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PURE PENICILLIN IN OPHTHALMOLOGY

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Until recent months supplies of penicillin in current use contained some 80 to 90% of impurities. In contrast most of the samples now generally obtainable contain a concentration of penicillin of up to 80%, and limited quantities of pure penicillin are becoming available.

Pure penicillin in calcium or sodium salt is a white crystalline substance devoid of any yellowish tinge. It is freely soluble and is more stable than commercial (impure) penicillin. In the dry form pure penicillin remains stable when kept at room temperature over a period of many months. Aqueous solutions remain active for fourteen days when kept at room temperature under sterile conditions, and retain full potency for up to four weeks when kept on ice. One milligramme of pure penicillin corresponds to 1,660 Oxford units.

The use of penicillin in ophthalmology, and particularly in intraocular infections, is still limited by considerable difficulties. In the first place, penicillin administered systemically in the usual clinical doses does not penetrate into the interior of the eye. Secondly, commercial penicillin instilled locally into the conjunctival sac in high concentrations is not well tolerated; there are discomfort, conjunctival hyperaemia, and, in extreme cases, damage to the corneal epithelium; moreover, with tolerated concentrations there is no penetration through the cornea into the interior of the eye. To overcome the obstacles to the passage of the drug into the interior of the eye, penicillin has been employed as subconjunctival and intravitreal injections, and iontophoresis of solution instilled into the conjunctival sac has been practised, but only with indifferent results. The limit of tolerance to subconjunctival injections, though varying with different samples of commercial penicillin, is about 600 to 2,000 units in 0.5 ml. of water. With such doses the intraocular concentrations of penicillin are again low (only a trace in the aqueous, according to Struble and Bellows (1944), who employed 2,500 units in the dog; though, in man, Rycroft (1945) obtained higher values by the use of 4,000 units subconjunctivally—0 to 3 units per ml. in five instances, and 10, 15, and 20 units in three more). Intravitreal injection of commercial penicillin is badly borne by the experimental animal (v. Sallmann, Meyer, and Di Grandi, 1944; Sorsby, 1945; Mann, 1946), and this procedure has distinct clinical disadvantages. Iontophoresis as advocated by v. Sallmann and Meyer (1944) also presents clinical difficulties, and is only doubtfully valid on theoretical grounds (Hamilton-Paterson, 1946). Since the value of penicillin as a local therapeutic agent is limited by the inability of the eye to support large doses of the commercial product, and since intolerance varies directly with the amount of impurity present, a study of tolerance of the eye to pure penicillin was undertaken, followed by preliminary investigations of the levels of concentration that can be reached intraocularly and of the effect of local medication on experimental intraocular infections. These results have been assessed against those obtained both experimentally by the systemic administration of massive doses of commercial penicillin and clinically by the use of pure penicillin locally.

Experimental Studies on Pure Penicillin

Rabbits were used throughout. Guinea-pigs were also used at first, but proved unsatisfactory, particularly when intraocular fluids had to be collected, and were therefore discarded. The rabbits were of a mixed breed and generally six months old, with an average weight of 1,500 g. The concentration of penicillin in the eye fluids, blood, and tissue extracts was estimated by the standard capillary tube method, as described by Fleming. Where ointment was introduced into the conjunctival sac, 0.1 ml. (=0.1 g.) was delivered into the lower fornix from a syringe with a wide-bore needle, and spread evenly over the globe through the closed lids; before aqueous was withdrawn for assessing the concentration of penicillin the conjunctival sac was thoroughly irrigated. Where penicillin was injected into the vitreous, the needle was entered at the equator of the proptosed eye and the drug injected centrally; a similar technique was used for introducing infection into the vitreous. Subconjunctival injections were made by the usual clinical method, and fluid from the aqueous was collected by limbal puncture (subconjunctivally), also in the proptosed eye. In assessing the concentration of penicillin in solid tissues, the parts were minced with scissors on a watch-glass, placed in 1 ml. of saline (2 ml. in the case of the sclerotic), and allowed to stand overnight in a refrigerator; the supernatant fluid was then tested

Tolerance

Pure penicillin in aqueous solution in concentrations of 10,000, 25,000, 50,000, and 100,000 units/ml. was well tolerated when two or three drops were instilled into the conjunctival sac at ten intervals of three minutes. There was no obvious irritability, nor any flushing of the eye. Likewise pure penicillin in ointment form was well borne in concentrations of 500, 1,000, 2,000, 4,000, 8,000, 25,000, 50,000, and 100,000 units per gramme. The ointment was made up in two different bases, one being "eucerin" L.M. base, and the other a specially prepared mixture of petroleum jelly and liquid paraffin (90 and 10 parts of each respectively). Some ointment still remained in the conjunctival sac after half an hour. Subconjunctival injections of 0.5 ml. of water containing 25,000 and 50,000 units of pure penicillin were also well tolerated. There was no reaction around the bleb produced by the injection, and the bleb had mostly disappeared within three to four hours. The vitreous too tolerated direct injection of pure penicillin: 0.1 ml. of saline containing 5,000 units (50,000 units/ml.) and 0.2 ml. containing 10,000 units produced a visible "globule" in the vitreous, with but little reaction around it and no ophthalmoscopically visible changes. Apart

from some scattering of the globule after six months (the total period of observation) there was practically no reaction of the vitreous or the globe as a whole.

These observations suggested that, in contrast to commercial penicillin, the pure product is remarkably well tolerated by the eye, so that ocular intolerance is not a factor of any significance in limiting its use. It should, however, be borne in mind that concentrated solutions of pure penicillin should be made up in water rather than saline; watery solutions containing 20,000 to 50,000 units of pure penicillin per ml. are isotonic with 0.9% sodium chloride, while saline solutions of such concentration are distinctly hypertonic (Ungar and Denston, 1946).

Concentration in Interior of Eye

In the Primary Aqueous (Chart I).—The level of penicillin in the aqueous obtained at different time intervals (*a*) after a single instillation of penicillin ointment in the conjunctival sac, and (*b*) after subconjunctival injection, was determined.

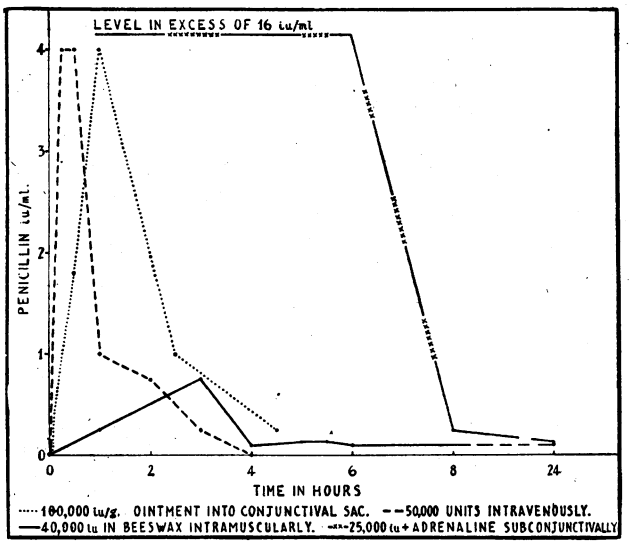

CHART I.—Penicillin levels in the primary aqueous of the rabbit after administrations by different routes.

(*a*) For instillation of pure penicillin ointment the base used was a mixture of petroleum jelly and liquid paraffin, as already indicated. Table I shows that penicillin penetrates in therapeutic levels through the cornea when ointments of high concentrations are used. Each reading in the table represents

TABLE I.—*Level of Penicillin (Units/ml.) in Primary Aqueous on Instillation of 0.1 g. of Concentrated Ointments of Pure Penicillin into Conjunctival Sac*

Concentration (units/g.)	At 1/2 hr.	At 1 hr.	At 2 hrs.	At 2½ hrs	At 3 hrs.	At 4 hrs.	At 4½ h.s.	At 22 hrs.
25,000	4, 4	1·5, 2, 2		0·125, 0·25, 0·25	0		0, 0	
50,000	8, 8	1·5, 2, 2, 3, 3, 4	1·5, 4	0·125, 0·125	0, 0, 0	0, 0	0, 0	0
100,000	2, 2	4, 4, 8		1, 1			0·25, 0·25	0

a single estimate, and the 44 readings recorded all refer to primary aqueous. These findings suggest that the more concentrated the ointment the higher is the concentration of penicillin in the aqueous, and that a therapeutic level is sustained for 2½ hours and possibly longer.

(*b*) The level of penicillin in the primary aqueous was also determined at different time intervals after the injection subconjunctivally of 25,000 units of pure penicillin in 0.5 ml. of water. As can be seen from the first column in Table II, adequate levels are quickly reached in the aqueous and maintained for at least 6 hours, and possibly longer. That the levels of penicillin reached and maintained by this procedure are the result of the quantity injected and not conditioned by the purity of the agent is shown by the findings recorded in the second column of the table, where it is seen that the distinctly irritating commercial penicillin gives concentrations somewhat similar to those of pure penicillin. The results in the last column suggest that when adrenaline is added to pure penicillin considerably higher levels are reached in the aqueous. (The penicillin was dissolved in 0.25 ml. of water to which 0.25 ml. of adrenaline 1:1,000 was added.)

That at least some of the penicillin in the aqueous reaches it through the blood stream rather than directly by penetrating

TABLE II.—*Levels in Primary Aqueous of Anterior Chamber after Subconjunctival Injection of 25,000 Units of Penicillin*

	Pure Penicillin	Commercial Penicillin (654–1,425 u/ml.)	Pure Penicillin with Adrenaline
	Units/ml.	Units/ml.	Units/ml.
At 15 minutes ..	2	16	
,, 30 ,, ..	16	16	
,, 1 hour ..			>16, 16
,, 1½ hours ..	10, 16	1, 4	
,, 2 ,, ..	4, 32	4	>16, 12
,, 2½ ,, ..	2, 4	1, 8	
,, 3 ,, ..	0·5, 2	2	
,, 4 ,, ..	4	4	6
,, 5 ,, ..	1, 1	0·25	
,, 6 ,, ..	0·5	1	>16, 0
,, 8 ,, ..			0·25
,, 15 ,, ..			0
,, 22 ,, ..			0·125
,, 24 ,, ..	0·5 (0, 0, 0·12, 0·06*)		

* Secondary aqueous.

the corneo-scleral angle is suggested by the findings recorded in Table III. When only one eye received a subconjunctival

TABLE III.—*Level of Penicillin in Primary Aqueous of Anterior Chamber after Subconjunctival Injection of 25,000 Units in Opposite Eye*

	Units/ml.
At 2 hours	4*
,, 3 ,, ...	0·25
,, 5 ,, ...	0·125

* The injected eye showed the value of 32 units at 2 hours.

injection of 25,000 units of penicillin a not insignificant concentration was obtained in the aqueous of the opposite eye at 2, 3, and 5 hours. That most of the penicillin injected subconjunctivally is indeed absorbed into the blood stream is shown by the findings in Table IV, which also suggest that absorp-

TABLE IV.—*Level of Penicillin in Arterial Blood after Subconjunctival Injection*

	A	B	C
	Units/ml.	Units/ml.	Units/ml.
At 1 hour	2, 2, 2		
,, 2 hours	0·25		
,, 2½ ,, ...		2	
,, 3 ,, ...	0·125 (1*)	0	
,, 3½ ,, ...	0·06		
,, 4 ,, ...	Trace, 1		
,, 5 ,, ...	0, 0·25	0	
,, 6 ,, ...		0, 0	0, 0·5
,, 24 ,, ...	0	0	0

A.—In rabbits receiving 25,000 units pure penicillin subconjunctivally in one eye and 25,000 units commercial penicillin in the other—i.e., a total of 50,000 units. B.—In rabbits after 25,000 units pure penicillin subconjunctivally in one eye only. C.—In rabbits after 25,000 units pure penicillin with adrenaline subconjunctivally in one eye only.

* 25,000 units pure penicillin subconjunctivally in each eye with adrenaline.

tion into the blood stream is rapid and that excretion is, too. Aqueous levels seem to be maintained longer than blood levels. The rapid absorption into the blood stream may explain why unmedicated subconjunctival injections of penicillin are less effective than injections with adrenaline; presumably the adrenaline subconjunctivally impedes absorption into the blood stream.

Concentration in Other Ocular Tissues on Application of Ointment and on Subconjunctival Injection.—No systematic study was undertaken, but the results shown in Table V indicate that adequate therapeutic levels are present in the cornea, sclera, and vitreous as late as 5 hours after a subconjunctival injection, and suggest that equally satisfactory results can be achieved by the application of ointments

TABLE V.—*Levels of Penicillin reached in Ocular Tissues on Application of Ointment and on Subconjunctival Injection of Pure Penicillin*

Tissue†	Ointment, 50,000 Units/g.; 0·1 g. instilled				Subconjunctival Injection of 25,000 Units
	At 1 hr.	At 2 hrs.	At 3 hrs.*	At 4 hrs.	At 5 hrs.
	Units/ml.	Units/ml.	Units/ml.	Units/ml.	Units/ml.
Cornea ..	2	0·75	0	0·25	0·25, 0·25
Lens ..	0	0·1	0	0	0, 0
Sclera ..	2	1	0·25	0·25	4, 2
Vitreous ..	1	4	0·2	0·2	0·15
Uvea ..	4	0·3	0	0	Not determined

* Arterial blood at 3 hours showed no penicillin.
† An experimental error of 0·1 unit/ml. was shown by the presence of that amount of penicillin in washings from the eye after washing with 6 ml. saline 2 hours following application of ointment. (Before this estimate was carried out the eye had been washed in two changes of saline.)

(Chart II). A copious flow of tears noted in one rabbit 2½ hours after instilling ointment, 100,000 units per gramme, revealed a concentration of penicillin of more than 16 units per ml. of tears.

Concentration in Aqueous and Vitreous in Infected Eyes after Subconjunctival Injection.—In the course of therapeutic experiments, recorded below, the level of the aqueous and vitreous in infected and treated eyes was determined at 5 hours and 24 hours after subconjunctival injection of 20,000 units with adrenaline. As can be seen from the second column of Table XIV, the aqueous at both 5 and 24 hours contained more than 2 units of penicillin, while the vitreous contained 0.1 and 0.25 unit respectively. Column 1 of the same table suggests that without adrenaline the values are not dissimilar.

Local Therapy with Pure Penicillin in Intraocular Infections

Two types of experimental infection and two modes of treatment—(*a*) subconjunctival injections and (*b*) the application of ointment—were studied. The anterior chamber was infected in 14 eyes and the vitreous in 16. In no case were both the anterior chamber and the vitreous infected. Treatment was begun within two hours after infection.

Anterior Chamber Infection.—(*a*) Three eyes were infected with suspensions of *Str. haemolyticus* and one with *Staph. aureus*, the suspensions containing 25,000,000 organisms per ml.; 0.1 ml. was injected into the anterior chamber by subconjunctival puncture at the limbus. Treatment consisted of subconjunctival injection of 25,000 units of pure penicillin twice daily for two days. As can be seen from Table VI, the process was controlled, but not completely; in two eyes there was still slight exudate along the pupillary margin on the fifth day, while one eye showed a more severe reaction,

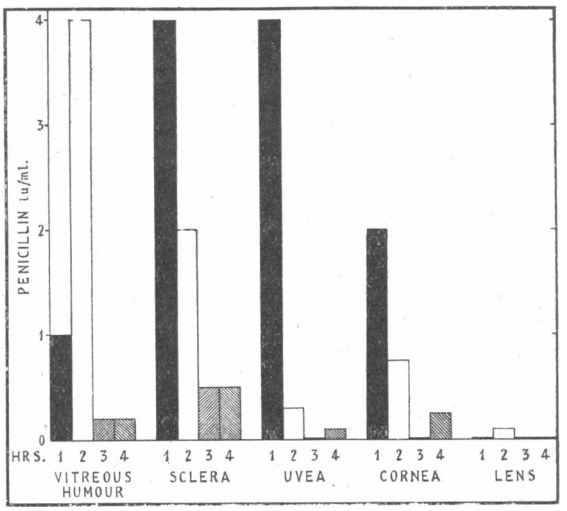

CHART II.—Penicillin levels in ocular tissues of rabbits after local application of ointment (50,000 units/g.).

and the fourth one a still heavier disturbance. These results were, however, better than the state of two untreated eyes, which were largely disorganized. Four further eyes infected less heavily with staphylococcus (1,000,000 organisms per ml.) and treated for a day longer did distinctly better. Only one eye showed exudate along the pupillary margin on the fifth day, while the remaining three were normal. Two untreated control eyes were disorganized by this time.

TABLE VI.—*Infections of Anterior Chamber: Treatment by Subconjunctival Injections and by Ointment*

Rabbit No.	Organism	Concentration of Infecting Fluid (Dose: 0·1 ml.)	Treatment	End-result (on 5th Day)	Remarks
			Subconjunctival Injection		
1	Staph. aureus 663 ..	25,000,000/ml.	25,000 units twice daily for 2 days	Slight exudate in anterior chamber	5 control eyes ended in a destructive suppurative reaction
2	Str. haemolyt. 618 ..	,,	,,	Exudate in anterior chamber	
3	,, ,, ..	,,	,,	Slight exudate in anterior chamber	
4	,, ,, ..	,,	,,	Considerable exudate in anterior chamber	
5	Staph. aureus 663 ..	1,000,000/ml.	20,000 units with adrenaline twice daily for 3 days	Eye normal	
6	,, ,, ..	,,	,,	Slight exudate in anterior chamber	
7	,, ,, ..	,,	20,000 units twice daily for 3 days	Eye normal	
8	,, ,, ..	,,	,,	,,	
			Ointment—0·1 g. three times a day for 3 days:		
9	,, ,, ..	,,	25,000 units/g.	,,	
10	,, ,, ..	,,	,,	,,	
11	,, ,, ..	,,	50,000 units/g.	,,	
12	,, ,, ..	,,	,,	,,	
13	,, ,, ..	,,	100,000 units/g.	Slight exudate in anterior chamber	
14	,, ,, ..	,,	,,	,,	

TABLE VII.—*Infections of the Vitreous: Treatment by Subconjunctival Injections and by Ointment*

Rabbit No.	Organism	Concentration of Infecting Fluid (Dose: 0·1 ml.)	Treatment	End-result (on 5th Day)	Remarks
			Subconjunctival Injection		
1	Staph. aureus 663 ..	1,000,000/ml.	20,000 units twice daily for 3 days	Eye normal	4 control eyes all ended in a destructive suppurative reaction The 10 eyes treated with subconjunctival injections were all outwardly normal, but Nos. 5, 6, 8, 9, and 10 showed some vitreous opacities
2	,, ,, ..	,,	,,	,,	
3	,, ,, ..	,,	20,000 units with adrenaline twice daily for 3 days	,,	
4	,, ,, ..	,,	,,	,,	
5	,, ,, ..	10,000,000/ml.	20,000 units twice daily for 3 days	,,	
6	,, ,, ..	,,	,,	,,	
7	,, ,, ..	,,	,,	,,	
8	,, ,, ..	,,	,,	,,	
9	,, ,, ..	,,	,,	,,	
10	,, ,, ..	,,	,,	,,	
			Ointment—0·1 g. three times a day for 3 days:		
11	,, ,, ..	,,	25,000 units/g.	Eye quiet but extensive vitreous organization	The 6 eyes treated with ointment showed vitreous organization, visible to the naked eye as a grey mass One control eye ended in a destructive inflammatory reaction
12	,, ,, ..	,,	,,	,,	
13	,, ,, ..	,,	50,000 units/g.	,,	
14	,, ,, ..	,,	,,	,,	
15	,, ,, ..	,,	100,000 units/g.	,,	
16	,, ,, ..	,,	,,	,,	

(*b*) Ointment (petroleum jelly and liquid paraffin base) was delivered into the conjunctival sac by a syringe three times daily for three days; the concentration of the ointment was 25,000 units/g. in two eyes, 50,000 in two more, and 100,000 in yet another two. The type and degree of infection were the same as with the second series treated with subconjunctival injection (0.1 ml. of a suspension containing 1,000,000 *Staph. aureus* per ml.), and the results were substantially the same. Five of the six eyes were normal on the fifth day, and one showed a slight exudate at the pupil margin. An untreated control eye was lost.

Vitreous Infection.—(*a*) Ten eyes were infected with *Staph. aureus* injected centrally into the vitreous by direct puncture at the equator: 0.1 ml. was injected in all cases, the concentration of the infecting fluid being 1,000,000 organisms per ml. in four eyes and 10,000,000 per ml. in the remaining six. Treatment was given twice daily for three days, and, as can be seen from Table VII, the results were remarkably good. Residual vitreous opacities were observed ophthalmoscopically in five of the ten eyes. The four control eyes were all lost.

(*b*) Six eyes were infected as for subconjunctival therapy, the concentration of the infecting fluid being 1,000,000 *Staph. aureus* per ml. Two eyes were treated with ointment 25,000 units/g. three times daily for three days, two with 50,000 units/g., and two more with 100,000 units. There was no evidence of active inflammation on the fifth day, but the vitreous was largely an organized grey mass. An untreated control eye was lost.

Comparative Experimental Studies on Massive Systemic Administration of Commercial Penicillin

Struble and Bellows (1944) have indicated that a concentration of 1 unit of penicillin per ml. of aqueous can be obtained if 12,800 units per kilo body weight are injected intravenously in the dog—a dose of the order of about 40 times that of the usual clinical dose in man. Town and Hunt (1946) and Town, Frisbe, and Wisda (1946) have extended these observations, and have shown that anterior-chamber infection in the rabbit can be controlled by injections of 5,000 units per kilo body weight intramuscularly at 3-hourly intervals. In confirming and extending these findings an attempt was made to assess the relative value of systemic and subconjunctival administration of penicillin. Commercial penicillin was used for systemic injections.

Concentration in Interior of Eye

In the Primary Aqueous (Chart I).—The level of penicillin in the primary aqueous was determined at different time intervals from 1/4 to 6 hours on intramuscular and intravenous injection of 25,000 and 50,000 units into rabbits. As can be seen from Table VIII an adequate therapeutic level can be reached in the aqueous by systemic injections of both 50,000 and 25,000 units, but it does not persist for longer than 3 hours. This is a shorter period than that obtained by subconjunctival injection—and incidentally at a lower level, too. In attempts to raise the aqueous level and to increase its duration several modifications of intramuscular injection were tried. The detailed results are given in Table IX.

When an equal quantity of adrenaline 1:1,000 was added to the solution of penicillin (of which 40,000 units were injected) no marked increase in level or persistence was obtained; nor were better results achieved with penicillin to which had been added hexamine (7%) in the hope that this might cause a more ready passage of penicillin into the aqueous. The results were likewise negative when adrenaline (0.5 ml. of 1:1,000) was injected subconjunctivally at the time the intramuscular injection was given. Better results were recorded when penicillin was given intramuscularly in beeswax. The eighteen readings obtained with this mode of administration suggest that low aqueous levels are reached and maintained for at least 6 hours. None the less it is clear from a comparison of Table II with Tables VIII and IX that when approximately equal quantities are injected the subconjunctival route gives higher and more sustained aqueous levels of penicillin. That aqueous levels reached by the injection of penicillin intramuscularly and intravenously are unlikely to be maintained after 3 hours or so is indicated by the level reached in the arterial blood by these methods of administration, and by all the modifications indicated except that in which beeswax was employed (Tables X and XI). With penicillin intramuscularly or intravenously the blood level is low within 2 hours, and this was substantially uninfluenced by all modifications except beeswax. With penicillin in beeswax injected intramuscularly a high arterial level was still present at 6 hours, and at 22 hours the two of the three readings obtained were still significantly high.

TABLE VIII.—*Aqueous Levels on Massive Systemic Administration of Penicillin*

	Intramuscular Injection		Intravenous Injection	
	25,000 Units	50,000 Units	25,000 Units	50,000 Units
	Units/ml.	Units/ml.	Units/ml.	Units/ml.
At 15 minutes ..	8		8	4
,, 30 ,, ..	1	4	8	4
,, 1 hour ..		2	1	1
,, 2 hours ..	0·5	1	0·25, 0·5	1, 4
,, 3 ,, ..		0·125	0·125	1
,, 4 ,, ..		0	0·1	0
,, 6 ,, ..		0	0	0

TABLE IX.—*Aqueous Levels on Modified Forms of Intramuscular Injections of Penicillin (40,000 Units)*

	Penicillin with Adrenaline	Penicillin with Hexamine	Penicillin in Beeswax	Penicillin Intramuscularly with Adrenaline Subconjunctivally
	Units/ml.	Units/ml.	Units/ml.	Units/ml.
At 1 hour	0, 2		0, 0·25, 0·25, 0·25	
,, 1½ hours	0·125			1
,, 2 ,,	1		0, 0·25	
,, 2½ ,,		0·125, 0·25		0·5
,, 3 ,,	1		0·25, 0·5, 0·75	
,, 4 ,,			0·1, 0·3	
,, 5 ,,	0·15		0·125	
,, 5½ ,,			0·125	
,, 6 ,,	0	0, 0	0·1, 0·125	0, 0
,, 8 ,,			0, 0	
,, 22 ,,	0			
,, 24 ,,			(?) 0·1	

TABLE X.—*Levels of Penicillin in Arterial Blood on Massive Systemic Administration*

	Intramuscular Injection		Intravenous Injection	
	25,000 Units	50,000 Units	25,000 Units	50,000 Units
	Units/ml.	Units/ml.	Units/ml.	Units/ml.
At 15 minutes ..	>8		>8	8
,, 30 ,, ..	>8	>8	>8	8
,, 1½ hours ..	1	2	1	0·25
,, 2½ ,, ..	Trace		0·25	
,, 3 ,, ..		0·6	0	0·125, 0·25
,, 3½ ,, ..		0		
,, 6 ,, ..		0, 0·125		0

TABLE XI.—*Levels of Penicillin in Arterial Blood on Modified Forms of Intramuscular Injection* (40,000 *Units*)

	Penicillin with Adrenaline	Penicillin with Hexamine	Penicillin in Beeswax	Penicillin Intramuscularly with Adrenaline Subconjunctivally
	Units/ml.	Units/ml.	Units/ml.	Units/ml.
At 1 hour ..			4	
,, 1½ hours ..			8	
,, 2 ,, ..	2		2	
,, 2½ ,, ..		0·25		
,, 3 ,, ..	2	0·5	1·5, 2, >16	
,, 4 ,, ..			3	
,, 5 ,, ..			2	
,, 5½ ,, ..			>16	0
,, 6 ,, ..	0·5	0, 0	2, >16	
,, 6½ ,, ..	0·25			0
,, 8 ,, ..			0·5	
,, 22 ,, ..	0		0, 1, 4	0

Concentration in Other Ocular Tissues (Chart III).—The level of penicillin in various ocular tissues was determined in one case 30 minutes after the intravenous injection of 50,000 units, and in a second case 2½ hours after an intravenous injection of 25,000 units (Table XII). These determinations indicate that penicillin administered in massive doses reaches in therapeutic levels all the tissues of the globe, the lens excepted.

Concentration in the Vitreous after Modified Intramuscular Injections.—As with the aqueous and arterial blood levels, there is nothing in the few findings available to suggest that any modification substantially affects the level of concentration in

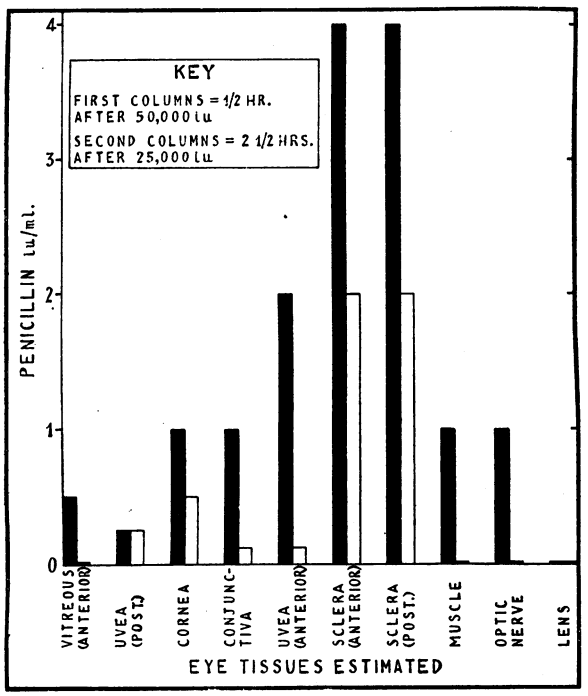

CHART III.—Showing distribution of penicillin in the tissues of the eyes of rabbits after intravenous injections of 50,000 and 25,000 units respectively.

TABLE XII.—*Levels of Penicillin reached in Ocular Tissues on Systemic Administration*

Tissue	30 minutes after 50,000 Units Intravenously	2½ hours after 25,000 Units Intravenously
Cornea	1	0·5
Lens	0	0
Anterior sclera ..	>4	2
Posterior ,, ..	>4	2
Anterior vitreous ..	0·125	0
Posterior ,, ..	0	4
Anterior uvea	2	0·125
Posterior ,, ...	0·25	0·25
Conjunctiva	1	0·125
Muscle	1	0
Optic nerve	1	0

the vitreous (Table XIII). Judging by the two readings recorded this would apply to beeswax-penicillin, too. (The one method that gave a high and sustained vitreous level was the injection of beeswax-penicillin subconjunctivally—a procedure that is clinically inapplicable, as it produces a severe reaction with gross corneal damage.)

Levels in the Aqueous and Vitreous of Infected Eyes.—As with subconjunctival penicillin, the level of the aqueous and vitreous of infected and treated eyes was determined at 5 hours and at 24 hours after intramuscular administration of 40,000 units in beeswax (Table XIV). The aqueous levels were low and the vitreous levels rather higher.

TABLE XIII.—*Levels of Penicillin reached in Vitreous on Systemic and Subconjunctival Administration*

Mode of Administration	At 1 hr.	At 2 hrs.	At 4 hrs.	At 22 hrs.	At 24 hrs.
	Units/ml.	Units/ml.	Units/ml.	Units/ml.	Units/ml.
40,000 units penicillin in beeswax intramuscularly	0·5			0	
40,000 units penicillin with adrenaline intramuscularly		0·25			
40,000 units penicillin intramuscularly with adrenaline subconjunctivally				0	
40,000 units penicillin in beeswax subconjunctivally in each eye		>2	1		0·25, 1

TABLE XIV.—*Random Estimates of Level of Penicillin in Aqueous, Vitreous, and Blood during Course of Treatment of Infected Animals*

Method of Treatment	Aqueous		Vitreous		Blood
	At 5 hrs.	At 24 hrs.	At 5 hrs.	At 24 hrs.	At 24 hrs.
	Units/ml.	Units/ml.	Units/ml.	Units/ml.	Units/ml.
Pure penicillin subconjunctivally (20,000 units)	1	0·5	0·15	0·5	
Pure penicillin with adrenaline subconjunctivally (20,000 units)	>2	>2	0·1	0·25	0
Penicillin in beeswax intramuscularly (40,000 units)	0·03	0·25	0·25	0·5	0·06, 1·125
Penicillin in beeswax (20,000 units subconjunctivally, with 40,000 units intramuscularly subsequently).		0·2		1·0	0·03

Treatment of Intraocular Infection by Intramuscular Injections of Massive Doses

Anterior Chamber Infection.—Two eyes were infected with *Str. haemolyticus* and two with *Staph. aureus*, 0.1 ml. of suspensions containing 25,000,000 organisms per ml. being injected into the anterior chamber, as in the experiments with subconjunctival penicillin therapy. Treatment consisted of intramuscular injection of 50,000 units of commercial penicillin twice daily for two days. As can be seen from Table XV, only one of these eyes became

TABLE XV.—*Infections of Anterior Chamber: Treatment by Intramuscular Injection*

Rabbit No.	Organism	Concentration of Infecting Fluid	Treatment	End-result (on 5th Day)	Remarks
1	Str. haemolyt. 618 ..	25,000,000/ml.	50,000 units in water twice daily for 2 days	Much exudate in anterior chamber	4 control eyes ended in a destructive inflammatory reaction
2	,, ,, ..	,,	,,	Panophthalmitis	
3	Staph. aureus 663 ..	,,	,,	Slight exudate in anterior chamber	
4	,, ,, ..			Eye normal	
5	,, ,, ..	1,000,000/ml.	40,000 units in beeswax twice daily for 3 days	,,	
6	,, ,, ..	,,	,,	,,	
7	,, ,, ..	,,	20,000 units in beeswax subconjunctivally twice on 1st day, and 40,000 units intramuscularly for 2 further days	Infection controlled but much irritability of eye	
8	,, ,, ..	,,			

TABLE XVI.—*Infections of Vitreous: Treatment by Intramuscular Injections*

Rabbit No.	Organism	Concentration of Infecting Fluid	Treatment	End-result (on 5th Day)	Remarks
1	Staph. aureus 663 ..	1,000,000/ml.	Penicillin in beeswax 40,000 units twice daily for 3 days	Eye quiet, but vitreous is largely an organized grey mass	4 control eyes all ended in a destructive inflammatory reaction
2	,, ,, ..	,,	,,	,,	
3	,, ,, ..	,,	,,	,,	
4	,, ,, ..	,,	,,	,,	
5	,, ,, ..	10,000,000/ml.	,,	Eye inflamed but vitreous organized	None of the 10 eyes treated could be regarded as having good function, though the inflammatory process was largely controlled
6	,, ,, ..	,,	,,	As 5, but more marked	
7	,, ,, ..	,,	,,	As 5	
8	,, ,, ..	,,	,,	Eye quiet, but extensive vitreous organization	
9	,, ,, ..	,,	,,	,,	
10	,, ,, ..	,,	,,	,,	

completely normal by the fifth day; in one eye there was minimal reaction, as shown by exudate along the free margin of the iris, while in another there was considerably more exudate. One eye showed the classical picture of panophthalmitis. The two untreated control eyes ended in a destructive suppurative reaction. Four further eyes infected less heavily with *Staph. aureus* (1,000,000 organisms per ml.) were treated in a modified manner, two being given 40,000 units in beeswax twice daily for three days, and two receiving 20,000 units in beeswax subconjunctivally twice on the first day, and 40,000 units in beeswax intramuscularly for two more days. These did distinctly better. The infection in the anterior chamber was completely controlled, but in the two eyes that received beeswax subconjunctivally there was much reaction from the beeswax. Two untreated control eyes were completely lost.

Vitreous Infection.—Ten eyes were infected with *Staph. aureus* by the same technique as used in the therapeutic experiments with penicillin subconjunctivally. Four eyes received 0.1 ml. of suspension containing 1,000,000 organisms per ml., while six eyes had a concentration of 10,000,000 organisms per ml. Treatment consisted of penicillin in beeswax 40,000 units twice daily for three days, and, as can be seen from Table XVI, the infection was controlled in seven of the ten eyes, but in all the eyes there was considerable disorganization of the vitreous. Though the infection could be regarded as largely controlled, these eyes could not be considered as giving a clinically satisfactory result.

Discussion on Experimental Results

The comparative aqueous levels reached by the use of pure penicillin in the form of ointments or of subconjunctival injections, and by commercial penicillin in massive systemic administration, suggest that the best results are likely to be obtained by subconjunctival injection—a conclusion that stands in spite of individual variations in the experimental animal. Moreover, high aqueous levels persist longer with subconjunctival injections than with the other two methods. The advantages of subconjunctival injection are borne out by the experimental results with infections of the anterior chamber and vitreous. Such infections respond well to subconjunctival therapy in doses of 25,000 units/ml. administered twice daily for three days. In contrast, vitreous infections, though controlled, hardly give clinically satisfactory results when treated either by ointment in the conjunctival sac or by massive systemic injections—at any rate in the dosage employed so far. It would appear that the two factors that put both local application of ointment and systemic administration at a disadvantage are lower initial penicillin levels intraocularly and the evanescent character of these levels. On the evidence available the addition of adrenaline to the subconjunctival penicillin injection would seem to be an advantage, but this requires clarification. For the moment it would seem that while pure penicillin applied locally, either as an ointment or as a subconjunctival injection, is a highly efficacious agent, and systemic administration in massive doses a most useful procedure, the balance of advantages in severe intraocular infections rests with subconjunctival injection with adrenaline and massive systemic administration.

Of these two procedures subconjunctival injection, though it has clinical disadvantages, would seem to be preferable. Apart from the fact that the experimental results indicate that in vitreous infections subconjunctival injection is the only promising procedure, it must be borne in mind that the animal results cannot be applied mechanically to man. In experiments on rabbits, largely identical doses were used either as subconjunctival injections or intramuscularly. Translated into terms of its application to man an intramuscular dose will have to be many times that of the subconjunctival dose. Clinically the question is, not whether a given dose should be injected subconjunctivally or intramuscularly, but whether a dose of 25,000 units of pure penicillin be given subconjunctivally or about fifteen times that amount intramuscularly. Even so it must be emphasized that the advantage, as judged by aqueous level and effect on experimental infections, lies with the smaller dose injected subconjunctivally. It is, however, possible that ultimately the frequent application of concentrated ointments may prove an adequate procedure.

The aqueous level in man after massive subconjunctival injection of pure penicillin has not yet been determined. There is therefore no evidence that the pharmacological and therapeutic experiments recorded here for the rabbit apply to man; but there is some indirect indication that essentially this is the case. In four patients who received 50,000 units of pure penicillin subconjunctivally the blood level was determined at hourly intervals between the first and tenth hours. Two patients had adrenaline together with the penicillin. As can be seen from Table XVII, the blood levels were not dissimilar from those obtained in the rabbit (see Table IV). Moreover, the patients receiving adrenaline showed a more consistent blood level, indicating that the penicillin was being absorbed only slowly into the blood stream. Presumably there was also slow absorption into the aqueous, allowing such level as may be reached in the aqueous to be more persistent. The similarity in this respect makes one hopeful that the pharmacological and therapeutic results seen in the rabbit apply to man.

TABLE XVII.—*Subconjunctival Injection of Pure Penicillin in Man: Blood Levels (Units/ml.) reached after 50,000 Units Injected Subconjunctivally*

	Penicillin Only		Penicillin with Adrenaline	
	First Patient	Second Patient	First Patient	Second Patient
At 1 hour ..	1	0·5	1	2
,, 2 hours ..	0·125	0·125	1	0·25
,, 3 ,, ..	Not tested	0	1	0·125
,, 4 ,, ..	0·03	0·125	1	Not tested
,, 5 ,, ..	0·1	0·125	1	0·25
,, 6 ,, ..	0·25	0	1	0·125
,, 7 ,, ..	0·03	0	0·25	0
,, 8 ,, ..	0·06	0	0·125	0
,, 9 ,, ..	0·06	0	0·5	0
,, 10 ,, ..	0	0	0·5	0
,, 23 ,, ..	0		0	

In the light of the experimental results it was felt that clinical trials with ointment of pure penicillin in high concentration, and with subconjunctival injections both with and without adrenaline, were justifiable, as was the use of commercial penicillin in massive doses in watery solution, or preferably in beeswax, injected intramuscularly.

Clinical Experiences

Pure Penicillin in External Infections

Adequate control of external infections of the eye by tolerated concentrations of commercial penicillin is readily obtained. The use of pure penicillin might conceivably give better results and avoid the occasional occurrence of irritation. These are possibilities that have not been explored to any extent, and the results so far obtained can be summarized briefly and are essentially observations on tolerance.

Ointments.—In five patients with acute conjunctivitis and in six children with blepharitis ointments containing up to 8,000 units of pure penicillin per gramme were well tolerated and effective. When instilled into the conjunctival sac some ointment could still be seen after an hour. There was no tangible difference whether "eucerin" L.M. base or petroleum jelly and liquid paraffin (90 and 10 parts of each respectively) was used. In subsequent trials only the latter base was used.

The tolerance of the eye to ointments containing 25,000, 50,000, and 100,000 units/g. was established by the successful use of such ointments in three cases of hypopyon ulcer, the ointment being instilled at hourly intervals during the first day and at two-hourly intervals subsequently. Tolerance to ointment containing 100,000 units/g. was also noted in infants with ophthalmia neonatorum (but an adequate clinical result could not be obtained, as the treatment of ophthalmia neonatorum by ointments is unsatisfactory, the ointment being difficult to apply when the lids are swollen, and it is, moreover, squeezed out of the conjunctival sac by the spasmodic contraction of the infant's lids).

Solutions and Suspensions.—Watery solutions of pure penicillin 10,000 units/ml. were used satisfactorily in the form of drops in three cases of acute conjunctivitis. Two drops instilled six times at five-minute intervals and subsequently six times at half-hourly intervals were well borne. In six cases of ophthalmia neonatorum concentrations of 10,000 and 12,000 units in methyl cellulose solution (2%, in a buffered aqueous medium) used in the same manner were likewise well tolerated, as was the use in four further cases of a suspension of pure penicillin in oil (castor oil or liquid paraffin) in a concentration of 10,000

units/ml. A suspension of pure penicillin in castor oil (10,000 units/ml.) instilled at hourly intervals for five days proved efficacious in a case of hypopyon ulcer.

Pure Penicillin in Intraocular Infections

The opportunity of studying the value of pure penicillin in eight cases of post-operative infection presented itself by the kind co-operation of colleagues, and the following remarks are based on their reports.

1. In a case of infection after cataract extraction in a diabetic patient one subconjunctival injection of 25,000 units was given on the seventh day after the infection had become established. There was no tangible improvement on the following day, and the eye was excised.

2. In another case of infection after cataract extraction subconjunctival injections of 50,000 units of pure penicillin were given on the sixth and seventh days after the onset of infection, combined with five doses of 100,000 units of commercial penicilin intramuscularly at 12-hourly intervals. There was considerable improvement, but some relapse on the ninth day, when the course was repeated. The infection was clinically controlled, but the eye now shows evidence of early shrinking. A course of sulphamezathine was given without result between the third and sixth days (before penicillin treatment).

3. In this case infection was noted at the first dressing 24 hours after a cataract extraction, and consisted of a localized exudate in the anterior chamber at the temporal side of the corneal incision. Powder of commercial penicillin (about 30,000 units) was sprinkled on the wound, and the procedure was repeated later in the day and again on the following morning, a total of 100,000 units being used. There was a distinct improvement, but the infection still persisted. Sixty hours after the operation a subconjunctival injection of 50,000 units of pure penicilin was given, and the following morning (72 hours after operation) the infection appeared under control, so that further treatment was suspended. Forty-eight hours later there was a relapse; two subconjunctival injections were given, with definite improvement by the following day, when two further injections were made, and one more the day after. Recovery since has been steady and uninterrupted.

4. In a further case of infection after cataract extraction treatment was begun after five days, and consisted in opening the anterior chamber and irrigating with 10 ml. solution of pure penicillin containing a total of 100,000 units. This was repeated on four subsequent days. The infection was checked, and though the eye is likely to be retained it is unlikely to have any useful vision. An organized mass of exudate is still present in the anterior chamber after 14 days. (A subsequent report suggests that after capsulectomy useful vision is likely to be present.)

5. A fully developed panophthalmitis was observed in a patient three years after a trephine operation for a glaucoma. Treatment consisted of drops of commercial penicillin 2,000 units/ml. at half-hourly intervals, with considerable improvement after 24 hours, when the cornea was clearer and a purulent infiltration of the vitreous could be seen. Treatment was continued for two more days without much result. Intramuscular injection of 100,000 units of commercial penicillin was then instituted at 3-hourly intervals for 72 hours, resulting in further control of the infection in the anterior chamber but not of that in the vitreous. Daily injection of 50,000 units of pure penicillin subconjunctivaily was begun 14 days after the patient first came under observation, and continued for 4 days. This led to the vitreous becoming less dense, and its reflex, as seen by oblique illumination, less yellow and more greyish; but the eye must be regarded as functionally lost.

6. In a further case of post-operative infection a simple extraction of a hypermature cataract had been performed with loss of fluid vitreous at the operation. The patient was a diabetic. At the first dressing, 24 hours later, slight mucoid discharge was seen, and penicillin drops 2,500 units/ml. were instiiled. Twenty-four hours later a severe infection was fully established: the lids were red and oedematous, chemosis was marked, and there was total hypopyon. A course of sulphamezathine was instituted, penicillin drops 2,500 units/ml. were instilled 2-hourly, and injections of penicillin intramuscularly were begun—two of 50,000 units at intervals of 6 hours and subsequently 25,000 units 3-hourly. During the 3 days this treatment was continued the condition steadily deteriorated, and pus began to exude from the corneal section. Subconjunctival injections of 50,000 units of pure penicillin in 0.5 ml. of 2% "novocain" were then given at 8-hourly intervals, with ointment 100,000 units/g. instilled into the conjunctival sac 2-hourly. After 6 days of this treatment the condition had improved to the extent that the patient was now able to open his eyes, and the infection had become localized to the upper segment of the anterior chamber. The injections were now causing pain, and these as well as the ointment were discontinued, atropine drops and fomentations only being used. Further improvement continued for 12 days, when there was a sudden worsening. The eye became intensely red and engorged and pus in the vitreous could be seen through the pupil. There was no perception of light. A complete hypopyon rapidly formed and the eye was eviscerated. The vitreous was found to be full of pus.

7. In a case of intracapsular extraction complicated by prolapse of vitreous the iris was muddy at the first dressing three days later. Twenty-four hours later a small hypopyon was present. A course of sulphamerazine was instituted and ointment of pure penicillin 50,000 units/g. instilled into the conjunctival sac 2-hourly. In spite of treatment continued for 3 days the hypopyon increased, and the patient showed intolerance to the sulphonamide. Treatment, apart from atropine drops, was changed to subconjunctival injections of 50,000 units of pure penicillin in 0.5 ml. of 2% novocain at 6-hourly intervals. After eight injections the hypopyon had disappeared; the eye was almost white but showed post-operative iritidic adhesions. Though the eye was saved, the ultimate outcome as regards vision is still uncertain.

8. A man aged 58 had undergone a second operation for retinal detachment by surface coagulation and three micropunctures. Ophthalmic catgut was used for re-attaching the external rectus severed during the operation, and an intragluteal injection of 50,000 units penicillin in oil was given prophylactically. At the first dressing 48 hours later there was much chemosis, the anterior chamber was deep, and the iris yellowish green. Two further intragluteal injections of 150,000 units of penicillin in oil were given the same day, and full doses of sulphamerazine instituted and continued for 7 days. On the following day the condition was worse, the cornea now being cloudy, and hypopyon was present. Further deterioration occurred during the next 24 hours; the vitreous seen through the remaining area of clear cornea was cloudy. Subconjunctival injections of 50,000 units pure penicilin in 0.5 ml. of 2% novocain with adrenaline were given at 6-hourly intervals, a total of 20 injections being used. Improvement was noted after the sixth injection, and at the end of the course of injections there was no hypopyon, the cornea was clear, and the iris less yellow; the anterior chamber was still deep. General administration of 150,000 units of penicillin in oil was continued daily for 3 days, when all treatment was suspended. On the following day the eye was quiet, the cornea clear, the iris normal in colour, and the anterior chamber almost normal in depth. Eight days later the patient was discharged. The eye is still somewhat red, there was a small hyphaemia, and there appears to be a haemorrhage in the vitreous.

Apart from these eight cases of post-operative infection three cases of infection of the vitreous associated with intraocular foreign body were treated.

1. A man aged 27 sustained a perforating injury of his left eye while using a hammer and chisel. The lens was semi-opaque, the pupil irregular, and there was no red reflex. A foreign body was extracted by the magnet from the vitreous on the same day, and a scleral suture inserted. Convalescence was uneventful for the 5 succeeding days, when suddenly much congestion and chemosis set in. Ointment of pure penicilin 100,000 units/g. was then instilled at 2-hourly intervals for 24 hours, and 50,000 units of pure penicillin in 0.5 ml. of water was injected subconjunctivally and repeated on eight further occasions at 12-hourly intervals. The injections proved painful. After the first two, which did not seem to influence the infection, the wound was explored and the scleral sutures removed, though they did not appear to be infected. In spite of continued treatment the infection progressed, and on the tenth day the eye was eviscerated. The vitreous was found to be a purulent mass. Two hours before evisceration 50,000 units of pure penicillin were injected subconjunctivally, and at evisceration the aqueous and some vitreous were collected for penicillin assay and culture. The penicillin content was found to be 32 units in the aqueous and 0.5 unit in the vitreous. A penicillin-sensitive *Staph. aureus* was present in the vitreous, but there were no organisms in the aqueous.

2. In a man of 21, whose right eye was hit by a small ball-bearing 48 hours previously, hypopyon filling a third of the anterior chamber, and grey opacities in a hazy vitreous, were present when he was first seen. Because of the established infection no immediate attempt at removing the intraocular foreign body was made. Ointment of pure penicillin 100,000 units/g. was instilled at 2-hourly intervals for 3 days, with but little effect. After 14 subconjunctival injections of 50,000 units of penicillin at 6-hourly intervals the infection seemed sufficiently controlled to warrant an attempt at magnet-extraction of the foreign body. There was, however, no response to the magnet. Two days later the infection flared up, and was not controlled by eight subconjunctival injections of 50,000 units. The eye had to be eviscerated, and the vitreous was found to be a purulent mass.

3. While hammering a boiler, three days before admission, a man aged 38 sustained a perforating injury to his right eye. On admission the vitreous was grey and a hypopyon occupying one-third of the anterior chamber was present. *X*-ray examination showed a foreign body located just outside the globe. A course of sulphamezathine was given unsuccessfully for 3 days, and then suspended for penicillin

therapy. This consisted in the instillation of ointment (100,000 units/g.) 2-hourly by day and 4-hourly at night, and of 20 subconjunctival injections of 50,000 units in 0.5 ml. of 2% novocain solution given at 6-hourly intervals. As a re-location put the foreign body as just inside the globe an attempt at magnet-extraction was made. This, however, proved unsuccessful. The hypopyon disappeared after 3 days' treatment with penicillin, and an organized opacity in the upper part of the vitreous could be seen. This mass has not been influenced by penicillin therapy, and though the treatment seems to have checked the development of panophthalmitis the eye is now shrinking and must be regarded as functionally lost.

Subconjunctival Penicillin in Interstitial Keratitis

Four patients were treated. A girl aged 19 years received twelve subconjunctival injections of 25,000 units in one eye, generally at daily intervals, together with a systemic course of 200,000 units daily for seven days. The injections were well tolerated, though some conjunctival adhesions seemed to form towards the end of the course. The other three patients were soldiers with interstitial keratitis developing apparently as a result of acquired syphilis. In the case of the girl there was rapid and progressive whitening of the eye. Three months later she still had a central corneal haze reducing vision to 6/18; this, however, practically disappeared during the subsequent two months, when vision rose to 6/9. Two of the men responded well to four and six subconjunctival injections of 25,000 units, vision rapidly becoming normal, though they had shown no response to classical local and antisyphilitic treatment. In the third man the response was poor.

Subconjunctival Penicillin in Hypopyon Keratitis

In addition to the three cases of hypopyon ulcer treated successfully with ointments of pure penicillin and one by penicillin in oily suspension there were five others treated by subconjunctival injection.

The first case was that of a man aged 68, who initially responded to pure penicillin ointment (100,000 units/g.) applied hourly for 12 hours. Three days later there was a sudden and severe relapse, the anterior chamber showing a total hypopyon within 24 hours. At this stage two subconjunctival injections of 25,000 units at intervals of 24 hours failed to influence the condition, the eye showing evidence of panophthalmitis. On admission the conjunctival swab had shown *Staph. aureus* microscopically, and culture revealed *Ps. pyocyanea* [? a contaminant]. Unfortunately no swab was taken of the contents of the anterior chamber when the eye was ultimately eviscerated.

In a second patient, a lady aged 83, initially more severely affected than the man with a hypopyon of five days' standing, the outcome was more favourable. Hourly instillation of pure penicillin in a suspension of castor oil (10,000 units/ml.) led to rapid improvement within 15 hours. As the cornea was still hazy, some hypopyon still present, and the general condition poor (the patient had a large carbuncle on the nose), two subconjunctival injections of 50,000 units with adrenaline were given at 12-hourly intervals. The eye was now normal in appearance, and penicillin in oil (10,000 units/ml.) was continued for a further 48 hours.

In a third patient, with hypopyon filling half the anterior chamber, pure penicillin in ointment form (25,000 units/g.) was applied at 2-hourly intervals for 48 hours with no marked improvement. One injection of 50,000 units with adrenaline was then given subconjunctivally, and the hypopyon diminished considerably. A second subconjunctival injection was given after 48 hours. Three days later the anterior chamber was clear. Application of ointment at 2-hourly intervals was continued throughout.

In a further case of hypopyon complicating an old-established iridocyclitis with secondary cataract and a tension of +3, treatment with atropine and penicillin drops 500 units/ml. at 3-hourly intervals for 5 days broke down some iris adhesions but did not affect the hypopyon or tension. Subconjunctival injections of 50,000 units of pure penicillin were now given on three occasions on alternate days, while ointment of pure penicillin 100,000 units/g. was instilled 3-hourly during the first 4 days. On the sixth day the hypopyon had become barely visible as a mere crescent. Further treatment by short-wave therapy brought the tension down to normal.

In a case of recurrent hypopyon iritis associated with rheumatoid arthritis, treatment for 12 days with ointment of commercial penicillin 800 units/g. gave no response. There was some improvement after subconjunctival injection of 50,000 units of pure penicillin daily for 3 days, and resolution after 14 days' treatment with penicillin ointment 100,000 units/g. instilled 2-hourly. The end-resuit was excellent, but it is doubtful whether penicillin treatment contributed to it.

Discussion

The studies recorded here indicate that pure penicillin is remarkably well tolerated by the eye, and that dosage need no longer be limited by the intolerance of the eye to the impure supplies available till recently. There seems to be no upper limit of concentration of drops and ointments of penicillin that can be instilled into the conjunctival sac, while massive amounts can be given subconjunctivally. It is also clear that ointments in high concentration instilled into the conjunctival sac allow adequate penetration into the anterior chamber of the eye. This applies still more to subconjunctival injections, so that the current teaching that adequate therapeutic levels cannot be obtained in the interior of the eye is no longer valid. It is also established that adequate levels of penicillin can be obtained by massive systemic administration. The results of biological assay are confirmed by the experiments in infection of the interior of the eye, for infections of the anterior chamber respond to instillation of concentrated ointments, to systemic administration of massive doses, and to subconjunctival injections. Infections of the vitreous are, however, only partially controlled by systemic administration and by the application of ointments, and subconjunctival injections appear to be the only satisfactory method of treating vitreous infections.

The clinical use of penicillin in intraocular infections still requires clarification. The range of efficacy of ointments for intraocular infections has still to be established, as has the frequency of application. Experimental findings suggest that adrenaline should be used together with pure penicillin for subconjunctival injections, but it remains for clinical trial to establish whether this is necessary or desirable, as also whether 2% novocain solution should replace water as a solvent for the penicillin in such patients who do not tolerate injections of 50,000 units subconjunctivally. Likewise clinical trial will have to establish the best way of giving massive doses of penicillin systemically—whether in aqueous solution or in oily suspension in beeswax. In intraocular infections involvement of the vitreous is always a grave complication. The experimental results recorded here indicate that even a low-grade infection has serious implications, possibly because of the disorganization of the vitreous consequent on physical alterations of its colloidal state. Only the most effective measures against bacterial action are therefore likely to be clinically efficient.

The limited clinical data recorded here bring out forcibly three essential points in penicillin treatment of intraocular infections. In the first place, early treatment is essential; little is to be expected once there is extensive disorganization of the eye from the suppurative reaction. Secondly, it is important to continue treatment for at least 24 hours, and possibly as long as 72 hours, after the eye is apparently normal, as otherwise residual infection may readily flare up—a point that is well appreciated in the treatment of ophthalmia neonatorum. Thirdly, in infection of the anterior chamber evacuation and irrigation at an early stage, supplementary to subconjunctival injections, may prove advisable, but it is clear that little can be expected from irrigation by itself, with its momentary antibacterial effect. The considerable amount of work that has been done on sustaining adequate levels of concentration of penicillin is in itself a strong indication against irrigation as a sole method of treatment.

The adequate use of pure penicillin for intraocular infections promises control of a hitherto uncontrollable condition, but the optimum modes of use have still to be established. At the moment the most promising approach would seem to lie with subconjunctival injections of 50,000 units of pure penicillin at intervals of 6 hours. In the case of vitreous infections it may prove necessary to combine subconjunctival with massive systemic injections, and possibly even direct intravitreal injection of pure penicillin.

Summary

Pure penicillin is well tolerated by the eye when applied locally in ointments containing up to 100,000 units per gramme or in watery solutions. Intravitreal injection of pure penicillin, though not free from secondary effects, is also well tolerated. Repeated subconjunctival injections of 50,000 units in 0.5 ml. of water are well tolerated.

Adequate therapeutic levels of penicillin can be obtained in the aqueous by the instillation of concentrated ointments into the conjunctival sac. Higher and more persistent levels are secured by subconjunctival injections. Adequate though rather more evanescent levels are obtained by the systemic administration of penicillin in massive doses. When subconjunctival injections are used the addition of adrenaline increases persistence; intramuscular injection of penicillin in beeswax also gives more sustained levels.

Experimental infections of the anterior chamber are readily controlled by the use of concentrated ointments, subconjunctival injections, and systemic administration of penicillin. In vitreous infections subconjunctival injection is the only procedure that was found satisfactory; no more than partial control is obtained by other methods.

Preliminary clinical trials indicate that the experimental results are largely applicable to man.

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PENICILLIN IN TREATMENT OF ACUTE PUERPERAL MASTITIS

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Since penicillin is now universally available, and especially as it has come to our notice that some clinicians are dissatisfied with its effect in acute puerperal mastitis, a short communication on our own somewhat limited experience would seem appropriate, and might serve as an encouragement for a further trial of our suggested technique. Theoretically, since the predominant causal organism in infection of the breast is *Staphylococcus aureus*, penicillin should prove effective. It appears to us that the unsatisfactory results of which we have heard have been due to (*a*) the use of local therapy only, or (*b*) underdosage. Vaughan Hudson (1944) found that local penicillin alone was not successful in acute soft-tissue infections unless they were entirely confined to the surface, and this is not the case by the time a diagnosis of acute puerperal mastitis is made. More recently Hodgkinson and Nelson (1945) have reported from the United States on 24 cases of acute puerperal mastitis successfully treated with large doses of penicillin administered systemically.

The principles underlying the treatment of this disease are, first, emptying of the breast, and, secondly, adequate control of the infection. The first principle may be attained by suppressing lactation by means of oestrogens, or by regular emptying with a breast pump, or by allowing the infant to suckle. We prefer to keep the breast empty by permitting the child to feed, but if the discomfort caused to the patient is very great then we temporarily discontinue suckling and give a small dose of stilboestrol (usually not more than 1 mg. in 24 hours). Adequate control of the infection can, in our opinion, be attained only by the systemic administration of *large* doses of penicillin. We administer it by 3-hourly intramuscular injections of 12,000 to 20,000 Oxford units.

Our criteria for starting treatment are pyrexia, associated with flushing, and hardening of the breast; but from some of our cases it appears that pyrexia with pain in the breast, even though there are no other changes, should be considered an indication for treatment.

Results

Case 1.—Primipara, aged 23. 6/11/45: Manual rotation and forceps delivery on account of persistent occipito-posterior presentation. Breast-feeding started. 14/11/45: Severe pain in the left breast on suckling. 15/11/45: T. 102° F. (38.9° C.); P. 100. Hard inflamed area in outer and upper quadrant of the left breast. Suckling very painful. Breast rested for 12 hours and emptied with pump. Penicillin started. Stilboestrol 0.5 mg. 16/11/45: T. 100° F. (37.8° C.). 17/11/45: T. 99.6° F. (37.55° C.). Breast fluctuating. 18/11/45: T. 99.4° F. (37.4° C.). Abscess aspirated and 25 ml. of pus obtained. 19/11/45: T. 98.4° F. (36.9° C.); P. 90. Aspiration again produced pus. No pain. Flush gone. 20/11/45: T. 98.2° F. (36.8° C.); P. 82. No pain. No pus obtained. Slight thickening at site of abscess. 21/11/45: T. 98.2° F. (36.8° C.); P. 72. Breast appears normal. Lactating well. 22/11/45: Penicillin discontinued. Total dosage, 1,050,000 Oxford units.

Case 2.—Primipara, aged 33. 3/11/45: Normal delivery. Breast-feeding begun. 14/11/45: Flushed left breast. T. 99° F. (37.2° C.); P. 100. 15/11/45: T. 102° F. (38.9° C.); P. 116. Suckling stopped for 12 hours. Stilboestrol 0.5 mg. Penicillin started. 16/11/45: T. 100° F. (37.8° C.); P. 116. Flush diminished. Less pain. Baby suckling. 17/11/45: T. 98° F. (36.7° C.); P. 96. 18/11/45: T. 98° F. (36.7° C.); P. 90. Breast normal. 20/11/45: T. 98° F. (36.7° C.); P. 80. Penicillin discontinued. Total dosage, 525,000 Oxford units.

Case 3.—Primipara, aged 21. 6/4/46: Normal delivery. Breast-feeding started. 16/4/46: Baby developed a septic finger, which was treated with penicillin. Breast-feeding continued. 20/4/46: Baby recovered. Mother's temperature, 101° F. (38.3° C.); P. 100. Flushed left breast. Peniciilin begun. Breast-feeding continued. 21/4/46: T. 103.8° F. (39.9° C.); P. 126. 23/4/46: T. 98° F. (36.7° C.); P. 80. Little pain, definite thickening and hardness inner and lower quadrant of left breast. 24/4/46: T. 98° F. (36.7° C.); P. 82. No flush. Thickening resolving. 25/4/46: T. 98° F. (36.7° C.); P. 82. Thickening almost completely resolved. 26/4/46: Breast normal. Penicillin discontinued. Total dosage, 600,000 Oxford units.

Case 4.—Para-2, aged 20. 8/4/46: Normal delivery. Breast-feeding started. 17/4/46: T. 101.2° F. (38.4° C.); P. 100. Flushing and thickening of the left breast. Penicillin begun. 18/4/46: T. 98.6° F. (37° C.); P. 104. 19/4/46: T. 100.8° F. (38.2° C.); P. 104. 20/4/46: T. 98° F. (36.7° C.); P. 90. Breast normal. 22/4/46: T. 98° F. (36.7° C.); P. 90. Penicillin discontinued. Total dosage, 600,000 Oxford units.

Case 5.—Primipara, aged 21. 20/4/46: Normal delivery. Breast-feeding started. 26/4/46: Cracked nipples. Breast rested for 12 hours. 27/4/46: T. 102° F. (38.9° C.); P. 130. No abnormality found on examining breasts. 28/4/46: T. 103° F. (39.4° C.); P. 130. Definite thickening and tenderness outer and upper quadrant of left breast. Penicillin begun. 29/4/46: T. 99.4° F. (37.4° C.); P. 96. Breast flushed and thickened. 30/4/46: T. 98° F. (36.7° C.); P. 98. Flush less. Thickened area considerably smaller. 1/5/46: T. 98° F. (36.7° C.); P. 90. No flush. 2/5/46: T. 98° F. (36.7° C.); P. 90. Breast normal. 4/5/46: T. 98° F. (36.7° C.); P. 80. Penicillin discontinued. Total dosage, 700,000 Oxford units.

Case 6.—Para-2, aged 26. 28/4/46: Normal delivery. Breast-feeding begun. Owing to shortage of beds this patient was transferred to the district on the third day of the puerperium. She herself attempted to discontinue breast-feeding on the tenth day and developed acute puerperal mastitis. 12/5/46: Readmitted to hospital. T. 100° F. (37.8° C.); P. 106. Tender flushed left breast. Thickened area 2 in. (5 cm.) in diameter in upper and outer quadrant. Penicillin started. Baby put back on breast and all artificial feeding stopped. 13/5/46: T. 100° F. (37.8° C.); P. 104. Breast flush limited to upper and outer quadrant. Tenderness also limited to this area. 14/5/46: T. 100° F. (37.8° C.); P. 88. Thickening now 1 in. (2.5 cm.) in diameter. Slight flush. Slight tenderness. 15/5/46: T. 97.8° F. (36.55° C.); P. 64. No flush. Slight thickening. 16/5/46: T. 98° F. (36.7° C.); P. 80. No thickening, flush, or tenderness. Penicillin discontinued. Total dosage, 500,000 Oxford units. Two weeks later this patient returned to the clinic. She was still lactating freely, but the baby was again being artificially fed. She was instructed to re-establish breast-feeding, but has since refused to return to clinic.

Case 7.—Para-3, aged 30. 29/4/46: Normal delivery. 5/5/46: Cracked nipples. Breast rested for 12 hours. 7/5/46: T. 101.8° F. (38.8° C.); P. 100. Right breast very flushed and tender. Penicillin started. 8/5/46: T. 98.4° F. (36.9° C.); P. 88. 9/5/46: