2. In heavy experimental infection of the vitreous (1,000,000 organisms of staphylococcus aureus) 5,000 units crystalline penicillin injected into the vitreous had some slight effect if given 20 hours after infection; panophthalmitis was prevented but the vitreous was organised. When treatment was begun 3 hours, or immediately after infection, 3—possibly 4—out of 6 treated eyes could be regarded as clinically functioning eyes.

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DISTRIBUTION OF PENICILLIN IN THE EYE AFTER INJECTIONS OF 1,000,000 UNITS BY THE SUBCONJUNCTIVAL, RETROBULBAR AND INTRAMUSCULAR ROUTES

BY

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IN earlier studies (Sorsby and Ungar, 1946 and 1947) it was shown that adequate therapeutic levels could be obtained intra-ocularly by injection of large doses of penicillin subconjunctivally. Attention was drawn to the fact that it was also possible to obtain adequate intra-ocular concentrations by systemic administration of massive doses. (Struble and Bellows, 1944; Town, Frisbe and Wisda, 1946; Town and Hunt, 1946; and Sorsby and Ungar, 1946.) It was also shown that the levels reached and maintained by subconjunctival injection were higher than those obtained by other routes. Subconjunctival injections gave higher and more persistent levels when the penicillin was dissolved in adrenalin solution 1 :1,000 instead of water. There also emerged the fact that the use of 50,000 units as a subconjunctival dose tended to give not only higher but more persistent intra-ocular levels of concentration than with doses of 20,000 units.

The present study deals with the levels obtained when the dose of penicillin was 1,000,000 units injected subconjunctivally in

the rabbit. These findings (Table I) are compared with those obtained on the injection of the same dose retrobulbarly (Table II) and systemically (Table III). The experimental technique and the methods of estimating penicillin levels employed have been described in the two earlier publications.

1.—Intra-ocular levels of penicillin on the injection of 1,000,000 units crystalline penicillin G. subconjunctivally

Crystalline penicillin G. (Glaxo) was used throughout. It is readily soluble; 1,000,000 units were dissolved in either 1 ml. of distilled water or 1 ml. of adrenalin solution 1 : 1,000. The injection was well tolerated and such conjunctival swelling as appeared had completely subsided within 48 hours. Occasionally a crescentic white infiltrate was seen on the limbus near the site of the injection. This, too, tended to disappear within that time. The following summary table shows the values reached in the aqueous and vitreous at different time intervals with the two different solvents.

SUMMARY TABLE I

Levels (u/ml.) reached in the aqueous and the vitreous on the subconjunctival injection of 1,000,000 units Crystalline penicillin G. dissolved in water or adrenalin solution 1 : 1,000.

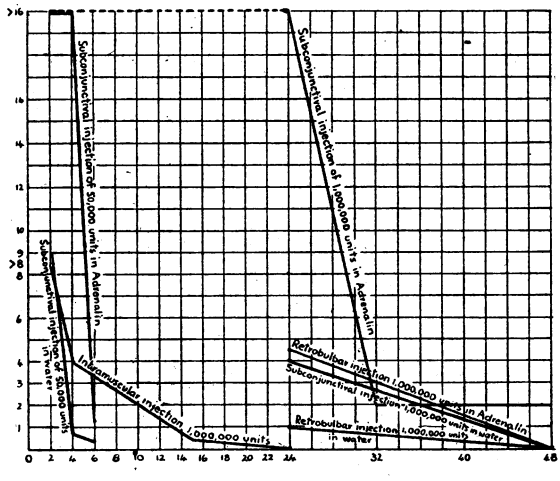
	Time after injection	Injected eye		Uninjected eye	
		Penicillin dissolved in water	Penicillin dissolved in adrenalin	Penicillin dissolved in water	Penicillin dissolved in adrenalin
Aqueous	24 hours	0·25, 8	>16	>2, 4	>4
	32 „	Not determined	>2	Not determined	0·25
	48 „	0	2, >2	0	0·05, 0·03
Vitreous	24 hours	0·125, 8	8	1, 4	0·25
	32 „	Not determined	>2	Not determined	0
	48 „	0	0·25, >2	0·25	0, 0·25

Note :—The different values recorded represent estimates in different animals.

The following conclusions appear warranted :—

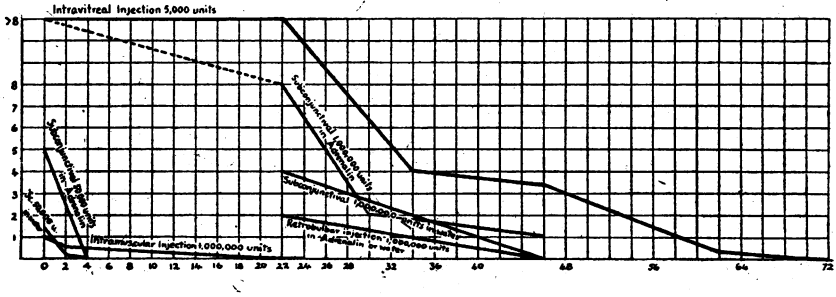
(1) In contrast to the levels reached with relatively low doses of penicillin, adequate concentrations lasting for at least 48 hours can

be achieved in the injected eye with subconjunctival injection of 1,000,000 units in adrenalin solution 1:1,000. With doses of 50,000 units in adrenalin the aqueous concentrations at six hours was 1·25 U/ml., and 0·03 U/ml. for the vitreous (Sorsby and Ungar, 1947); with a dose of 1,000,000 units the aqueous concentration after 48 hours was of the order of 2 U/ml. and the vitreous concentration between 0·25 and 2 units. The vitreous level on subconjunctival injection of 1,000,000 units in adrenalin is of the same order as that obtained by direct intra-vitreal injection of 5,000 units (Graphs 1 and 2).



GRAPH 1.

Levels of penicillin u/ml. in the aqueous.



GRAPH 2.

Levels of penicillin in the vitreous.

(2) The value of adrenalin in establishing high levels and maintaining them is apparent from the comparison of the first and second column of summary table I; without adrenalin the levels are both lower and less persistent; at 48 hours neither the aqueous or vitreous contained any penicillin when the agent was injected without adrenalin (Graphs 1 and 2).

(3) Much of the penicillin injected subconjunctivally diffuses in the surrounding tissue. Though the blood showed no penicillin at 32 hours and at 48 hours when adrenalin was used as the solvent for penicillin, considerable levels could be obtained in the uninjected eye. Part of the intra-ocular concentration in the injected eye may be produced by systemic absorption from the subconjunctival depot. This fraction is, however, not significant as can be seen from the intra-ocular levels obtained by the injection of 1,000,000 units penicillin intramuscularly. (Recorded below, section 3.)

2.—Intra-ocular levels of penicillin on the injection of 1,000,000 units crystalline penicillin G. retrobulbarly

When a dose of 1,000,000 units of crystalline penicillin G. is injected deep into the orbit, high intra-ocular levels can be obtained

SUMMARY TABLE II

Levels (u/ml.) reached in the aqueous and the vitreous on the retrobulbar injection of 1,000,000 units Crystalline penicillin G. dissolved in water or adrenalin.

	Time after injection	Injected eye		Uninjected eye	
		Penicillin dissolved in water	Penicillin dissolved in adrenalin	Penicillin dissolved in water	Penicillin dissolved in adrenalin
Aqueous	24 hours	1, 1	1, 8	1, 1	1, 0·5
	48 ,,	0·25, 0·125	0·06, 0·06	0·25, 0·06	0·125, 0
Vitreous	24 hours	2, 2	2, 2	0·5, 0·5	0·5, 0·5
	48 ,,	0·125, 0·03	0·03, 0·125	0·03, 0·25	0·06, 0·03

Note:—The different values recorded represent estimates in different animals,

in both the aqueous and vitreous at 24 hours, and effective antibacterial levels are still present at 48 hours. As can be seen from the summary table II there is no tangible difference in the levels reached in the injected and the uninjected eyes (suggesting ready diffusion throughout the surrounding tissues). When penicillin is injected in adrenalin solution the levels obtained with retrobulbar injection, though considerable, are distinctly lower than those obtained by subconjunctival injection.

The levels obtained with retrobulbar injection of adrenalin solution of penicillin, though lower than those obtained from subconjunctival injection, are, however, distinctly higher than those obtained from intramuscular injection (Graphs 1 and 2).

3.—Intra-ocular levels of penicillin on the injection of 1,000,000 units amorphous yellow penicillin intramuscularly

Summary table III shows the levels reached in the aqueous and vitreous on the injection of an adrenalin solution of 1,000,000 units amorphous penicillin intramuscularly.

SUMMARY TABLE III

Levels (u/ml.) reached in the aqueous and the vitreous on intramuscular injection of 1,000,000 units penicillin dissolved in water.

Time after injection	Aqueous	Vitreous
1 hour	>8, >8	>8, 4
2 hours	>8, >8	1, 1
3 „	8, 8	2, 1
4 „	4, 4	0·5, 0·25
15 „	>2, >2 ; 0·25, 0	>2·0, 0·25 ; 0, 0
24 „	0, 0 ; 0, 0	0, 0 ; 0, 0

(Each set of two values represents the readings in the right and left eyes of an animal).

It will be seen that after four hours the vitreous level is low and the aqueous level has dropped considerably. At 15 hours there is still a considerable aqueous level and a lesser vitreous level, but at 24 hours, all the levels are nil. It is clear that local administration, whether by the retrobulbar or subconjunctival route, is superior to intramuscular injection (Graphs 1 and 2). As the systemic dose for man to correspond to 1,000,000 units intramuscularly in the rabbit must run into many millions, intramuscular injection has no advantage over local administration and many disadvantages.

In the rabbit doses lower than 1,000,000 units appear to give relatively poor results. This is seen from summary table IV showing concentrations reached with injections of 500,000 units and 250,000 units.

SUMMARY TABLE IV

Levels (u/ml.) of penicillin reached in the aqueous and vitreous on the intramuscular injection of 500,000 units and 250,000 units penicillin dissolved in water.

	Aqueous	Vitreous
500,000 units After 4 hours ...	1, 2	0·06, 0·1
250,000 units After 4 hours ...	0·5, 0·5; 2, 2; 0·25, 0·5; 0·5, 0·5	0·06, <0·06; 0·5, 0·5; 0·03, 0; 0, 0·03
After 5 hours ...	2, 2	0·5, 0·125
After 6 hours ...	1, 0·5; 0·03, 0·03; 0·06, 0·125	Tr., Tr.; 0, 0; Tr., Tr.
After 7½ hours ...	0, 0·03; Tr., Tr.	0, 0; 0, 0

(Each set of two values represents the readings in the right and left eyes of an animal).

TABLE I

Distribution of penicillin in ocular tissues after subconjunctival injection of 1,000,000 units crystalline penicillin G in 1·0 ml. of water or adrenalin solution 1 : 1,000.

	Penicillin levels in units per ml. of fluid or per gm. of tissue						
Solvent	Distilled Water			Adrenalin 1 : 1,000			
Hours after injection	24 hours		48 hours	24 hours	32 hours	48 hours	
INJECTED EYE							
Aqueous	0·25,	8	0	< 16·0	> 2	> 2,	2
Vitreous	0·125,	8	0	8	> 2	> 2,	0·25
Cornea	1,	30	15	528	22	> 36,	42
Lens	10,	< 0·3	20	4	> 5	> 6·5,	< 0·1
Anterior sclera ...	> 8,	5·5	7·5	—	6	> 10,	—
Posterior sclera ...	> 8,	14	3·12	—	> 10	7·0,	—
Anterior uvea ...	< 8,	44	3·0	—	> 12	7·0,	—
Posterior uvea ...	< 10,	25	< 4·5	> 300*	> 36	50,	6·8*
Extra-ocular muscles	6,	12·5	30	—	> 50	> 50,	—
BLOOD	0·00	—	—	—	0·00	0·00	—
UNINJECTED EYE							
Aqueous	> 2,	4	0	> 4	0·25	0·05,	< 0·03
Vitreous	1,	4	0·25	0·25	0	0,	0·25
Cornea	5,	1·8	< 4·5	40	> 12	> 16,	0·72
Lens	> 2·5,	< 0·3	< 0·7	4·5	0·6	> 3·0,	0·15
Anterior sclera ...	0·38,	5	18	—	> 3·2	> 8,	—
Posterior sclera ...	1·6,	18	7·5	—	> 5·0	> 6,	—
Anterior uvea ...	> 8,	< 0·4	< 2·25	—	> 10	> 10,	—
Posterior uvea ...	5,	2·5	< 6	< 25*	> 20	> 16,	0·65*
Extra-ocular muscles	> 20,	7·5	3·9	—	> 30	> 30,	—

* Posterior tissues.

(The different values recorded represent estimates in different animals).

TABLE II

Distribution of penicillin in ocular tissues after retrobulbar injection of 1,000,000 units crystalline penicillin G in 1·0 ml. of water or of adrenalin solution 1 : 1,000.

	Penicillin levels in units per c.c. of fluid or per gm. of tissue							
Solvent	Distilled Water				Adrenalin 1 : 1,000			
Hours after injection	24 hours		48 hours		24 hours		48 hours	
INJECTED EYE								
Aqueous	1,	1	0·25,	0·155	1,	8	0.06,	0.06
Vitreous	2,	2	0·125,	0·03	2,	2	0.3,	0.125
Cornea	> 30,	> 30	—		< 30,	> 30	—	—
Anterior sclera ...	> 20,	> 20	—		> 20.	> 20	—	—
Posterior sclera ...	13,	15	—		7,	14	—	—
Anterior uvea ...	20,	20	5,	2·5	5,	30	40,	2.5
Posterior uvea ...	> 22,	> 22	—		> 20,	> 19	—	—
BLOOD	0·25,	0·25	0,	0·03	0·125.	0·125	0,	0
UNINJECTED EYE								
Aqueous	1,	1	0·25,	0·06	1,	0·5	0.125,	0
Vitreous	0·5,	0·5	0·03,	0·25	0·5,	0·5	0.06,	0.03
Cornea	4,	6	3·5,	5·5	4,	4	2.5,	5.3
Anterior sclera ...	5,	16	3·5,	4·5	16,	9	2.3,	3.5
Posterior sclera ...	6,	6	1·5	2·5	6,	6	2.4,	0.75
Anterior uvea ...	0·75,	3·5	4·5	2·2	3·5,	1·5	2.2,	2.2
Posterior uvea ...	0·65,	1·2	4,	4	4.	0·5	0·75,	3

(The different values recorded represent estimates in different animals).

TABLE III

Distribution of penicillin in ocular tissues after intramuscular injection of doses of 250,000, 500,000 and 1,000,000 units of amorphous yellow penicillin in distilled water.

Dose injected ...	250,000 units				500,000 units	1,000,000 units					
Hours after injection	4 hours	5 hours	6 hours	7½ hours	4 hours	1 hour	2 hours	3 hours	4 hours	15 hours	24 hours
Aqueous	0·5, 0·5;	2, 2;	1, 0·5;	0, 0·3;	1, 2·0	>8·0, >8	>8, >8	8, 8	4, 4	2·0, 2·0;	0. 0.
	2, 2;	—	0·03, 0·03;	Tr. Tr.	—	—	—	—	—	0·25, 0;	0. 0.
	0·25, 0·5;	—	0·06, 0·125	—	—	—	—	—	—	—	—
	0·5, 0·5;	—	—	—	—	—	—	—	—	—	—
Vitreous	0·6, <0·06;	0·5, 0·125;	Tr. Tr.	0, 0;	0·06, 0·1	>8·0, 4	1, 1	2, 1	0·5, 0·25	2·0, 0·25;	0. 0.
	0·5, 0·5;	—	0, 0;	0, 0;	—	—	—	—	—	0, 0;	0. 0.
	0·03, 0;	—	Tr. Tr.	—	—	—	—	—	—	—	—
	0, 0·03;	—	—	—	—	—	—	—	—	—	—
Cornea	0·5, 0·25;	0·18, 0·21;	<0·22, 0·18;	—	0·75, 0·75	>72, 44	8 5, 7	9·5, 8·75	4·5, 4	—	—
	0·25, 0·18;	—	—	—	—	—	—	—	—	—	—
Anterior tissues ...	0·08, 0·07;	0·11, 0·26;	<0·1, 0·1;	<0·045, <0·045;	0·5, 0·2	>30, >32	16, 9	2, 6·5	6·0, 7	0·65, 0·65;	0. 0.
	0·08, 0·09;	—	<0·875, 0·045;	<0·06, <0·04;	—	—	—	—	—	0, 1·25;	0. 0.
	0·08, 0·2;	—	0·06 0·04;	—	—	—	—	—	—	—	—
	1·2, 0·8;	—	—	—	—	—	—	—	—	—	—
Posterior tissues ...	0·12, 0·18;	0·18, 0·16;	0·165, 0·21;	<0·1, <0·07;	0·25, 0·2	>56, >48	20, 24	22, 15	18, 10	0·3, 0·65;	0. 0.
	0·125, 0·165;	—	<0·08, <0·09;	<0·07, <0·06;	—	—	—	—	—	0, 1·15;	0. 0.
	0·046. 0·5;	—	<0·05, <0·05;	—	—	—	—	—	—	—	—
	0·375, 0·625;	—	—	—	—	—	—	—	—	—	—
Lid conjunctiva ...	0·75, 1·0;	0·51, 0·44;	0·2 <0·46;	—	3·2, 1·6	>40, >40	24, 32	40, 40	25, 15	—	—
	0·33, 0·34;	—	—	—	—	—	—	—	—	—	—
Bulbar conjunctiva ...	1·25, 1·2;	0·8, 0·51;	0·3, 0·3;	—	4, 3·75	>136, >60	144, >56	50, 23	23, 20	—	—
	<1·2, <1·5;	—	—	—	—	—	—	—	—	—	—
Blood	2, 0·5	0·5 —	0·5, —	2, 2	4	>64 —	>64 —	>64 —	>16 —	0·13, 0·13	0·25; 0·06
	>4, >4	— —	>4, >4	— —	— —	— —	— —	— —	— —	— —	— —

Each set of two values represents the reading in the right and left eyes of an animal.

Discussion and Summary

The present study confirms and extends the established observation that penicillin penetrates in adequate therapeutic levels into the interior of the eye if sufficiently massive doses are employed systemically. It is also shown that the local administration of penicillin, whether by retrobulbar or subconjunctival route, gives distinctly higher and more maintained intra-ocular levels than an injection of a corresponding dose intramuscularly. This applies to all ocular tissues and not only to the aqueous and vitreous. The effect of adrenalin in reaching and maintaining high intra-ocular levels is more marked with subconjunctival injections than with retrobulbar injections. When doses of 1,000,000 units crystalline penicillin in adrenalin solution 1 :1,000 are injected subconjunctivally, experiments in the rabbit suggest that an adequate level is reached and maintained in both vitreous and aqueous for at least 48 hours. The high level reached and maintained in the vitreous by this dose and mode of administration is particularly noteworthy, for neither massive intramuscular injections nor injections of 50,000 units in adrenalin subconjunctivally give high or persistent levels of penicillin in the vitreous. This dose and mode of administration would appear to render superfluous any direct intravitreal injection of penicillin.

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THE CONTROL OF EXPERIMENTAL INFECTIONS OF THE ANTERIOR CHAMBER AND OF THE VITREOUS BY SUBCONJUNCTIVAL AND RETROBULBAR INJECTIONS OF CRYSTALLINE PENICILLIN IN DOSES OF 1,000,000 UNITS

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IT was shown in an earlier study (Sorsby and Ungar, 1946) that infection of the anterior chamber in the experimental animal could be controlled readily by subconjunctival injections of 25,000 units