PENICILLIN IN TREATMENT OF COMMON EXTERNAL EYE INFECTIONS

BY

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The value of penicillin in the treatment of infections of the eyes was established in 1944 and 1945. Sorsby fully reported on the rapid cure of infants suffering from ophthalmia neonatorum when treated with penicillin drops. Rycroft, who had to deal with a large number of infected intraocular war injuries, treated his cases with penicillin given subconjunctivally or injected into the anterior or posterior chambers of the eye. Other observers reported on the value of penicillin drops, ointment, and lamellae in ocular infections, and on penicillin introduced into the eye by iontophoresis. The latter method of treatment has not been generally adopted.

This short paper gives an account of the use of penicillin for one year in the out-patient department of a children's hospital (Queen's Hospital for Children) and the ophthalmic department of a general hospital (Hampstead General Hospital). Penicillin was given to out-patients in these hospitals for use at home.

External Eye Infections in Children

The most common external eye infections seen in children are: (i) blepharitis; (ii) conjunctivitis, often associated with corneal ulcerations; and (iii) lacrimal sac infections. Mothers often bring infants, a few weeks old, who have suffered from a discharging eye since birth. Pressure on the lacrimal sac of the discharging eye will cause a profuse flow of pus from the lacrimal punctum, thus establishing the diagnosis of an infection of the lacrimal sac resulting from an obstruction of the lacrimal duct.

Other observers have now established that organisms causing the more common external eye infections (staphylococci, pneumococci, Morax-Axenfeld bacilli, etc.) are penicillin-sensitive. Conjunctivitis and blepharitis seen among children in London are in most cases due to a staphylococcal infection; it was therefore considered unnecessary to take swabs from the conjunctivae of the hundreds of children and infants treated in the casualty and the ophthalmic out-patient departments before penicillin was prescribed. All cases of blepharitis (ulcerative and squamous) and of conjunctivitis were treated for the past year with penicillin drops or ointment. Cases of corneal ulceration were also given atropine and hot steaming.

Blepharitis, which in the past so often resisted all forms of treatment, clears up quickly with penicillin ointment, but it very often recurs when treatment is stopped; the mothers are therefore advised to continue applying the ointment to the lids as a prophylactic twice a week for several weeks and to report at once if the condition recurs.

Conjunctivitis amongst infants and children also clears up within a few days when treated with penicillin. Penicillin drops (1,000 or 2,000 units per ml.) are given to the mothers in a bottle provided with a bakelite cap and a rubber washer; an eye dropper is fixed through an aperture in the bakelite cap. (The same type of bottle is used by the manufacturers of albucid eye drops.)

The mothers are told to keep the penicillin in the pantry (refrigerators do not exist in the patients' houses). Drops are to be used four times a day; at least three or four are to be instilled on each occasion. The bottle contains about half an ounce (14 ml.) of penicillin solution, which is sufficient for more than a week's treatment. The mother is asked to bring the child again a week later. In severe infections the penicillin is dispensed in the strength of 2,000 units per ml. In all other cases a strength of 1,000 units per ml. is ordered.

Lacrimal sac infections in infants take weeks, often months, to clear up. Penicillin drops—2,000 units per ml.—were used in 30 infants suffering from this condition. The drops were given to the mothers to be used, as in conjunctivitis cases, four times a day. The muco-purulent discharge ceased in most cases

after a week's treatment. In many cases the eye continued to water. Penicillin was continued in these cases for three weeks. If at the end of that period watering had not ceased the lacrimal duct was probed under ethyl chloride general anaesthesia. Twelve cases out of the total of 30 had to be probed. This procedure takes only a few minutes, and one probing of the obstructed lacrimal duct in an infant suffices to cure the condition. Penicillin drops are ordered for another week after probing.

External Eye Infections in Adults

In the ophthalmic out-patient department of the Hampstead General Hospital very few children are seen. The most common external eye infections amongst adults are: (i) conjunctivitis, and (ii) chronic blepharitis, which is usually of the seborrhoeic type with a secondary staphylococcal infection. It is often associated with seborrhoea capitis and infected seborrhoeic dermatitis of the external ear (auditory meatus) and of the skin behind the ear. (iii) Industrial eye injuries are also seen frequently, the common ones being corneal abrasions, corneal foreign bodies, and lime and cement burns of the conjunctiva and cornea. Lime burns are often severe in nature, and extensive corneal ulceration may follow, with pus in the anterior chamber (hypopyon ulcer). Patients suffering from lime burns are admitted to the hospital and are treated with penicillin drops (2,500 units per ml.) instilled into the eye every hour. Sulphonamides are administered by mouth, and, if the condition is severe, fever therapy (T.A.B. vaccine 0.1 or 0.2 ml. in saline) is also given intravenously.

Conjunctivitis is not as common in adults as in children, and it is usually associated with ulceration of the cornea; the marginal corneal ulcer is the most common type. This infection is again largely caused by staphylococci and Morax-Axenfeld bacilli. These two organisms are penicillin-sensitive. Pneumococci and Koch-Weeks infections are seen less frequently—the pneumococcus is penicillin-sensitive. Koch-Weeks bacilli are only slightly penicillin-sensitive, but infections with these organisms are cured with penicillin in a concentration of 1,000 or 2,000 units per ml. Conjunctival swabs are therefore taken only in very severe and unusual cases; the majority of the out-patients were treated with gutt. penicillin 1,000 or 2,000 units per ml., given to them for treatment at home. The same instructions as to storing the penicillin in the pantry and not leaving the bottle of penicillin solution exposed to air are handed to patients. Drops are to be used four times a day. If the infection is severe an ounce (28 ml.) of penicillin is given for one week's treatment and the patient is told to instil six drops of penicillin on each occasion. All cases clear up very quickly. Patients suffering from corneal ulceration are given the same treatment, combined with atropine drops and hot steaming of the eye. They are instructed to return to the hospital every day, to be seen by the house-surgeon. Deep and extensive corneal ulcers are carbolyzed—in most cases carbolyzation is not necessary—and the ulcer shows signs of healing within a few days. Dendritic corneal ulcers which are due to a virus infection are resistant to penicillin treatment, and these ulcers are carbolyzed and treated with gutt. albucid (sulphacetamide) 30%, atropine, and hot steaming of the eye.

Blepharitis, which, as already mentioned above, is most often of the seborrhoeic type, responds rapidly to penicillin treatment if secondary staphylococcal infection is present. The ulcerative type with red crusted lid margins is usually due to a secondary infection, and penicillin ointment is given to the patient to be used at home twice a day.

Allergic Skin Reactions due to Penicillin

A number of adults, after using penicillin drops or ointment, returned to the hospital with a marked redness and oedema of the skin of the lids, often extending to the skin of the cheek and forehead. The condition cleared up within a few days when penicillin was stopped. These patients are allergic to penicillin, and were suffering from a penicillin-produced allergic dermatitis. Skin-patch testing proved their sensitivity to penicillin.

These skin reactions to penicillin were not caused through the use of any particular fatty base in the penicillin ointment—they occurred also after the use of penicillin drops prepared by dissolving the drug in distilled water. Penicillin dermatitis

of the lids was seen among patients throughout the past year, and was not due to any particular batch of penicillin. Other observers also reported on these allergic skin reactions after the use of penicillin; but it is not yet established whether they are due to impurities which are still present in the penicillin supplied for general purposes. Pure white penicillin was not tried in these patients who were found to be penicillin-sensitive to the generally used yellowish preparation. I did not attempt to desensitize those of my patients who were penicillin-sensitive. In all such cases penicillin treatment must be discontinued.

It is worthy of note that none of the children treated with penicillin showed any allergic skin reactions.

Industrial Eye Injuries

Corneal abrasions, superficial burns of the cornea and conjunctiva, and patients who had corneal foreign bodies are best treated with gutt. penicillin. The drops are supplied to the patients for use at home. Three days' treatment usually suffices to heal the injured cornea and conjunctiva.

Potency and Stability

The life of penicillin in solution is limited. Penicillin is hydrolysed in the presence of moisture. The stability of penicillin is also greatly affected by the pH of the solution; the optimum pH is stated to be 6. Departure from this pH on either side leads to a considerable increase in the rate of deterioration. The rate of deterioration increases more rapidly on the acid side of pH 6, so that pH 6 to pH 6.5 is usually considered the best range. By interpolation, the rate of deterioration of a solution is twice as great at pH 7.5 and pH 5.2 as it is at pH 6. Temperature has a considerable effect on the stability of penicillin, the rate being approximately double for every 3° C. rise. Salts of certain metals destroy penicillin. The more important ones appear to be copper, lead, and mercury; iron also inactivates the substance. Oxidizing agents such as potassium permanganate and hydrogen peroxide will destroy penicillin, although the substance seems to stand up fairly well to reducing agents.

The actual life of penicillin in solution varies from batch to batch. Investigations carried out in the Glaxo Laboratories within the last twelve months have shown that the stability of the drug in solution is fairly high: even at room temperature its potency remained at between 90 and 100% for eight days. On the fourteenth day the potency of penicillin in solution kept at room temperature usually falls to about 75% of the original strength.

The pH of the solution has a much greater effect on the stability of the penicillin. Benedict and others have demonstrated that at pH 6 penicillin in solution remained stable for 360 hours, whilst at pH 5 (the acid side) and at pH 9 (the alkaline side) the stability lasted only 120 hours. In the preparation of drops and ointment for ophthalmic use it is essential to get the pH of these preparations as near as possible to the pH of tears. The pH of tears is 7.2. It is most fortunate that penicillin dissolved in distilled water has a pH between 6 and 6.5; such solutions are therefore not irritating to the eyes. Water not only inactivates penicillin but also provides a medium for the growth of penicillin-resistant organisms. These organisms produce penicillinase, which destroys penicillin. The drop-bottles must therefore be carefully sterilized.

Penicillin Eye Drops

At Queen's Hospital for Children the following method of preparation of penicillin eye drops is adopted. The drops contain 1,000 or 2,000 units per ml. in sterilized distilled water. 20 ml. of distilled water is poured into bottles fitted with a bakelite cap and rubber washer and then autoclaved at 10 lb. (4.5 kg.) pressure for half an hour. When penicillin drops are required two or four tablets of sodium penicillin (B. & W.), according to the strength required, are added to each 20 ml. The tablets supplied are of three different strengths—9,500, 10,000, and 10,500 units per tablet.

Penicillin Ointment

When penicillin ointment was first prepared for ophthalmic use "lanette" wax was employed as a base; but it was found

that the ointment was irritating to the eyes, as the pH of this fatty base is on the acid side and becomes more acid when the ointment is stored. "Lanette" wax was therefore discarded for ophthalmic use, and eucerin L.M. was found to be the best base for penicillin eye ointment. Within the first nine months the penicillin eye ointment was prepared with water: the penicillin was first dissolved in distilled water and then added to the eucerin L.M. At present water is not used in the making of ophthalmic ointment, and the stability of this preparation will therefore be very much greater. The penicillin is not soluble in the fatty base of the ointment, but it will dissolve in the tears fairly rapidly. When applied to the lids the moisture of the skin, and the tears which are constantly wetting the lid margins, will dissolve the penicillin. The delayed release of penicillin is advantageous in prolonging the action of penicillin.

The method of preparation of penicillin eye ointment as used at the Queen's Hospital for Children is given below.

The ointment is prepared in the strength of 400 units per gramme. 200,000 units of penicillin in powder form are rubbed down in a sterile mortar with a little sterile liquid paraffin. 500 g. of eucerin L.M. base (previously sterilized by heating in a sterotherm at 150° C.) are gradually incorporated. The ointment is transferred to sterile jars, using a sterile spatula.

The official B.P. method of preparing oculentum penicillin is as follows:

Penicillin (calcium salt)	100,000 units
Yellow soft paraffin	90 g.
Wool fat	10 g.

Melt together the yellow soft paraffin and the wool fat, filter while hot through coarse filter-paper placed in a heated funnel, and sterilize the mixture by heating at 150° C. for one hour. Place the penicillin (calcium salt) in a sterilized mortar and triturate with a small quantity of the basis until smooth; then incorporate the remainder of the basis gradually. Distribute into small sterile collapsible tubes and close.

The official B.P. oculentum has not yet been tried. It will be essential for the dispenser to obtain wool fat and paraffin molle in an anhydrous state. Samples of commercial wool fat and paraffin molle are known to contain varying amounts of moisture. It is also hoped that the ointment will retain a pH very near to 6 for a few weeks: a change to the acid side due to decomposition of the wool fat would destroy the penicillin. In the present state of our knowledge eucerin L.M. has the necessary requisites for an oculentum base: (i) it has very little moisture; and (ii) it does not turn acid and is considered by many pharmacists to be a superior base to wool fat in the preparation of oculentum penicillin.

Stability of Penicillin in Eye Drops and Ointment

To ascertain the stability of penicillin in the eye drops used at Queen's Hospital for Children, two bottles of eye drops as dispensed to out-patients were sent to Glaxo Laboratories. A

Graph showing the potency of penicillin eye drops; original potency, 2,000 units/ml. — = Refrigerator, - - - = Room temperature. This solution was exposed to the air on frequent occasions. (The apparent increase in potency is, of course, an assay error, the accuracy of the method being about $\pm 10\%$.)

biological assay was carried out. The deterioration of the penicillin in the eye drops at refrigerator and at room temperature is shown in the accompanying Graph.

The bottles were frequently opened and exposed to air in the same way as when the patients use them for treatment in their own homes. The solutions retained 50% of the original penicillin activity for about three weeks at room temperature, and

longer in the refrigerator. If one takes into account the undoubted fact that penicillin solutions, in the first place, are often of greater concentration than is therapeutically necessary, the useful life of the solution can be taken as being two to three weeks, and possibly longer. In one case the solution seems to have increased in strength. This, of course, is due to an assay error. The method of assay normally has a margin of error of plus or minus 10%, which is reasonable for any biological assay method.

The penicillin ointment was also sent to the Glaxo Laboratories for examination. The original pH of the ointment was 7.1, and this did not change significantly on standing. A biological assay on the ointment was not carried out. The penicillin ointment was prepared without water, and its stability at room temperature is probably that of the dry penicillin—this means that it will probably last longer than six weeks. The pH of the eye drops was 6.35, and this fell but very slightly.

These findings confirmed our clinical experience that the penicillin eye drops and ointment have an ideal pH value for ophthalmic use and are therefore not irritating to the eyes. They also confirmed that the excellent results obtained in the treatment of out-patients suffering from external infections of the eye were due to the high content of penicillin in the eye drops and ointment which were dispensed for use at home for one or two weeks.

Summary

Penicillin eye drops and ointment were used for one year at Queen's Hospital for Children and at the Hampstead General Hospital in the treatment of external eye infections. These preparations were given to the patients for use at home. The clinical results were excellent.

Allergic skin reactions of the lids and the skin of the face arising from the use of penicillin drops or ointment are described.

A biological assay of the penicillin eye drops proved that the content of penicillin when the eye drops are kept at room temperature, and with the bottles frequently opened and exposed to air, was 80% of its original potency at the end of fourteen days.

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HYPERSOMNIA ASSOCIATED WITH ABNORMAL HUNGER: THE KLEINE-LEVIN SYNDROME

BY

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Abnormalities of sleep are commonly considered as falling into two classes—narcolepsy (including sleep paralysis, cataplexy, and sleep hallucinosis) and hypersomnia. In hypersomnia the patient can be aroused with difficulty from the prolonged sleep. The pathology of the condition is obscure, and it may be associated with various pathological states, such as cerebral tumour, encephalitis, head injury, endocrine and metabolic upsets, and toxic or infective conditions of the nervous system. Attention has been called by Kleine (1925) and Levin (1929,

1936) to certain cases of hypersomnia in which morbid hunger is exhibited during the attack, accompanied by motor unrest and mild confusion. In view of the rarity of the condition the following two examples are considered worthy of record.

Case I

Male aged 18, working as a milling operator. His previous health had been good, save for occasional attacks of bronchitis in winter. His mother (aged 50) and father (aged 52), one sister (aged 22), and two brothers (aged 26 and 22) were alive and well. One brother (aged 30) complained of attacks of sleepiness (noted at end of this case report).

History of Present Illness.—In 1939, at the age of 12, following an attack of "influenza" (then epidemic in the town in which he was living), he noticed a tendency to sleepy attacks at school. About the age of 14½, when he started work as an office-boy, these attacks became pronounced. They occurred every three to six months and lasted from one to five days: During them he became very drowsy and would sleep if he closed his eyes. They occurred anywhere, even at meals or when he was standing up. During the attack he was unusually irritable, difficult to rouse, and felt "confused and muddled" if he was roused. There was definite abnormal hunger but no excessive thirst. He experienced no physical discomfort and had no unusual thoughts or dreams. The attacks wore off gradually, and for a day or two he felt somewhat "depressed and touchy." Sleep between the attacks was normal. Observers seeing him in an attack noted that the drowsiness came on usually in the morning and rapidly became severe; there was no abnormal behaviour, but he was slow to answer if roused and appeared "dazed." He was irritable, and when touched seemed to resent it intensely, throwing off the touching hand and contracting his muscles sharply. "He tended to curl himself up like a hedgehog." One attack had occurred during the "blitz" on Coventry in November, 1941, and he had "slept like a baby during the eleven hours that bombs were dropping." There were no hypnagogic hallucinations and no evidence of cataplexy or sleep paralysis. He had no other complaints, and lived a normal healthy life.

Physical Examination.—He appeared healthy. Speech was slow and deliberate, but there was no evidence of delayed cerebration or encephalitis. General physical examination revealed no abnormality in the nervous system, heart, chest, abdomen, or urinary system. Ophthalmoscopically the disks and fundi were clear. B.P. 122/80.

Special Examinations.—Urine acid; specific gravity 1012; no albumin or sugar present. R.B.C., 4,250,000 per c.mm.; W.B.C., 8,400 (polymorph leucocytes 40%, lymphocytes 57%, eosinophils 1%, hyaline cells 2%); haemoglobin, 90%. X-ray examination showed no abnormality of skull or pituitary fossa; a chest film revealed slight bronchial catarrh but no other abnormality. B.S.R. was 6 and 10 mm. at 1 and 2 hours. Blood Wassermann and Kahn tests negative. Lumbar puncture revealed a clear fluid with no increase in pressure. Examination of C.S.F.: Cells, 1 per ml.; protein, 20 mg./100 ml.; no excess of globulin; chlorides, 720 mg./100 ml.; sugar, 55 mg./100 ml.; culture remained sterile. Wassermann and Lange reactions negative. Electro-encephalography revealed no abnormality either at rest or during overbreathing. A fairly high potential alpha rhythm was noted in the occipital lobes.

Carbohydrate Metabolism.—A glucose tolerance curve gave figures of 66, 84, 105, 55, 63, 68 mg./100 ml. (fasting and at half-hourly intervals thereafter). On a low-carbohydrate diet (80 g. per day) he showed no abnormal response to exercise. An insulin tolerance test was carried out after a diet of 400 g. of carbohydrate had been given for three days, and following a fast of three hours (Fraser, 1938, 1941). After the administration of insulin the blood-sugar figures were 76, 32, 62, 64, 64, 74 mg./100 ml. (fasting and at 20, 30, 40, 60, 90 minutes thereafter). There was a slight fall in blood pressure and a feeling of hunger, but no other abnormal symptoms.

Progress.—While under observation an attack developed, the general features of which agreed with those described. The hypersomnia was well marked, and there was mild confusion with irritability accompanied by motor restlessness. The appetite was increased and could fairly be described as ravenous. There was no hypoglycaemia.

Investigation of the patient's brother, who complained of sleepiness, was also carried out. This revealed a picture of disturbance of sleep rhythm and features suggesting an encephalitis. The condition, dated from an attack of "sunstroke" in 1935, and was not similar to that of Case I.

Case II

Male aged 29. His previous health had been good, save for occasional attacks of tonsillitis. His mother (aged 60) and father (aged 62), three brothers (aged 40, 36, and 30), and three sisters (aged 38, 35, and 33) were alive and well.

History of Present Illness.—In 1936, when aged 20, the patient developed attacks of drowsiness, sometimes coming on first thing