inactive form. The interior of the eye probably never had been infected.

5. Miss B., aged 69 years. This patient had a painful blind eye of some years' standing. She attended with three corneal ulcers and hypopyon. Cultures showed staph. albus (coag. neg.), Corynebact. type III. Two thousand one hundred and seventy-five units of penicillin were run into the anterior chamber. The pus disappeared and the ulcers began to heal in two days. They had practically gone in a week, but the eye was excised for pain and was found to contain a malignant melanoma. The penicillin had undoubtedly had a beneficial effect on the ulcers.

6. I.A., aged 52 years. This patient had a perforating injury with a piece of wood. The eye was obviously infected but only staph. albus could be grown. Twenty-four hours after the injury 2,500 units of Pfizer penicillin were used to irrigate the anterior chamber. A temporary improvement occurred but the eye remained irritable and painful and was excised six weeks later. The penicillin here had no effect on an eye in which one might have expected a good result.

It would appear that intra-ocular injection of high concentrations of penicillin is justifiable in severely injured or infected eyes but that the best results are to be expected when the infection is confined to the anterior segment of the eye and where the penicillin does not come in contact with the vitreous. Further work with purer solutions might give better results in these cases.

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PENICILLIN IN OPHTHALMOLOGY*†

The bacteriological, experimental, and clinical evidence of its value, including a personal series of 125 clinical cases

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ABERDEEN

I.—Bacteriology

SINCE the whole of penicillin is based on a proper understanding of its bacteriological properties, these will be briefly referred to first.

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(1) RESISTANCE OF ORGANISMS.

(a) *Different organisms.*—The original classification of Gram positive as penicillin sensitive, and Gram negative as insensitive, broadly speaking still holds good (Abraham *et alia*, 1941). One of the commonest organisms in ocular pathology, staph. aureus, is among the most sensitive, and another fairly frequent ocular pathogen, the streptococcus pyogenes, is also very sensitive. The pneumococcus, one of the most dreaded enemies in ocular infection, is well down the list of sensitivity, and varies with its type (moderately or slightly sensitive), though with stronger concentrations the most resistant type can be brought within the range of penicillin therapy. The haemophilic group is relatively insensitive (Fleming, 1944), but two cases in this series of infection with haemophilus conjunctivitis have responded well to penicillin therapy. This is because increasing concentrations of penicillin bring within the range of therapy even relatively insensitive organisms (Helmholz and Sung, 1944) *e.g.*, compared with the sensitive staph. aureus, an increase of 240 times in penicillin concentration brings *B. proteus* within the range of therapy.

(b) *Different strains of the same organism.*—Penicillin sensitivity varies widely with different strains of the same organism. This has been confirmed by Bentley and Thompson (1945) with the staph. aureus. twenty per cent. of these were found to be resistant to 0.1 unit c.c. which is the concentration obtained by parenteral penicillin, while ten per cent. still grew in a concentration of 10 units/c.c., but very few in 50 units/c.c. Despite this, their clinical results with local penicillin therapy were equally good in all cases, showing that high local concentrations can overcome even resistant organisms and that therefore a relatively resistant organism is no contra-indication to penicillin therapy.

(c) *Adaptation.*—Acquired resistance to penicillin has been described by 'Abraham *et alia* (1941) and 'Todd, Turner and Drew (1945). The latter workers, by repeated subculture in penicillin, increased the resistance of organisms staph. aureus to penicillin 3,000 times: but they rapidly lost this resistance on further subculture without penicillin. But other workers (Rake *et alia*, 1944) found that pneumococci did *not* lose their acquired resistance. It is to be hoped that loss of acquired resistance will prove to be the rule with the majority of organisms (rather than an acquired permanent fastness, as in the case of sulphonamides).

(2) CONCENTRATION OF PENICILLIN.

This must be determined by the sensitivity of the organism concerned. Garrod (1945) suggested that there was nothing to be gained by using high concentrations, and that 1 unit per c.c. was as effective as 1,000/c.c. This may well apply to the penicillin

sensitive organism, but not to the slightly sensitive one. In general, the old maxim, "The greater the dose, the surer the effect," applies to penicillin therapy as well as to other therapeutic agents. From the present series it appears that a concentration of 1,000 units/c.c. is best for the average bacterial ocular infection.

(3) ACIDITY.

The activity of penicillin is quickly lost in acid solutions and some loss occurs even in weak acids (pH 5 to 7) Garrod (1945). In ocular therapeutics, it is significant that *boric acid* impairs the action of penicillin Bigger (1944a) and *adrenaline* 1:500 inhibits the activity of penicillin Cameron (1945). This latter effect has been proved to be due to the acidity of adrenaline hydrochloride, which has a pH of 2 Riddell (1945), while adrenaline solution has no inhibitory effect.

(4) INCOMPATIBILITY.

Apart from adrenaline hydrochloride and boric acid, it seems that all the commonly used drugs in ophthalmology may be safely used without any appreciable impairment of penicillin activity. These include atropine, eserine, cocaine, argyrol, fluorescein, etc. Rycroft (1945) Cameron (1945). Bacteriostatic drugs like proflavine and sulphathiazole do have a slightly retarding effect on the antibacterial action of penicillin when organisms are in the resting phase but the effects are so slight that they are of no clinical significance.

(5) EFFECT ON TISSUE AND CELLS.

Penicillin is completely innocuous to the tissues and has practically no inhibitory effect on *leucocytes*, being less lethal to leucocytes than sulphonamide (Abraham *et alia*, 1941). On the other hand, its activity is not diminished by the *number of bacteria* present, but indeed the more pus and organisms present, the more striking the effect of penicillin. It has been found in this series and by other workers (Sorsby and Hoffa, 1945) that cases of acute conjunctivitis with most discharge clear more quickly than those with less. This may be connected with the suggested selective action of penicillin on dividing organisms (Bigger, 1944b).

(6) SUMMARY:

Thus, penicillin is the ideal drug for bacterial infections of the eye, being:—

- (1) harmless to the delicate ocular structures in high concentration;
- (2) lethal to sensitive bacteria in low concentration, and to slightly sensitive bacteria in high concentration;
- (3) acting well in the presence of purulent discharge; and

- (4) having no lethal effect on leucocytes in therapeutic concentrations.

II.—Experimental evidence

Experimental work has been done on (1) penetration of penicillin into the normal and inflamed eye, and (2) control of infection in the eye by penicillin.

(1) PENETRATION

(1) EXTERNAL APPLICATION :

(a) *Normal cornea* (Sallmann and Meyer, 1944) using drops of 2,500/c.c. every 20 minutes and ointment of 2,500 units/gm. every $\frac{1}{2}$ hour, found that penicillin did *not* penetrate into the aqueous of rabbits. By using a corneal bath of 2,500 units/c.c. for 5 minutes they found an antibacterial concentration in the aqueous lasting from $\frac{1}{2}$ to 2 hours after the bath. This concentration was increased 10 times by using iontophoresis.

(b) *Inflamed cornea*: Leopold and Lamotte (1945) found that drops or ointment of 500 units per c.c. or gm. penetrated through an inflamed cornea into the aqueous in inhibitory concentration, and remained for $1\frac{3}{4}$ hours.

(2) SUBCONJUNCTIVAL INJECTION :

Bellows (1944) found that penicillin given by this method in rabbits appeared in the *aqueous* after $\frac{1}{2}$ an hour, and (Rycroft, 1945b), using damaged human eyes, also found penicillin penetrated into the aqueous by this route in $\frac{1}{2}$ an hour. Similar experiments on *vitreous* by (Rycroft, 1945b) and (Leopold, 1945) proved that small amounts of penicillin reached the vitreous by this route in $\frac{3}{4}$ hour.

(3) INTRA-AQUEOUS INJECTION :

This, of course, is the most certain way of achieving a high *aqueous* concentration, and also enables penicillin to reach the *vitreous* sooner than the subconjunctival route ($\frac{1}{4}$ hour) (Leopold, 1945).

(4) INTRA-VITREOUS INJECTION :

Sallmann, Meyer and Grandi (1944) have found that the antibacterial activity of the vitreous persists for at least 24 hours after direct intra-vitreous injection of penicillin, and similarly (Rycroft, 1945a) found penicillin in the vitreous 48 hours after direct injection. After 12 hours, such an injection becomes fairly evenly distributed from its depot through the vitreous. One injection of pure penicillin was found to be innocuous to lens, vitreous and retina, but more than one injection of pure, or the use of crude penicillin, usually caused slight permanent changes in these tissues.

(5) INTRAMUSCULAR AND INTRAVENOUS INJECTION :

(a) *Normal eyes* : Sallmann and Meyer, using very large doses, found minute amounts in the aqueous, especially after paracentesis, but none in the vitreous. With moderate doses (4,000 units/kg) Leopold (1945) found *NO* penicillin in either aqueous or vitreous.

(b) *In inflamed eyes*. Leopold found small amounts in aqueous and vitreous, even with moderate doses.

(6) SUMMARY : (See Table 1.)

(1) *Drops and ointments* are useless for intra-ocular penetration if the cornea is normal, but penetrate an inflamed cornea.

(2) The local external methods that ensure penetration with a normal cornea are (1) *Corneal bath* (increased concentration with iontophoresis). (2) *Subconjunctival injection* (aqueous and vitreous). (3) *Intra-aqueous injection* (aqueous and vitreous).

(3) A single *intra-vitreous injection* is reasonably safe.

(4) *Systemic administration* does not produce inhibitory concentrations in the aqueous or vitreous, except by massive doses, and local therapy attains much higher levels.

TABLE I—Penetration of Penicillin *

Method of Application	Cornea (normal)	Aqueous	Lens	Iris	Vitreous
Drops, ointment, into conjunctival sac	Moderate (superficial)	—	—	—	—
Corneal bath	High	Moderate	—	Moderate	—
Iontophoresis	High	High	Moderate	High	Slight
Subconjunctival injection	Moderate	Moderate	Slight	Moderate	Slight
Intra-aqueous injection	Moderate	High	Moderate	High	Moderate
Intra-vitreous injection	—	—	—	—	High
Systemic therapy ... (massive dose)	—	Slight	—	Slight	Trace

* These values refer to normal eyes in experimental animals

(2) CONTROL OF INFECTION.

(1) *Corneal lesions* : Robson and Scott (1943a, 1943b) controlled experimental staph. aureus and pneumococcal infections in rabbits' corneae by penicillin therapy (hourly drops). They found that eyes which would otherwise have been lost were saved if treatment was started within one hour of infection. When treatment

was instituted after 24 hours, it had only a slightly beneficial effect, if any. This demonstrates the importance of early treatment in any potentially infected corneal injury.

(2) *Intra-ocular infection* : Sallmann (1943, 1944) induced experimental intra-ocular infection in rabbits by injecting cultures of staph. aureus and pneumococci into the anterior chamber. The infection was controlled in the majority of cases by local penicillin, applied by a corneal bath, with or without iontophoresis. He found that if treatment was instituted within 6 hours, the infection could be controlled, and that an injured lens was an indication for the higher concentration obtained by iontophoresis. He also reports (Sallmann, 1944) that iontophoresis has been used in a series of human eyes with no ill effect to the cornea : he used a lucite tube with a broad flare like the scleral part of a contact lens, and a diameter of opening approximately that of the cornea. But Wright and Harris (1945) using iontophoresis, found corneal damage in several cases.

(3) VITREOUS INFECTION.

Sallmann, Meyer and Grandi (1944) injected a culture of staph. aureus into the vitreous of rabbits. Without treatment, all eyes were lost. If treatment was delayed for 24 hours, again all eyes were lost. If 500 units of penicillin were injected into the vitreous within 12 hours all eyes (series of 20) were saved. With similar injections of sulphacetamide ten per cent., all eyes were lost. These results with intra-vitreous penicillin are striking, and such a method of therapy appears worthy of extended clinical trial. Using a similar technique, Leopold (1945) found the subconjunctival and intra-aqueous injection of penicillin enabled him to control the vitreous infection in 4 out of 10 rabbits : i.e., less successfully than intra-vitreous injection.

(4) SUMMARY.

The methods indicated are :—

- (i) *Corneal lesions* : Frequent drops or, if severe, corneal baths.
- (ii) *Infections of anterior segment* : Corneal baths, iontophoresis, subconjunctival injection or intra-aqueous injection.
- (iii) *Infections of posterior segment* : Intra-vitreous injection.

III.—Clinical evidence (125 cases)

A. SUPERFICIAL BACTERIAL INFECTIONS : (117 cases).

(1) *Method of application* : (a) *Ointment* : In this series ointment has been used in blepharitis only, in strength 500 units/gm., in 30 per cent. lanette wax. After repeated application, it was found in certain cases to give rise to irritation of the lid margin, and probably a better base than lanette wax will be found. The

ointment keeps its activity fairly well, if kept cool (not necessarily in a refrigerator) and still retains some potency after 100 days (Peterkin, 1945).

(b) *Drops*: In this series, drops have been widely used and well tolerated. Scarcely any patients complained of any sensation on instillation of the drops: a few had a transitory smarting for $\frac{1}{2}$ minute. Two cases developed penicillin sensitivity (see later). The disadvantage of using drops is that after 48 hours at room temperature they have considerably degenerated in strength (Lancet, 1945) and so must either be kept in a refrigerator or freshly made up every 24 or 48 hours.

(c) *Oculet*s: In a small series of cases, these were found to be less well tolerated than the drops, and patients complained of a feeling of F.B. in the eye for up to $\frac{1}{2}$ hour after insertion, which was approximately the time taken by the oculet to dissolve completely. The increased irritation may have also been partly due to the calcium penicillin (as opposed to the sodium penicillin of the drops). The big advantage of oculets is that they are stable at room temperature for 2 months or more.

(2) *Frequency of treatment*: Treatments were given 4 hourly day and night in severe cases: the 2 a.m. dose was omitted after the acute phase was over. Irrigations with normal saline and instillation of one per cent. atropine were also given when indicated.

(3) *Results*: (1) *Blepharitis* (19 cases). In the present series of 19 cases, using penicillin ointment 500 units/gm. in 30 per cent. lanette wax 4 hourly, it was found that: (a) the majority of acute and acute or chronic cases, both ulcerative and squamous, responded well to treatment, and 10 out of 14 achieved clinical cure in 6-7 days. In some cases the response was dramatic, and a fairly severe blepharitis would be practically clear in 2 days. But 4 of the 14 did badly. All 4 had greasy skins, with chronic seborrhoea of the scalp and face. (i) One was infected with a penicillin resistant staph. aureus. (ii) One had an associated dermatitis of eyebrow which re-infected the eye, causing a flare-up of the blepharoconjunctivitis. (iii) One improved on treatment but did not clear. A switch to liquor tinctorium (0.5 per cent. gentian violet + 0.5 per cent. brilliant green) cleared the residual infection in one day. (iv) One case of mild squamous blepharitis of both eyes was cleared in 5 days by liquor tinctorium while the penicillin treated eye took 10 days.

The chronic seborrhoea appeared to be the underlying factor in all 4 cases. Bellows (1944) describes a similar penicillin failure in a case of chronic seborrhoea.

(b) *Chronic Blepharitis*: (ulcerative). In a small series of 5 cases, the findings were inconclusive, but on the whole unfavourable to penicillin.

(1) One mild infection of 20 years' duration cleared more quickly on penicillin than the dye (6 days).

(2) In two cases of bilateral infection, the lid treated with liquor tinctorium was white in 12-15 days, while the penicillin treated eye remained red-rimmed. The latter was rapidly cleared by a switch to the dye.

(3) One case was improved in 10 days, and then became irritated presumably by the ointment base.

(4) The average results were: 2 cases improved in 14 days, but red rimmed; 2 cases cured in 14 days; 1 case improved in 10 days, then irritated.

These results correspond to those of Crawford and King (1944) who also found persisting residual erythema of the lid-margin after 2 weeks' treatment. In this series, it was noticed that the residual erythema after penicillin treatment was greater than that after treatment with liquor tinctorium.

(c) *Summary*: (i) There is a definite place for penicillin ointment in the treatment of blepharitis, and in some cases it effects a dramatic cure, though relapse later is possible.

(ii) In cases of chronic seborrhoea, liquor tinctorium is preferable to penicillin ointment.

(2) ACUTE CONJUNCTIVITIS: (MUCO-PURULENT) (31 cases).

Previous observers agree that penicillin is of great value in acute conjunctivitis, and it is here that the writer has found the most effective field for penicillin therapy.

(a) *Clinical Cure*. In a series of 31 cases of acute mucopurulent conjunctivitis, clinical cure was obtained in an average of $5\frac{1}{2}$ days in 30 cases. The response was in almost every case extremely gratifying and often dramatic, and better than any other therapeutic agent in the writer's experience. As noted by Sorsby and Hoffa, (1945), the worst cases often attained the quickest cures. Several cases of very severe conjunctivitis (staph. aureus) with a completely closed eye, gross chemosis and copious discharge, responded so rapidly that in 4 days the eyes were white and normal. In this series treatments were given 4 hourly, but in severe cases more frequent treatments (e.g., hourly drops) would probably give even more rapid cures, as found by Bellows (1944), who cured 13 out of 15 cases of mucopurulent conjunctivitis in 48 hours with hourly drops; and Sorsby and Hoffa (1945a, 1945b) who cured cases of ophthalmia neonatorum in 48 hours, also with $\frac{1}{2}$ or 1 hourly drops; and more recently with drops every 5 minutes; and Bietti (1944) who cured 16 cases of ophthalmia neonatorum with hourly drops in 24 hours.

The findings in this series with 4 hourly treatments are similar to those of (Milner, 1944) and (Crawford and King, 1944) who also found an average of 5 days for clinical cure.

(b) *Insensitive organisms* : The commonest organism found was a penicillin sensitive staph. aureus, but the only penicillin failure in this group was due to infection with a penicillin resistant staph. aureus. The eye improved a bit on penicillin, but did not clear, and on the sixteenth day, while still under treatment, the eye relapsed. Staph. aureus was found to be still present on the conjunctival culture, and further penicillin therapy proved useless.

(c) *Slightly sensitive organisms* : (See Table II.) (1) Two cases of Koch-Weeks conjunctivitis proved a marked superiority of penicillin over silver nitrate (one per cent. paint) and proflavine 1:1,000 drops. Both cases were equal bilateral infections; one eye was treated with penicillin (1,000 units/c.c. in one case: penicillin-sulphathiazole powder in the second case), while the other eye was treated with an initial paint with silver nitrate one per cent. followed by 1:1,000 proflavine drops 4 hourly. In both cases the penicillin treated eye was white in 4 days, while the other eye remained violently inflamed even after 8 days' treatment. Even though the organism is only slightly sensitive (in this series it grew freely through a smear of 2 units of penicillin), such infections can be controlled by the high local concentrations applicable to the conjunctival sac. Similar results with Morax Axenfeld bacillus, bacillus of Petit, and Koch-Weeks bacillus infections have been reported by Crawford and King (1944), Cashell (1944), and Bietti (1944), where the cases responded clinically to penicillin even though the organisms were only slightly penicillin sensitive "in vitro."

TABLE II

Diagnosis	Time for clinical cure	
	Penicillin treated eye	Eye treated with Silver nitrate and proflavine
Acute mucopurulent Koch-Weeks conjunctivitis	Case 1: 4 days Case 2: 4 days	20 days 18 days
Acute mucopurulent conjunctivitis—diphtheroids	6 days	11 days
Acute follicular conjunctivitis: culture sterile; corneae clear	12 days	18 days

Note—In all these cases the eyes were equally severely affected.

(2) One case of *B. proteus* kerato-conjunctivitis occurred in this series. Treatment with 100 units/c.c. drops proved useless, but a strength of 500 units/c.c. rapidly cleared the conjunctivitis (7 days).

The superficial keratitis took considerably longer (4 weeks), and the conjunctivitis tended to recur after 2 weeks' continuous penicillin. This case of infection with such a resistant organism is an indication for very high local concentrations and more frequent application, e.g., 2,000 units per c.c. hourly at first.

(3) One case of severe bilateral infection (eyes equally affected) in which culture from both eyes showed a profuse growth of diphtheroids was treated, one eye with silver nitrate one per cent. paint and proflavine drops 1:1,000, the other eye with penicillin. The penicillin treated eye was white in 6 days: while the other remained acutely inflamed and slightly chemosed, and took 11 days to whiten. Sorsby and Hoffa (1945) have noted that the diphtheroid has proved more stubborn to penicillin therapy than other organisms considered more pathogenic. In this case the response was less dramatic than in others, but penicillin was clearly the superior method.

(d) *Optimum Concentration*: In several bilateral infections the response to treatment was as rapid with 100 units/c.c. as with 1,000/c.c., but these were all due to penicillin sensitive organisms. Since organisms vary so widely in sensitivity, the stronger concentration of 1,000 units/c.c. is recommended for routine use as being surer of clinical cure and less liable to allow relapse to occur (*q.v.*).

(e) *Relapse* (see Table III). (1) In this series 4 out of 31 cases relapsed, 2 during treatment, and 2 after treatment was stopped (2 days and one month). (i) The cases relapsing during treatment were due to slightly sensitive staph. aureus; one responded slowly to further penicillin, the other did not. (ii) Of the others, the case which relapsed 2 days after cessation of treatment responded more slowly the second time (Koch-Weeks infection) this was probably a cross infection from the other (still infected) eye; while the case which relapsed after one month responded well the second time.

These findings fit in with the bacteriological observations on acquired penicillin-resistance by slightly sensitive organisms, a resistance which is slowly lost with the passage of time. This suggests that the greater the interval between clinical cure and relapse the more likely is a good response to further penicillin therapy.

(2) In equal numbers of cases (15) only one of the 1,000/c.c. series relapsed, while 3 of those treated by other methods did. Hence 1,000/c.c. appears the best strength to prevent relapse.

(3) If treatment is stopped too soon, a relapse may occur. This has been found experimentally and clinically, and it is recommended that treatment should be continued for 48 hours after a complete (apparent) clinical cure.

(f) *Other Types of Conjunctivitis*. Where there is no bacterial infection, as in many cases of chronic conjunctivitis, episcleritis, trachoma, no direct effect can be expected from penicillin therapy.

nor has any been found in this series. (One case of episcleritis and two of chronic trachoma showed no response.) But if there is also co-existing secondary infection, as in 3 cases of old trachoma with superadded secondary infection treated in this series, penicillin is effective in eliminating this, and so enabling the inflammation to subside more quickly. In trachoma, the eyes whitened with penicillin therapy, but the follicles and pannus, though quiescent, remained, indicating that there had been no primary action on the trachoma itself. It seems that the deciding factor as to the efficacy of penicillin is the presence or absence of a positive conjunctival culture.

(g) *Summary* :—(1) Penicillin is established as the *most effective* therapeutic agent for acute muco-purulent conjunctivitis, including ophthalmia neonatorum.

(2) The method of choice appears to be drops of 1,000 units/c.c. applied 4 hourly (or oftener in the acute phase).

(3) Treatment should be continued for 48 hours after apparent clinical cure, to prevent relapse.

(4) Other types of conjunctivitis will be beneficially affected by penicillin if there is a positive conjunctival culture.

(3) ACUTE KERATO-CONJUNCTIVITIS AND CORNEAL ULCERATION. BACTERIAL IN ORIGIN (50 cases).

In acute kerato-conjunctivitis, the conjunctival lesion may predominate, with only slight corneal involvement; or the corneal lesion may predominate, with extensive corneal infiltration and/or ulceration. In the present series there were 50 cases, 38 in which the corneal involvement was relatively mild, and 12 in which it was severe. The commonest infecting organism was staph. aureus (29 cases), usually haemolytic; the others included staph. albus: diphtheroids, and one each of strept. haemolyticus, B. proteus, B. subtilis and M. catarrhalis: several cultures were sterile. Treatment was irrigation with normal saline if discharge was present; atropine 1 per cent. if the corneal lesion was moderately severe; otherwise penicillin only (1,000/c.c. 4 hourly).

(a) *Clinical Cure*. (1) In the case with *relatively mild* corneal involvement, clinical cure was obtained in all 38 cases in an average of 8 days. (This is comparable to a similar group of cases described by Crawford and King (1944) that averaged $7\frac{1}{2}$ days for clinical cure.) A few were left with faint corneal nebulae, but the majority were completely clear. Equally rapid clinical cures were obtained with all three strengths used—100, 500 and 1,000 units/c.c. (but see under "Relapse," para. (c), for further discussion).

In the cases of severe corneal involvement, 10 of the 12 were clinically cured in an average of 12 days. Two cases did not respond to penicillin alone. In one, a deep corneal abscess was already

present on admission, and did not respond to penicillin drops. In the other which was a haemolytic strept. infection after 10 days the marginal infiltration of the cornea was spreading deeper into the corneal substance despite continued penicillin therapy. In both these cases curettage and carbolicisation were necessary to clear the infection.

A more continuous method of applying penicillin (e.g., corneal bath) might have yielded better results.

(2) The corneal lesion was invariably slower in responding to penicillin than the conjunctival one, a result to be expected from the avascularity and slower metabolism of the cornea. The conjunctiva was normal in approximately half (mild group) or a third (severe group) the time that the cornea took to clear.

(3) Penicillin may give deceptive clinical results regarding clinical cure. In several cases the eye was white while the cornea still stained. And in other cases there was persisting superficial corneal infiltration, marginal or diffuse, for more than 2 weeks after the eye was white, though at the end of that time the cornea was completely clear. Thus a white eye, apparently cured, may still have an active corneal lesion that must be treated.

(4) In 2 cases that developed superficial punctate keratitis as a complication of severe conjunctivitis, one case, a bilateral infection, was cleared in 11 days in the penicillin treated eye, while the other eye, not any more severely affected, took 20 days to clear on proflavine (and also developed an ulcer that required carbolicisation). The other case was the severest of the whole series, with gross corneal infiltration, marginal and diffuse, of both eyes, spreading deep into the substance of the cornea, and with a severe coincident conjunctivitis. One eye was treated throughout with penicillin, and ultimately became white and normal after 4 weeks. The other eye, treated with proflavine 1:1,000, remained slightly red at this stage, and then developed a superficial punctate keratitis, from which the penicillin treated eye remained free. It seems that penicillin does have a beneficial effect on superficial punctate keratitis if there is co-existing bacterial conjunctivitis.

(b) *Optimum Concentration*:—As in acute conjunctivitis, it was found that 100, 500 and 1,000 units/c.c. strengths were all equally rapid in effecting clinical cure (except in the *B. proteus* case) but not equally good for preventing relapse (*q.v.*)

(c) *Relapse*: (See Table III). Of the 48 cases clinically cured, 6 were known to relapse. (A complete follow-up of all cases was impossible owing to overseas service conditions, but this covered at least 70 per cent. and a period of 3 months after cure.)

It was observed that:—

- (1) None of the 1,000u/c.c series relapsed.
- (2) Four of the 500u/c.c. series relapsed, a high incidence (4:13).

(3) Two relapses occurred in the 100u/c.c. series, each time in the same man, 10 days and 19 days after cessation of treatment.

These facts seem to indicate that :—

- (1) 1,000 units/c.c. is the best strength for preventing relapse.
- (2) 100 units/c.c. is too low a concentration for routine use.
- (3) Continuation of treatment for 48 hours after apparent clinical cure is advisable to prevent relapse, which frequently occurred in this series using the weaker concentrations of penicillin.

TABLE III—*Relapse Incidence*

Disease	Concentration of penicillin	No. of cases cured	No. of relapses	Relapse incidence
Acute mucopurulent conjunctivitis	All methods	30	4	1 : 7.5
	(i) 1000 units c.c.	15	1	1 : 15
	(ii) Other methods (weaker strengths)	15	3	1 : 5
Acute kerato-conjunctivitis	All methods	48	6	1 : 8
	(i) 1000 c.c.	22	—	—
	(ii) 500 c.c.	13	4	1 : 3
	(iii) 100 c.c.	8	2	1 : 4

(d) *Summary* :—From the above results the following deductions are made :—

(1) That penicillin is established as of real value in the treatment of acute kerato-conjunctivitis.

(2) That the only cases that may require treatment additional to penicillin drops are those with deep corneal involvement. Here a continuous application of penicillin should be considered.

(3) That the best concentration to use is 1,000 units/c.c. 4 hourly, or oftener in the acute phase.

(4) That treatment should be continued for 48 hours after apparent clinical cure to prevent relapse.

(4) NON-BACTERIAL CORNEAL INFECTIONS : (8 cases).

Corneal infections that are non-bacterial in origin do not, as expected, respond to penicillin therapy.

In the present series, 2 cases of dendritic ulcer, 2 of post herpetic keratitis, 2 of superficial punctate keratitis and 2 of corneal ulceration of unknown aetiology were treated for one week with 1,000u/c.c. drops 4 hourly. All had sterile cultures, and none responded to penicillin, all being as inflamed after one week's treatment as at the start, and the corneal lesion being unchanged. Similar observations have been made by other workers (Milner, 1944; Wright, 1945; Bietti, 1944) on dendritic ulcer and herpetic keratitis.

It seems established then that in non-bacterial (virus) infection of the cornea, penicillin is of no value.

(5) SUPERFICIAL INJURIES OF THE EYE (Conjunctiva and Cornea).

Five cases of moderately severe superficial injuries to the eye were treated with penicillin. Treatment was supplemented with irrigations with normal saline (if discharge was present), liquid paraffin, and atropine (if there was deep corneal involvement). The cases included 2 chemical burns, 1 scald and 2 abrasions.

(a) *Conjunctiva* :—(1) The caustic soda burn involved superior palpebral conjunctiva and a segment of the bulbar conjunctiva. Treatment was with penicillin oculets 100 units each 4 hourly, and was started within 6 hours of injury, before infection supervened.

The conjunctiva was healed and the eye was practically white in 4 days. This good result was obtained despite an initial reaction to the first oculet, which started within $\frac{1}{2}$ hour of application, and consisted of severe pain, increased injection and chemosis. Subsequent oculets were well tolerated. The cause of this reaction was probably a combined effect of mechanical irritation by the slowly-dissolving oculet, and irritation by the calcium penicillin of the oculet (as opposed to the less irritant sodium penicillin of the drops) on the injured conjunctiva. It is probable that drops would have been less irritant here.

(b) *Cornea* :—Two cases of corneal abrasion were treated :—

(1) One was clear, and was healed in 2 days and white in 5 days, possibly not any more quickly than by other methods.

(2) One was infected. The cornea was healed in 6 days and the eye white in 10 days. This is the type of injury where penicillin is of real value, as it sterilises the conjunctival sac, and so enables healing to take place more quickly.

(c) *Conjunctiva and Cornea* :—(1) The scald was a severe injury, involving palpebral and bulbar conjunctiva, and the whole of the corneal epithelium, with considerable secondary infection. Treatment was with penicillin drops 1,000 units/c.c. 4 hourly (+ irrigations, atropine and liquid paraffin). The conjunctiva and the corneal epithelium were healed by the 9th day, but much ciliary injection and deep corneal infiltration persisted, and the eye did not whiten till the 26th day.

(2) The carbide burns involved conjunctiva and cornea of both eyes, with considerable secondary infection.

The right eye was less severely injured, and on proflavine 1:2,000 the cornea was healed in 4 days and the eye white in 8 days. The left eye was more extensively injured, for the whole corneal epithelium was burnt off :

Treated with penicillin sulphathiazole powder t.i.d., the cornea was healed in 8 days and the eye white in 15 days—i.e., approximately twice the time the other eye took. But in view of the severity of the lesion, the result was considered good.

Conclusions :—In superficial injuries of the eye, penicillin drops

are of great value (a) in preventing secondary infection by early application after injury; and (b) if infection has supervened, in sterilising the conjunctival sac while the injured tissues recover.

They should be used (1,000 units/c.c.) as early as possible in all cases of superficial injury to the eye.

(6) OPHTHALMIC OPERATIONS :

Penicillin sterilises the conjunctival sac more efficiently than any other known drug, and is recommended for routine use, pre- and post-operatively, in all eye operations. It has been used routinely in over 100 major operations during the present series, about 50 per cent. of these being intra-ocular. Every case that was clear pre-operatively remained so. The only exception was a case of a septic scleral wound (see next section), where the wound was dirty pre-operatively. In all other cases, including many potentially infected penetrating wounds, the eye remained perfectly clear post-operatively. It is recommended that one or two drops of penicillin 1,000 units/c.c. be given one hour or less before operation, and that drops be given at the end of the operation and subsequently at every dressing.

B. DEEP OCULAR INFECTION :

From the experimental work reported in Section II, one would expect that deep ocular infection in the cornea and inner eye, that is bacterial in origin, might respond to methods of continuous application (*e.g.* corneal bath) or special methods of application (iontophoresis, subconjunctival or intra-vitreous injection).

(1) DEEP KERATITIS AND HYPOPYON ULCER.

(a) *Bacterial in origin* (3 cases).—In the present series, 2 cases already referred to under "kerato-conjunctivitis" developed deep corneal abscesses that did not respond to 4 hourly drops of 100 units/c.c. Similarly one case of deep keratitis with a small hypopyon (conjunctival culture staph. aureus) did not respond to this method, but was rapidly cleared with T.A.B. shock (50 million units I.V.). In this type of case, for effective penicillin therapy, treatment must be by $\frac{1}{2}$ and 1 hourly drops or continuous application t.i.d. by a type of contact lens [Juler and Young (1945) : Wright and Harris (1945)].

(b) *Non-bacterial in origin* : (3 cases)—Two cases of deep keratitis and uveitis following dendritic ulcer were treated with 1,000 units/c.c. 4 hourly with no improvement. They were also given 4 daily injections of subconjunctival penicillin (2,000 units in 2 minims saline), also with no clinical improvement either in the keratitis or the uveitis. One case of severe deep disciform keratitis of unknown aetiology (Kahn and all other investigations negative) did not respond to 4 hourly drops; and a course of systemic

penicillin (total of 400,000 units intramuscularly in 3 hourly doses of 15,000 units) produced no clinical change whatsoever.

These results confirm the view that if the infection is non-bacterial in origin (*e.g.*, post-herpetic), penicillin therapy is of no value.

(2) INTRA-OCULAR INFECTION OF THE ANTERIOR SEGMENT.

(a) *Non-traumatic* (3 cases)—In this series there were 3 cases of infective uveitis, treated with subconjunctival injections of 2,000 units of penicillin daily for 4 days. 2 cases were of post-herpetic uveitis referred to above, and no improvement in the uveitis was noted. Since the original infection was a virus, these negative results were only to be expected.

One case of acute uveitis (cyclitis and choroiditis of undetermined aetiology: all investigations negative except for doubtful radiological focus of infection in L mid-zone of lung) had (i) macroscopic k.p., (ii) many cells in the anterior chamber seen with the slit-lamp, and (iii) a patch of acute choroiditis up and out from the disc. He was given 2,000 units of penicillin subconjunctivally daily for 4 days. On the 4th day, the macroscopic k.p. had disappeared, those that remained were seen with the slit-lamp to be shrinking, and there were only a few cells in the anterior chamber, *i.e.*, the infection was regressing rapidly. He was also given atropine and heat. The clearance of the cyclitis (by the 12th day it had completely cleared) appeared to be more rapid than usual, but whether this was due to the penicillin or not remains to be decided.

(1) *Conclusions*:—It seems reasonable to suppose that in uveitis due to penicillin sensitive organisms (*e.g.*, gonococcal) penicillin will be of value, and Dunnington and Sallmann (1944) describe three cases (one of gonococcal iritis, two of meningococcal endophthalmitis) all treated successfully by combined local (iontophoresis) and parenteral penicillin. By combining both methods, one attacks the primary focus and also gets a high intra-ocular concentration.

(2) In uveitis due to virus infections, penicillin is of no value, while in that large group of cases of undetermined aetiology, further work is required to prove its value one way or the other.

(b) *Traumatic*:—One case of traumatic Tenonitis and uveitis was treated with subconjunctival penicillin in this series with excellent results. Infection was present in a partially penetrating scleral wound (shell wound) and was lit up by the removal of the metallic scleral F. B. (magnetic). Three days after operation, infection was spreading through Tenon's capsule, sclera and uveal tract, uncontrolled by penicillin drops 1,000 units/c.c. 4 hourly. A course of oral sulphathiazole, started on the 4th day, had no effect in checking the infection. On the 6th day the condition was

rapidly deteriorating, with severe chemosis, Tenonitis and iritis, the anterior chamber being very deep and choked in its whole height and depth with macroscopic cells and exudate. There was an evening temperature of 99.4° F. Panophthalmitis appeared imminent.

At this point (6th day) the first subconjunctival injection of 4,000 units of penicillin was given and repeated daily for 6 days. The first injection prevented further deterioration, and rapid improvement ensued, so that by the 12th day the iritis had cleared and by the 15th day the eye was whitening and the media were as clear as before the operation. It appears that this eye was definitely saved by subconjunctival penicillin.

Conclusions :—Several methods of penicillin therapy for anterior segment infections attain good intra-ocular concentration, and have been used by different workers—drops $\frac{1}{2}$ -1 hourly (Cashell), iontophoresis (Dunnington and Sallmann), intra-aqueous injection (Cashell and Rycroft), with varying results.

(1) If the cornea is damaged or inflamed, $\frac{1}{2}$ or 1 hourly drops of 2,500 units/c.c. appears the method of choice.

(2) If the cornea is normal, subconjunctival injections b.d. or

(3) corneal bath with or without iontophoresis b.d. is indicated for high intra-ocular concentration.

(4) Results from intra-aqueous penicillin do not so far seem to justify the extra trauma involved being added to the already wounded eye.

The value of penicillin in cases of this type is not yet established. Rycroft (1945a) found that T.A.B. shock was more efficacious in clearing hypopyon iritis following a penetrating wound than any method of penicillin therapy, and it may well be that this type of infection, with sterile aqueous and hypopyon, being non-bacterial in type, will prove to be more amenable to the older methods than to penicillin therapy. But if an obviously septic wound is present, as in the case described in this series, penicillin therapy is definitely indicated.

(3) INTRA-OCULAR INFECTION OF THE POSTERIOR SEGMENT.

(a) *Non-traumatic* (1 case).—One case of uveitis, with cyclitis and choroiditis, referred to in section (2), cleared well in the anterior segment with subconjunctival penicillin 2,000 units daily for 4 days, but the acute choroiditis 3 disc-diameters up and out from the disc was completely unaltered, and took its own slow course of resolution (3-4 weeks).

Bellows (1944) reported a similar failure with local and parenteral penicillin in 2 cases of exudative choroiditis.

While penicillin has not so far proved of value in the average case of choroiditis, cases of endophthalmitis that are bacterial in

origin have responded to therapy with penicillin and sulphadiazine. Dunnington and Sallmann (1944) report 2 cases of metastatic endophthalmitis following meningococcal meningitis that were treated, one eye with penicillin iontophoresis (2,500 units/c.c.), the other eye with sulphadiazine iontophoresis: they were also given oral sulphadiazine. The eyes were all saved, but the penicillin treated eye did better than the sulphadiazine treated one. Such infections with penicillin sensitive organisms should be indications for combined local and parenteral penicillin therapy, but in cases of choroiditis of undetermined aetiology (? septic focus) penicillin has not so far proved to be of any value.

(b) *Traumatic: Infections of the Posterior Segment: Endophthalmitis.*—This condition is probably the commonest cause of blindness in penetrating war wounds of eyes that are not totally destroyed. After a severe injury, the anterior segment usually recovers and the eye whitens. But after 7-10 days or more from the time of injury or even earlier, a yellow vitreous reflex may appear and spread to all segments of the vitreous, no matter what treatment is employed. Vision is finally reduced to p.l. or is totally lost, and the eye softens and shrinks. The effect of penicillin in controlling such dreaded complications of eye wounds is therefore of the greatest importance.

(1) *Rycroft* (1945a) reported 5 cases of such an endophthalmitis in penetrating war wounds, treated by intra-vitreous penicillin (2-5,000 units, 1,000 units per minim). In 2 cases the penicillin was injected through the posterior sclerotomy wound at the time of magnet extraction of the F.B. In the other 3 cases it was injected through the sclera after reflection of the conjunctiva and partial incision of the sclera. In all cases, some degree of endophthalmitis was present, varying in type from the slow, quiet type with a white eye, to the acutely turbid vitreous with an acutely inflamed eye. In no case was any improvement noted after the intra-vitreous penicillin, and the endophthalmitis pursued its course, the end result being loss of vision and usually shrinkage of the globe.

In all cases, culture of the vitreous and the F. B. was sterile. This means that this type of infection is not frankly bacterial, and hence the failure of penicillin.

(2) *Dunnington and Sallmann* (1944) treated 2 cases of endophthalmitis following cataract extraction, both without success. They were given penicillin-iontophoresis and parenteral sulphadiazine. One went on to ring abscess of the cornea and panophthalmitis and was excised: a positive vitreous culture for staph. aureus was obtained. In the other case, the eye was not excised, but was blind, with a hazy cornea, pupil blocked with exudate, and presumably an infected vitreous.

(3) *Bietti* (1944) reported 12 cases of infected anterior and

posterior segments following cataract extractions or trauma, treated by subconjunctival, intra-aqueous, intra-vitreous and parenteral penicillin. They all did badly if the vitreous was infected except one, where 3 injections of intra-vitreous penicillin were given, and the eye was saved from panophthalmitis.

(4) In this series one case of penetrating corneo-scleral wound developed acute iritis, traumatic cataract, and, on the 12th day, early endophthalmitis. On the 14th day a course of intra-muscular penicillin (total 400,000 units) was started but it had no effect on the endophthalmitis. The eye later became quiet, but began to shrink and became totally blind.

Conclusions :—(1) Parenteral penicillin reaches the vitreous in only negligible concentrations, and is of no value in this type of case.

(2) Iontophoresis gives a moderate vitreous concentration, as does subconjunctival injection. But no successful results have been reported by these routes.

(3) From experimental evidence, the intra-vitreous route is the method of choice (see section II), but only one clinical success has been reported in the literature available overseas, that of Bietti (1944). It should be noted that treatment in the experimental vitreous infections was given within 12 hours if penicillin therapy was to be effective, and that if it was delayed for 24 hours, all eyes were lost. It is possible that within 12 hours of injury, there is an active bacterial infection, and that if used at this early stage, penicillin therapy will be effective. As the endophthalmitis progresses, the nature of the infection appears to change to a non-or sub-bacterial type, and the vitreous culture is sterile. Only in a very fulminating case is a positive vitreous culture obtained (Dunnington and Sallmann).

It seems that subconjunctival penicillin (4,000 units) which has been shown to penetrate into aqueous and vitreous, might be of value as a prophylactic if given within 12 hours of injury, and that if there is any reason to suspect endophthalmitis, direct intra-vitreous injection of 4,000 units is indicated also being given, if possible, within 12 hours of infection.

(4) SUMMARY OF TREATMENT OF DEEP OCULAR INFECTIONS :

(1) Penicillin is of value in deep infections of the eye that are bacterial in origin. In this small series, subconjunctival injection proved of value in one case (see Table IV).

(2) The methods of choice appear to be :—

(i) Deep corneal infections (1) Drops 2,500 units/c.c. $\frac{1}{2}$ or 1 hourly or (2) Corneal baths 2,500 units/c.c. t.i.d. with or without iontophoresis.

(ii) Infections of the anterior segments (1) Corneal baths t.i.d.

with or without iontophoresis. (2) Subconjunctival injections 2-4,000 units b.d.

(iii) Infections of the posterior segment (1) Subconjunctival penicillin 2-4,000 units as a prophylactic measure. (2) Intra-vitreous penicillin 2-4,000 units as a therapeutic measure.

Penicillin Sensitisation :—It appears that in a small percentage of cases, local penicillin may give rise to sensitisation in the form of an eczematous dermatitis (Barker, 1945; Michie and Bailie, 1945; Peterkin, 1945). It has been noted (Berger, 1945) that repeated application of crude penicillin to large raw surfaces is likely to cause sensitisation, due to the large protein content of such preparations, and not due to the penicillin itself. This seems the likely cause in 2 of the 3 cases reported here.

In this series there were 3 cases of local penicillin reaction. Two developed eczematous dermatitis, and one developed a flare-up of iritis following sub-conjunctival penicillin.

Case 1 had had a previous intra-muscular course of penicillin, and penicillin drops (1,000/c.c.) for 3 weeks (endophthalmitis after a penetrating wound). While still on penicillin drops he developed a (unilateral) muco purulent conjunctivitis and weepy dermatitis of the cheek. It was made worse with penicillin cream, and cleared when both the drops and cream were stopped. A recurrence of conjunctivitis and dermatitis occurred when one drop of penicillin was instilled later on, as a sensitivity test.

Case 2, a Russian, had several relapses of secondary infection (acute kerato-conjunctivitis) on top of an old trachoma. The first attack cleared well on penicillin drops 1,000/c.c. 4 hourly. While being treated for his first relapse, which occurred 12 days after discharge, *i.e.*, during his second course of penicillin drops, he developed a slight dermatitis of the cheek that was easily controlled. Some dermatitis was already present when he was admitted 13 days later for his second relapse. He was again put on penicillin drops, and the dermatitis became progressively worse, though the eye itself improved a bit. Atropine was stopped with no improvement of the dermatitis, but withdrawal of the penicillin effected a rapid improvement. A patch test was negative, but clinically this was a case of penicillin sensitivity. The two previous courses may have been predisposing factors, the dermatitis in the first relapse may have been an initial attack, and in the second relapse profuse epiphora washed the penicillin over the area of dermatitis.

Case 3 had a deep post-herpetic keratitis and uveitis that had proved resistant to treatment, including local penicillin drops (1,000 units/c.c.) and 4 daily injections of subconjunctival penicillin (2,000 units each). A second course of subconjunctival penicillin was given 10 weeks later, but the first injection (5,000 units) produced a violent flare-up in a uveitis that had been grumbling

on for months. An intra-dermal penicillin sensitivity test was negative, and yet this seemed to be a true penicillin reaction.

TABLE IV—Results of Penicillin Therapy in this series
(a) Superficial Infections :—

Type of case	Total number	No. of cases clinically cured	No. of cases improved	No. of cases not improved	No. of cases of relapse
Blepharitis					
(a) Acute ...	14	10	4	—	—
(b) Chronic ...	5	2	3	—	—
Conjunctivitis					
(a) Acute ...	31	30	1	—	4
(b) Chronic ...	3	3	—	—	—
Acute Kerato-conjunctivitis					
(a) Moderate ...	38	38	—	—	6
(b) Severe ...	12	10	—	2	—
Non-bacterial corneal infections	9	3*	—	6	—
Superficial injuries	5	5	—	—	—

* Also had secondary (bacterial) infection

(b) Deep Infection :—

Type of case	Total number	Clinical cure (subconjunctival injection)	Improved	Not improved (drops, subconjunctival, intra-vitreous, parenteral penicillin)
Deep Keratitis (non-bacterial)	4	—	—	4
Infection of anterior segment				
(a) Traumatic ...	2	1	—	1
(b) Infective ...	3	1?	—	2
Infection of posterior segment				
(a) Traumatic ...	2	—	—	2
(b) Infective ...	1	—	—	1

All three cases were probably due to a sensitisation to the protein in the penicillin solution through prolonged application.

Final Summary (see Table IV)

(1) Penicillin is established as the most effective therapeutic agent for acute superficial bacterial infections of the eyes.

(2) It is indicated in non-bacterial infections only if secondary bacterial infection is present or threatened.

(3) In deep ocular infections bacterial in origin, penicillin must be used in continuously high local concentrations. Its greatest value is as a prophylactic or early therapeutic measure.

(4) Local sensitisation to penicillin is described.

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