

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DELAY IN THE UNION OF FRACTURES

BY

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While it is a common practice to describe the normal healing of fractures as a process which extends over a period of a certain number of weeks, it is recognized that the rate of union is not the same in all areas. Fractures occurring in the neck of the femur and in the carpal scaphoid unite slowly and uncertainly, probably on account of the peculiarity of their blood supply and the difficulty of maintaining the fractured surfaces in apposition for a sufficiently long period. A similar sluggishness in the normal process of union is also found in fractures of the tibia, particularly in the region of the junction between its middle and lower thirds. At this site delay in union is common and definite non-union is occasionally seen, apparently in spite of adequate treatment. In this case the delay cannot be attributed to difficulty in maintaining apposition of the fractured surfaces, but seems to be caused by the absence of any vascular muscle attachment to this area of the bone and by the necessary restriction of blood supply to an easily torn nutrient artery. The lagging in the normal process of union at this point has long been appreciated, but since the beginning of the war the delay has been greater and has occurred in a higher percentage of cases than previously.

Rate of Union

Figures collected by different surgeons with respect to the normal rate of union of any particular fracture are of comparatively little value, because the standard varies so greatly as to what clinical and x-ray evidence constitutes union. It is therefore impossible to set down any specified number of weeks as the normal period for union in a particular fracture treated adequately and continuously, but it can be agreed that if, after fourteen to sixteen weeks of complete immobilization, union is not yet present in a perfectly reduced fracture of the tibia the designation of delayed union may safely be applied.

Owing to the transference of patients in wartime from one hospital to another it has been possible to examine a very large number of fractures at all stages of treatment, and the original impression that the rate of union of fractures of the tibia is much slower than previously has become a conviction. The reason for this alteration in the normal rate of union must be either a change in the patient's metabolic processes or some alteration in the generally accepted standard treatment for this type of fracture. It seems impossible to accept the suggestion of a change in the patient's metabolic processes, especially as there has been little or no alteration in the rate of union of fractures of other bones. The only alteration in treatment during the past few years is the almost universal adoption of non-padded plaster casts for the treatment of every fracture of the lower limb.

For the promotion of union in any fracture there must be apposition of the fractured surfaces and immobilization of the broken bone for a period long enough to permit consolidation of the callus. Fractures will unite even though there is not exact apposition of the broken surfaces; in fact, it has been shown by Wardle that the rate of union in a fractured tibia is greater with slight overlapping of the bone ends than with perfect apposition. Similarly, if complete immobilization has not been secured union may occasionally take place rapidly and completely. This is illustrated in fractures of the clavicle and in fractures of