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aged twenty-nine. Since then there have been no symptoms of neurological disease.

CASE 31. Female. Sudden onset of left visual failure eleven years ago, when aged twenty-six. Patient refused to be examined and said she was quite well.

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TREATMENT OF SEVERE INFECTED CORNEAL ULCERS BY SUBCONJUNCTIVAL INJECTIONS OF PENICILLIN TWICE DAILY WITHOUT HOSPITALIZATION, WITH SHORT REVIEW OF OTHER METHODS*

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OCULISTS, like myself, who work alone in their clinics without medical assistants, look for a method of penicillin administration, which is practical, efficient and economic for the successful treatment of infected corneal ulcers. By the word "practical" I mean that it should not cause much strain either to the doctor or to the patient, or to his attendants at home, and should not interfere with their sleep. By the word "efficient" I mean that it should be able to control the infection instantly so that it spreads no more, and this control must be followed by rapid improvement and progressive healing. By the word "economic" I mean that the method should

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not imply the use of much penicillin, as some patients are unable to pay the cost of penicillin if massive doses are to be used daily for few days. This point assumes special importance when we notice that severe infected ulcers of the cornea in Egypt mostly occur in the poorer classes who do not seek for medical advice except when their condition is very bad.

A brief review of the chief methods used is necessary, and we have to consider them in the light of the three criteria mentioned above.

One of the methods of penicillin administration for ocular affections is the systemic mode of administration used for a great variety of infections in general medical practice. Penicillin need not be administered intra-muscularly in aqueous solution or saline every three hours as this is not practical, but it can be given in massive doses suspended in oil and beeswax twice daily.

Sorsby and Ungar (1946a) showed that penicillin administered systemically in massive doses reaches in therapeutic levels all the tissues of the globe, the lens excepted. By massive doses is meant the injection of 25,000 to 50,000 units intra-muscularly or intravenously into rabbits of an average weight of 1.5 kilograms. Duke-Elder (1947) commenting on this fact says that this dose is of the order of 40 or 50 times that of the usual clinical dose in man. We can imagine that massive doses administered systemically for ocular purposes must be very expensive apart from the other disadvantages such as difficulty of administration.

Local therapy by subconjunctival injections is much more economic than massive therapy by systemic administration. It may be noted that whenever subconjunctival injections of penicillin are mentioned in this paper only the pure crystalline white calcium or sodium salt is meant because it is well tolerated. Sorsby and Ungar (1947) showed that substantial concentrations of penicillin in the ocular tissues many times the usual therapeutic level can be obtained by the subconjunctival injection of crystalline penicillin in a dose of 50,000 units and that adequate levels persist for 6 hours. Sorsby and Reed (1947) subsequently elaborated their method of local penicillin therapy in cases of hypopyon formation by 12 to 16 subconjunctival injections of 50,000 units every 6 hours, followed by the 4 hourly instillation of penicillin ointment in a concentration of 100,000 units per gram. Among their group of 66 cases with hypopyon, there were 39 cases of infected corneal ulcers.

These authors made a detailed analysis of these cases of infected corneal ulcers with hypopyon treated by different methods of local penicillin therapy. They show subconjunctival injections to be the method of choice. It was successful in 18 out of 21 cases so treated. In three patients subconjunctival injections of penicillin proved inadequate and general sulphonamide therapy was applied. This

method of penicillin therapy by subconjunctival injections every six hours cannot be applied except in hospitals with resident doctors who can give the injections by night. Moreover as it entails the use of 200,000 units per day, it cannot be said to be economic. But there is no doubt that it is the most efficient method.

For general penicillin therapy the use of penicillin in oil and bees-wax has greatly reduced the number of injections so that two injections can be given daily. The question, as to whether the same material can be used subconjunctivally twice daily, arises. Sorsby and Ungar (1946b) found by animal experiments that such a procedure gave a high and sustained level of penicillin, but it was clinically inapplicable in ocular affections as it produces a severe reaction with gross corneal damage.

It was by chance that I was forced to try the use of two injections of penicillin daily. During the summer of 1947, a shortage of the supply of penicillin occurred in Egypt, and it was very difficult to get it except for few patients after complicated procedures. Under such a condition, extreme economy in the use of penicillin was necessary. The first case in which subconjunctival injections of penicillin were used by me is worth being reported in detail as it impressed upon me the efficiency of subconjunctival injections twice daily, as well as its superiority over some other methods of local penicillin therapy.

Case Report with Comment

On 18th July, 1947, M.S., a male rural infant, aged 18 months, was brought to my clinic by his parents. There was a history of typhoid fever of one month duration, towards the end of which he became very thin and developed an opacity in the right eye since four days ago and in the left eye since two days ago. On examination, he was found to be very emaciated, but there was no fever, and apart from his eyes, there was no other abnormality. The right conjunctiva was injected. There was a large deep ulcer in the right cornea, which occupied almost all the lower half of the right cornea and encroached on the upper half, covering the whole pupillary area. Its base was dirty, sloughing and thin and there was a severe hypopyon occupying about one quarter of the anterior chamber. The left conjunctiva was injected. There was an ulcer in the lower part of the left cornea occupying about one sixth of the corneal surface. No hypopyon existed in the left eye.

General treatment by the appropriate diet, vitamins and tonics was carried out by a paediatrician.

It was evident that the right eye was in a most serious state and there was a great danger of its being lost. In an attempt to save the right eye, I decided to use penicillin in this case, and to use it

economically as there was a great shortage of this drug at that time. An amount of 10 c.c. of distilled water was put in a bottle of 100,000 units of crystalline penicillin; 3 c.c. of the solution were taken, and diluted with 9 c.c. of distilled water so that a solution containing 2,500 units per c.c. was obtained, and this was used as drops for both eyes after a preliminary wash of the eye. The treatment started at about 10 a.m., and consisted of the instillation of two drops of that solution in each eye every minute for the first half-an-hour, then every five minutes for the next half-an-hour. At the end of the first hour, the left ulcer improved, and its base became clearer. The improvement in the right ulcer was dramatic. Its base which was very dirty, became clearer to a marvellous extent. The application of drops for the first hour was carried out by the nurse, but after this first hour, I sent the patient home with instructions to his parents to instil the drops every half-an-hour. At 7 p.m., I saw the patient again and the condition of both ulcers was as bad as when first seen. The parents denied any neglect, but probably there was gross neglect, as the type of parents, who bring their child to medical treatment only when the disease is far advanced, are usually negligent. It is equally possible that in this case half-hourly instillations of penicillin drops were not adequate. Again I repeated the instillations just as in the morning, every minute for the first half-an-hour, then every five minutes for the next half-an-hour. Again the same marvellous improvement occurred, and again I sent the patient home with instructions to use drops every half-an-hour as long as either of his parents could keep awake by night, noting that penicillin in oil and beeswax for systemic administration was not available. Next morning both eyes were seen to be as bad as when first seen. It seemed that though the case responded well to penicillin, some change in the mode of administration must be made. Probably half-hourly instillations at home were not adequate but more frequent instillations were very tedious to the attendants and did not seem to be practical. Probably some neglect in following the instructions was responsible for the failure. Subconjunctival injections seemed to offer a mode of treatment which the attendants could not affect by their neglect. These had to be carried out twice daily, as I could not give them more frequently with convenience. 0.5 c.c. of the solution already prepared in the bottle was injected twice daily in each eye. This amount contained 5,000 units of penicillin. Seven subconjunctival injections were given in each eye over a period of three and a half days. Rapid and progressive improvement was noticed during this short course. Apart from atropine ointment twice daily no other treatment was applied locally.

Towards the end of the course the base of each ulcer was quite clear and the right hypopyon disappeared. Owing to the shortage of penicillin no more injections could be given. Lamellae of penicillin,

each of 250 units, and penicillin ointment of a concentration of 1,000 units per gram were prescribed and were ordered for use every hour alternately. They were used during daytime and most of the night, and the application was made by the mother at home. Twenty-four hours from the onset of the use of lamellae and ointment, the base of the ulcers on both sides became gray and infiltrated.

This indicated that penicillin injections should be resumed, but no crystalline penicillin was available for further injections. Two days later the right ulcer perforated with the formation of a small prolapse of iris. Rapid healing of the right ulcer followed the occurrence of the iris prolapse. Healing of the left ulcer occurred without prolapse.

The behaviour of the right ulcer seemed to show that lamellae and ointments of the concentration mentioned above are not so efficient as subconjunctival injections. Moreover the difficulty of their application safely in infants and young children, who often struggle during their application, renders their use at home unsafe in cases of ulcers with thin base because of the danger of inducing perforation. Also the possibility of neglect exists with such types of patients.

Further Development and Details of the Method of Subconjunctival Injection of Penicillin Twice Daily

The case mentioned above pointed to a method of penicillin administration which was practical, efficient and economic. It was worthy of further trials and attempts towards perfection.

Patients dislike subconjunctival injections and the majority object to them. Two instillations of 1 per cent. pantocaine solution at three minutes intervals while the eyes are closed are harmless to the epithelium and produce sufficient anaesthesia to allow the prick of the needle to be done almost painlessly.

Apart from the prick of the needle, the mere infiltration of fluid under the conjunctiva causes some pain while the fluid is actually passing and for some time afterwards and this pain can be easily abolished if 1 per cent. novocaine solution in non-pyrogenic distilled water is used instead of simple distilled water in the preparation of penicillin solution.

A concentration of 20,000 units per c.c. was found to be quite satisfactory in cases where 10,000 units per c.c. was not quite satisfactory. Therefore to a bottle of 100,000 units of crystalline penicillin salt, 5 c.c. of 1 per cent. novocaine solution in distilled non-pyrogenic water was added, and 0.5 c.c. was injected subconjunctivally twice daily, at about 9 a.m. and 8 p.m., each injection being given after two instillations of 1 per cent. pantocaine solution. The eye is opened and partially fixed by a pair of Desmarres' retractors applied to the lids with their tips introduced into the fornices if the patient is unable to open and fix his eye while the injection is being given subconjunctivally at a distance of 2 to 3 mms. from the limbus.

The use of Desmarres' retractors is specially valuable when the injection is given above the limbus. It is advisable to change the site of injection every time. Even in unsteady nervous children, the injections can be safely given. The trunk and hands are fixed by another nurse; the nurse holding Desmarres' retractors assists slightly in fixing the head by the same hands; and the doctor can use one hand for fixing the head while the other hand holds the syringe and gives the injection.

One bottle of 100,000 units is enough for a course of 5 days which is usually sufficient. The addition of adrenalin chloride solution to penicillin solution to render it less readily absorbable into the general circulation is liable to destroy the penicillin especially because of the long period of 5 days over which the acid adrenalin chloride acts on penicillin while it is in the bottle until it is completely exhausted. The destructive effect of solutions, even of poor acidity on penicillin was demonstrated by Garrod (1945). Therefore no adrenalin chloride solution, which is acid, may be added to penicillin solution (Cameron 1945).

One course of 10 injections is usually sufficient for almost all cases. At the end of the course the healing of the ulcer is progressing well, and it is quite sufficient to use frequent wash and hot fomentations after stopping the injections. If the slightest sign of infiltration recurs, the course may be repeated partially or completely according to the discretion of the oculist.

In addition to penicillin injections, atropine ointment 1 per cent. twice daily is applied as a routine in all cases, except in eyes predisposed to glaucoma.

No other local or general treatment was applied in the majority of cases as long as the injections were given. But frequent wash and hot fomentations were used after the course was completed.

In a small proportion of cases, the improvement produced by the first few injections was slight. In them the use of frequent wash, hot fomentations and local sulphadiazine ointment 5 per cent. every two hours, in addition to subconjunctival injections of penicillin, helped to accelerate cure.

It may be noted that in general medical practice some practitioners dislike the use of penicillin in oil and beeswax, and use massive doses of penicillin in water two or three times daily with good clinical results. The success of subconjunctival injections twice daily runs parallel with the success of massive doses of aqueous solutions of penicillin administered twice or thrice daily in general medical practice.

If there is muco-purulent or purulent discharge in the conjunctival sac in cases of corneal ulcers, subconjunctival injections of penicillin should not be administered before the discharge is controlled by

penicillin drops in the mode suggested by Sorsby for ophthalmia neonatorum. A solution of crystalline penicillin of a concentration of 2,500 units per c.c. is prepared. Two drops are instilled into the eye every minute for the first half-an-hour, then every five minutes for the next half-an-hour. At the end of half-an-hour, the discharge practically ceases in penicillin sensitive cases, but the drops should be continued every five minutes for another half-an-hour. Then subconjunctival injections can be started. If the discharge is resistant to penicillin drops, subconjunctival injections are contraindicated for obvious reasons. The micro-organism causing the ulcer is that of the associated conjunctivitis and as the discharge causing the conjunctivitis is not controlled by penicillin, the micro-organism is penicillin resistant and no useful purpose is served by subconjunctival injections. Moreover there is obvious danger of deep infection in the orbit. Fortunately, cases of conjunctivitis with severe ulcers of cornea are usually sensitive to penicillin.

Comparative Value of this Method

No attempt is made to compare the therapeutic value of the method of subconjunctival injections of penicillin twice daily with the method of subconjunctival injections every six hours. The practical disadvantages of the latter method have already been mentioned.

A comparison between this method of two subconjunctival injections of penicillin daily as detailed above and the routine older methods of treatment without penicillin is to be considered.

In pre-sulphonamide days the routine treatment of infected corneal ulcers was by frequent wash, hot fomentations and atropine ointment. To these, foreign protein therapy was very frequently added. Milk injections are the form in which foreign protein is usually administered in Egypt. Ten c.c. of sterile milk are administered intra-muscularly every other day. A course of 2 to 5 injections is usually given. Milk injections usually cause rapid clearing of infected corneal ulcers, but very frequently ulcers grow much deeper and even perforate while milk injections are administered, and ophthalmologists in Egypt believe that this increase in depth, and even perforation, are provoked by milk injections.

General sulphonamide therapy formed a substitute for milk injections and was used in addition to frequent wash, hot applications and atropine ointment. Sulphathiazole was administered in doses of one gram. four or five times daily. This treatment could not control the progress of the ulcer for 2 or 3 days or even more. Severe ulcers frequently perforated in spite of this treatment.

Penicillin therapy, in the method detailed above, has the great value of immediately controlling and stopping the progress of the

ulcer from the first injection. Then the base and margins of the ulcer quickly get progressively clearer, and gradually healing occurs. Only severe infected ulcers of the cornea were selected for this form of therapy. Milder forms of corneal ulceration were excluded as they responded rapidly to older methods of treatment. The severe cases selected for penicillin therapy were 26 in number. Some of them were traumatic with or without hypopyon but most were secondary to purulent conjunctivitis and a few were secondary to mucopurulent conjunctivitis. Most of them responded rapidly, almost immediately to subconjunctival injections of penicillin as detailed above. The progress of the ulcers was stopped after the first injection, then the base and margins became clearer and progressive healing followed.

Few cases showed slight response and the improvement produced by the first few injections was slight. In them penicillin can be said to be inadequate and the use of frequent wash, hot fomentations and local sulphadiazine ointment 5 per cent. every two hours during daytime, in addition to subconjunctival injections of penicillin helped to accelerate cure. Not a single case of perforation occurred in this series of 26 cases of severe infected corneal ulcers.

Conclusions

This method of treatment yields better results than the older methods of treatment in which general sulphonamide therapy or foreign protein therapy formed a part of the treatment. This claim is supported by general clinical observation as mentioned above, but no comparative statistics were made. This method is considered to be a practical, efficient and economic mode of penicillin administration in severe infected corneal ulcers.

Summary

A method of treatment of severe infected corneal ulcers by subconjunctival injections of penicillin twice daily is described.

The value of this method compared with the older methods of treatment is discussed. This value is demonstrated by general clinical observation but no statistics were made.

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