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THE TREATMENT OF SEPTIC ULCER OF THE CORNEA BY LOCAL APPLICATIONS OF PENICILLIN*

BY

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FROM THE PENICILLIN UNIT, ST. MARY'S HOSPITAL, PADDINGTON

REPORTS from various sources have shown that the therapeutic results of penicillin applications to the eye are beneficial and occasionally dramatic.

Examples are to be found in the papers on catarrhal ophthalmias (Milner, Cashiell, Crawford and King), ophthalmia neonatorum (Sorsby and Hoffa) and in deep infections (Rycroft).

Septic ulcer of the cornea with or without hypopyon is a matter of considerable clinical severity, and it is a fact well known to ophthalmologists of experience, that the prognosis with regard to the immediate cessation of the ulcerative process is a matter depending not only upon the virulence of the infecting organism, but also in a marked degree upon the general condition of the patient. The prognosis varies definitely with the age of the patient. In children ulcer with hypopyon responds well to ordinary routine treatment; but in old broken-down persons the prognosis may be bad indeed.

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The recognised treatments of septic ulcer are numerous and varied, and it has been a source of interest through a number of years to one of us (F.A.J.) to see the enthusiasm accorded to new forms of treatment, relegated in due course to the long list of "also ran."

A recent vaunted local treatment, sodium sulphacetamide, does not appear to have convinced surgeons, in Southern England at any rate, of its outstanding value. It was therefore with hope that clinical treatment with penicillin was started and this report is considered by the authors to show that we have in this new remedy a powerful agent for good in this devastating disease.

No attempt has been made in this series to evaluate the effect of intramuscular penicillin; the product has been used by local methods only:

The number of ulcers treated to date is 23, two of which (No. 7) occurred in the same eye with an interval of one month between the attacks.

We have ventured to assess the results as excellent in 14 cases, good in five cases, poor in two cases and bad in two cases.

The ages of those affected can be grouped as follows:—

Seven over 60 years old; of these, four did excellently and three did well.

Six between 50 and 60 years; one of these did badly (No. 1), three did excellently, and two did poorly (Nos. 14 and 19).

Seven were between 40 and 49 years; two did well, and five excellently.

One was aged 35 years and did not react to penicillin (No. 4, *Bac. Pyocyaneus*).

One was only 14 years of age, and reacted excellently.

Method of use.—The routine treatment has been to instil two drops of the solution on to the lower conjunctiva or if possible on to the cornea itself. After some seconds the instillation is repeated.

This programme is carried out hourly by day, and two hourly by night until the condition is obviously under control, when longer intervals are permitted.

In addition, atropine sulphate is used three or four times daily, and a flap cover over the eye is attached to the forehead.

The solution used is of sodium penicillate in strength 500 units to the c.c. : the drops are well tolerated by the tissues.

In a number of cases, with or without the previous application of decicain, a few crystals of the salt have been applied to the surface of the corneal ulcer itself, the eyelids being held apart by the fingers for approximately a minute after the positioning of the crystals. It was soon found that this application caused no undue reaction to the tissues of the cornea and conjunctiva, and that it could be repeated at discretion with impunity. In some cases the subsequent pain was severe, necessitating morphia or a retrobulbar

injection of 4 per cent. procain. It is suggested that impurity in the drug is the cause of this pain.

Recently, it has been the practice to curette beneath the overhanging edge the underlying infiltrated tissue with a small sharp curette or spud, so that the subsequent trituration of the crystalline salt should enable the latter to attack the infection more vigorously. It is hoped that the severer types of case will respond more readily with this method.

With increasing experience, this method of attack, the rubbing of the strong salt well into the severely infiltrated part of the cornea, is being made use of more frequently. It would seem only reasonable to expect that such a method would give the best chance for the drug to attack or stultify the infection, for the flow of lymph is from the periphery of the cornea, and toward the surface, whilst the increase of tissue tension, even without increased intra-ocular tension, must interfere with the diffusion of the salt into the infected deeper tissues.

This method has also been found of service in disciform keratitis, the surface being scratched or abraded with a Graefe knife, and the crystals rubbed in.

A similar procedure in late infections occurring through trephine blebs has been hopeful in its results. It would seem that a crystal allowed to dissolve on the surface of a trephine bleb exercises a beneficial effect on an infection which has already reached the aqueous and even the vitreous.

Bacteriology.—The bacteriology should be investigated both by smear and by culture, from the ulcer itself and from the lower conjunctival fornix. It is important that the investigations should be made but penicillin treatment should not be delayed until the cultures are developed. In these urgent cases penicillin treatment should be commenced immediately and if next day the cultures show only insensitive organisms it can be discontinued. Insensitive organisms are rare in the conjunctiva: the *Bac. pyocyaneus* was the only one met with in the present series, and that only in one case. The others encountered were all sensitive: the list was as follows:—

- Pneumococcus in 5 cases.
- Staphylococcus aureus in 7 cases.
- Streptococcus in 5 cases.
- Morax-Axenfeld diplobacillus in 3 cases.
- Pneumobacillus in 2 cases.
- Bac. *Pyocyaneus* in 1 case.

An incident of interest was the frequent negative report of smear and/or culture. The use of fluorescein is sometimes responsible for this, whilst previous treatment may at times clear the surface or the lacrimal lysozyme may have a surface effect.

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TABLE I

Case No.	Name	Sex	Age	Days Treatment before healing	Hypopyon	Ulcer, Description, etc.	Bacteriology	Tension	Treatment	Comment
1	J. W. B.	M.	53	24	Sticky	Severe, dense, 1/5 of cornea	? Pneumobacillus	+	Gutt. Pen. 2 days; increase of ulcer; cautery; S. section; albug. Further spread	Bad result, bacteriology uncertain, possibly non-sensitive
2	R. C.	F.	63	14	1/5	Severe, central, 5 mm. diam.	Strep.	N.	Gutt. Pen.	No spread after start of pen. drops
3	E. T.	M.	51	4	1/5	Moderate; circular infiltrate, 2 1/4 mm. diam.	Morax-Ax.	N.	Gutt. Pen.	Very rapid healing
4	?	F.	35	?	None	Severe: 1/3 of cornea	Pyocyanus	N.	Gutt. Pen.; rapid spread; cautery; S. section; albug.	No response to pen.; organism non-sensitive
5	V.	M.	71	18	1/5	Severe: chemosis; 5 mm. diam.	Staph.	+	Gutt. Pen.; on second day S. section and cautery; entropion operation. No further spread	Severe case in old man; healed
6	C. H.	M.	69	5	2/5	Severe: central, 5 mm. diam.	Pneumococ. Staph. Pneumobac.	Full	Gutt. Pen.	No improvement for 2 days then rapid healing
7a	R.	M.	65	7	None	Moderate, 3 mm. excentric. Iritis Central	Staph. Strep.	N.	Gutt. Pen.	Physique poor; a coal-tar worker for 40 years. Rapid healing. The relapse recurred one month later and healed rapidly
7b	R.	M.	65	4	Small		?	Full	Gutt. Pen.	
8	V. H.	M.	14	2	None	Small, cornea hazy	?	N.	Gutt. Pen.	An infected site of an f. b. with infiltrated edges, and whole cornea hazy. Rapid healing

TABLE I—continued

Case No.	Name	Sex	Age	Days Treatment before healing	Hypopyon	Ulcer, Description, etc.	Bacteriology	Tension	Treatment	Comment
9	J. B.	M.	49	12	2/5	Circular, central, severe	Negative	+	Gutt. Pen. 2nd day no better, crystals applied to ulcer. 4th day worse; spread; paracentesis; pen. into A.C. 5th day no undue reaction; 6th day ulcer clean; 8th day marked progress	Did well after paracentesis but not before; bacteriology unknown
10	M.	M.	65	10	4	Severe, nearly whole cornea yellow	Negative	++	Gutt. Pen. 2nd day pen. crystals to ulcer. 3rd day pen. crystals to ulcer. 4th day worse; S. section, sol. pen. into A.C. 7th day improving. 14th day T. n., much improved	This was a grossly neglected case with high tension; it responded well after section but not before. The eye was retained with large ant. synechia
11	S. A.	M.	50	12	Small	Circular, 4mm. diam. Grey base. Yellow edges	Morax-Ax.	N.	Gutt. Pen. 2nd day better; crystals on ulcer. 5th day no improvement. 7th day hypopyon gone, much improved	Good response
12	W. T.	M.	75	8	Minute	Large area of infection of margin of an abrasion over centre of cornea	Staph. Strep.	Full	Gutt. Pen. 2nd day crystals on ulcer. 3rd day I. +1, hypopyon more. 4th day marked clearing	Good response on 3rd day in a fragile old man, who developed mental derangement and intestinal stasis from atropine (?)
13	J. W. P.	M.	57	7	Minute	Circular in upper part. Infiltrated at lower edge. 3 mm. diam.	Pneumococcus	N.	Gutt. Pen. 3rd day slight spread downwards, crystals on ulcer. 6th day improvement marked	Good response. Crystals seemed to benefit

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TABLE I—continued

Case No.	Name	Sex	Age	Days Treatment before healing	Hypopyon	Ulcer. Description, etc.	Bacteriology	Tension	Treatment	Comment
14	A. S.	M.	58	21	+	Severe, circular, infiltrated, fibrin in A.C.	Strep.	+	Gutt. Pen. 2nd day crystals to ulcer. 4th day ulcer larger below, hypopyon $\frac{1}{4}$. T. +. crystals on ulcer, S. section. 7th day no further spread. crystals to cornea. 11th day still leaking, no spread. 20th day eye quieter, cystoid scar	Severe neglected case in a man of poor physique and spirit. Eye saved, but ant. synechia developed, with fistula
15	T. C.	M.	46	8	Small	Circular, infiltrated, 4 mm. diam., chemosis, discharge	Morax-Ax.	N.	Pen. crystals at once, then gutt. pen. 2nd day improving. 4th day improvement marked, no hypopyon. 8th day healed	A boiler maker of grayish facies. Excellent result
16	B.	M.	40	4	1/5	Circular, small, 2 mm. diam., sloughing base, lymph behind cornea	Staph.	N.	Started Pen. drops at 7 p.m., 2 hourly by night, hourly by day. On 2nd day at 10 a.m. improvement was dramatic. Post corneal lymph had gone and hypopyon almost gone. On 4th day eye nearly white, hypopyon gone	Excellent result in a healthy man
17	R. A.	M.	48	14	1/4	Two circular areas one 4 mm., one 1 mm., chemosis; discharge; haze of cornea throughout	Staph.	+	Pen. crystals at once to both ulcers; gutt. pen. 2nd day pen. drops, 500 units. 4th day chemosis less, hypopyon less, tension still. 7th day better but central infiltration, etc. marked; crystals applied after gentle curetting. 10th day tension normal, hypopyon gone, corneal vesiculation. 11th day p. small, mydrine	A delayed good result. Patient has tendency to rosacea. The case was an infected abrasion which had had much treatment elsewhere, viz.—pure carbolic, atropine, penicillin cream

TABLE 1—continued

Case No.	Name	Sex	Age	Days Treatment before healing	Hypopyon	Ulcer, Description, etc.	Bacteriology	Tension	Treatment	Comment
18	C. U.	M.	40	6	None	2 mm. severe; corneal haze; infiltration above & below	Pneumococcus	N.	Pen. crystals on ulcer. pen.	Benefit on 2nd day. Excellent healing
19	F. H.	M.	59	24	Small	2 mm., deep gross infiltration	Pneumococcus	+	1st day pen. crystals applied. 2nd day spread downward, pen. crystals applied. 3rd day spread upwards, Saethisch section. 4th day no spread. 5th day spread upwards, pen. crystals pushed up under edge. 24th day no further spread, corneal fistula. 43rd day quiet, no fistula, ant. synechia. Vision 6/36	Spread in spite of crystals on ulcer and S. section. Delayed result classified as poor
20	H. P.	M.	43	4	None	4 x 3 mm., corneal haze, yellow infiltration	Staph.	N.	Pen. crystals to ulcer. Rapid healing	Excellent result
21	L. P.	F.	46	4	Small	Extensive stain, infiltrated edge below	Pneumoc.-Strepto.-Viridans.	N.	Gutt. pen. Rapid healing	Case in which infection followed carbolic acid of dendritic ulcer with large area of epithelial loss

Clinical course.—In a few cases, especially of the less advanced types, the improvement has been dramatic, and in 12 to 14 hours it may be obvious. More frequently, however, especially in advanced cases in ill nourished persons, it may be several days before amelioration is obvious. Cases with much conjunctival discharge usually get rid of the latter in 24 to 48 hours.

Cases with secondary glaucoma.—It is in these cases that delay in improvement is most marked, and it has been necessary to perform Saemisch's section on account of spread of ulceration in five eyes in addition to that with the non-sensitive (*B. Pyocyaneus*) infection. In two of these penicillin solution was run into the anterior chamber without any harm to the interior of the eye, but it is doubtful if such a procedure is worth while, for the hypopyon has been found sterile on each occasion.

Following the operation, there has been further spread of ulceration in two cases (case 1, in which the infection may well have been from a non-sensitive organism, and case 19).

We have come to the conclusion that Saemisch section should not be delayed in cases in which improvement is not materialising and especially where the intra-ocular tension is raised. Rycroft endorses this view and points out the superiority of a Saemisch section over a simple paracentesis; we are in agreement with this, but are not so happy as he is when he states that there is no risk of the formation of broad anterior synechiae. We feel sure, however, that the benefits are outstanding, and suggest that the incision into the anterior chamber need not be a large one, although the swollen infiltrated cornea should be cut through over a wide area.

Addendum

A note on the compatibility of penicillin with the drugs used in ophthalmology in solutions and ointments.

Rycroft and Cameron have given interesting cultural results of various substances which might be thought to modify the action of penicillin and similar experiments have been carried out here, though not all of them with similar results. From the tests made we can state that solutions of the following chemicals in common use in Ophthalmic therapy do not interfere with the potency of penicillin by tests *in vitro*: atropine sulphate, cocaine hydrochloride, homatropine hydrobromide, procaine and decicain. Fluorescein, however, in higher concentrations, inhibits penicillin to a small extent and might, perhaps, be avoided in immediate use with penicillin.

Rycroft's tests seem to indicate that vaseline and adeps lanae interfere with the action of penicillin. We have not found this. Penicillin mixed with both of these substances retained its activity for ten to twelve weeks in the refrigerator. At room temperature,

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FIG. 3.—Lanoline and penicillin (200 units), four months in refrigerator.
Vaseline and penicillin (200 units), two months at room temperature.
Penicillin control (5 units).

however, the vaseline ointment was active for seven weeks but the lanoline ointment was inactive. Experiments suggest that vaseline and lanoline vary in their action in accordance with their water content. With a completely anhydrous base, penicillin fails to diffuse *in vitro*, but satisfactory results may be obtained by the addition of 10-20 per cent. water to the base.

Lannette-wax cream has occasionally been found irritating to very sensitive skins but penicillin-lanoline is totally non-irritating. The latter is too hard for ready use when removed from the refrigerator and is best prepared with arachis oil in the proportion of three parts adeps-lanae to one part arachis oil.

The photographs show the area of inhibition of staphylococcus on agar plates around cups in which penicillin preparations had been placed. The darker areas around the cups represent the zones of inhibition.

Summary

The result of treatment of septic ulcer of the cornea by local applications of penicillin is reported in twenty-three cases. The crystalline salt can be applied to the ulcer itself without harm. Saemisch section is advocated in serious cases. The results are considered favourable.

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ANNOTATION

The Ophthalmological Vineyard

In the 20th chapter of St. Matthew's gospel will be found the well remembered parable of the labourers in the vineyard. For ourselves we may acknowledge that we have always thought that those who were engaged first had cause for dissatisfaction when the last comers received the same wage. All the emphasis seems to be on the side of the master. 'Friend, I do thee no wrong Is it not lawful for me to do what I will with my own?' We can understand the labourers viewing the matter in a different light, and those who had toiled all day being indignant at the last comers being paid at the same rates. It is not in human nature to work for twelve hours for a penny or any other wage when you can get as much for only one hour's work. Probably the parable contains more than appears in this superficial view. What has this got to do with ophthalmology? The parable came into our mind on reading letters on the subject of demobilisation from Army service. Those who have borne the burden and heat of the day, many of whom have been overseas for more than three years, will have a legitimate cause for grumbling if they are not returned to civil life as soon as possible after peace has been declared in Europe. If it is not possible to grant speedy release from Army service might it