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COMMUNICATIONS

DISTRIBUTION OF PENICILLIN IN THE EYE AFTER SUBCONJUNCTIVAL INJECTION*

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ADEQUATE intra-ocular concentrations of penicillin can be reached by both systematic administration of massive doses (Struble and Bellows, 1944; Town, Frisbe and Wisda, 1946; Town and Hunt, 1946 and Sorsby and Ungar, 1946) and by the application of highly concentrated ointments and subconjunctival injections (Sorsby and Ungar, 1946. In a previous study we indicated that the highest and most persistent intra-ocular concentration is obtained by means of subconjunctival injection especially when combined with adrenalin; the first of these findings has been confirmed and extended by Andrews (1947) and the second by the data recorded in the present communication.

The technique employed is that recorded in our earlier study.

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Cocaine analgesia is used. Each of our values represents the average of two findings, which generally showed a close approximation. Where adrenalin was used, a solution 1 :1,000 was the solvent employed instead of water.

Experimental data

1. *Preliminary experiments on the effect of adrenalin.*—Table I shows the intra-ocular levels reached on the subconjunctival injection of 20,000 units of penicillin with and without adrenalin. Though there are slight discrepancies the following conclusions seem valid :—

(1) One hour after injection the level of penicillin in the various intra-ocular tissues is generally rather higher where adrenalin had been used.

(2) After 3 hours the difference is more distinct. Where adrenalin had not been used penicillin tends to disappear from the eye. In contrast substantial intra-ocular levels are present where adrenalin was employed.

(3) Both these findings are reflected in the uninjected eye: where adrenalin has been used the intra-ocular levels are rather higher and definitely more persistent.

It would therefore seem that adrenalin acts by preventing the rapid elimination of the penicillin from its subconjunctival depot.

2. *Effect of dose on intra-ocular levels.*—When 50,000 units of penicillin are injected subconjunctivally the intra-ocular levels reached are generally considerably more than $2\frac{1}{2}$ times those obtained with 20,000 units, as can be seen from a comparison of the corresponding data in Table I. Moreover it would seem that the levels reached are more persistent.

The following summary table brings out some of the salient features.

Subconjunctival injection	Level in									
	Aqueous		Vitreous		Cornea		Anterior uvea		Posterior uvea	
At	1 hr.	3 hrs.	1 hr.	3 hrs.	1 h .	3 hrs.	1 hr.	3 hrs.	1 hr.	3 hrs.
20,000 units ...	10·0	0·06	0·5	Trace	>30	0·8	>6·1	0·375	11·5	0·38
50,000 units ...	17·0	3. 0	5.0	1·50	76	18·75	70·0	8·75	140	11·25

This disproportion is emphasised when the values obtained for injection with adrenalin are examined, as can be seen from the following summary table.

Subconjunctival injection with adrenalin	Level in									
	Aqueous		Vitreous		Cornea		Anterior uvea		Posterior uvea	
At	1 hr.	3 hrs.	1 hr.	3 hrs.	1 hr.	3 hrs.	1 hr.	3 hrs.	1 hr.	3 hrs.
20,000 units ...	1·0	0	2·0	0·125	>80	>10	>14	>3	>32	>8
50,000 units ...	>32·0	> 20	17	0·5	>1,440	450	775	60	>750	20

3. *Effect of adrenalin on intra-ocular levels.*—Comparison of the data in Tables II and III shows the marked effect of adrenalin in raising the intra-ocular levels of penicillin. The effect is apparent within a quarter of an hour and would appear to be maximal at 2—3 hours, declining after that, so that at 6 hours the adrenalin values are generally of the order of twice those obtained without adrenalin.

The following summary table and figs. 1—4 bring out some salient features.

Penicillin levels

At	¼ hr.	1 hr.	2 hrs.	3 hrs.	6 hrs.
Aqueous					
without adrenalin ...	24	17	9	3	0·56
with adrenalin ...	>32	>32	>32	>20	1·25
Vitreous					
without adrenalin ...	7	5	1·5	1·5	0·06
with adrenalin ..	>17	17	5·0	0·5	0·03
Cornea					
without adrenalin ...	950	76	25·0	18·75	1·5
with adrenalin ...	>860	>1440	925	450	2·5
Anterior uvea					
without adrenalin ...	160	70	1·25	8·75	0·34
with adrenalin ...	>290	>775	510	60	0·6
Posterior uvea					
without adrenalin ...	200	140	9·5	11·25	1·12
with adrenalin ...	>550	>750	230	20	0·6

TABLE I

Comparison of the Distribution of Penicillin in Ocular Tissues after Subconjunctival Injection of 20,000 units Pure Penicillin with and without Adrenalin.

	Penicillin levels in units per c.c. of fluid or per gm. of tissue			
	1 hour after injection		3 hours after injection	
	Without adrenalin	With adrenalin	Without adrenalin	With adrenalin
INJECTED EYE				
Aqueous	10	1·0	0·06	0
Vitreous	0·5	2·0	Trace	0·125
Cornea	>30	>80	0·8	>10
Lens	0·25	1·0	0	0·06
Anterior sclera ...	>7·5	>12	0·95	>4
Posterior sclera ...	>12	>12	1·25	>4
Anterior uvea ...	>6·1	>14	0·375	>3
Posterior uvea ...	11·5	>32	0·38	>8
Optic Nerve... ...	1·0	1·0	0	0·5
Extra-ocular muscles	>18	12	0·75	>4
BLOOD	4·5	8	0	1
UNINJECTED EYE				
Aqueous	2·125	1·0	0	0
Vitreous	0·03	0·25	0	0·125
Cornea	0·487	1·25	0·63	3·5
Lens	0·03	0		0·125
Anterior sclera ...	1·32	3·0	0·5	3·5
Posterior sclera ...	0·84	1·5	1·25	>4
Anterior uvea ...	0·3	0·25	0·09	0·6
Posterior uvea ...	0·15	4	0·18	1·5
Optic Nerve... ...	0·125	0·5	0	0
Extra-ocular muscles	0·37	4	Trace	1·2

TABLE II

Distribution of Penicillin in Ocular Tissues after Subconjunctival Injection of 50,000 units Pure Penicillin in 0·5 of Distilled Water

	Penicillin levels in units per c c. of fluid or per gm. of tissue						
Hours after injection :	¼ hr.	½ hr.	1 hr.	2 hrs.	3 hrs.	4 hrs.	6 hrs.
INJECTED EYE							
Aqueous	24	19	17	9	3	0·75	0·56
Vitreous	7	2·5	5	1·5	1·5	0·12	0·06
Cornea	950	97	76	25	18 75	4 87	1·5
Anterior sclera ...	>660	380	120	11	16	7·25	2
Posterior sclera ...	580	450	153	30	15·4	8·5	2
Anterior uvea ...	160	60	70	1·25	8·75	4·2	0·34
Posterior uvea ...	200	110	140	9·5	11·25	Trace	1·12
Extra-ocular muscles	310	140	140	23·75	17·5	9·5	1
BLOOD	16	16	8	0·35	0	0	0
UNINJECTED EYE							
Aqueous	2	2	1	0·5	0·25	0	0
Vitreous	0·5	0·12	0·25	0·12	0	0	0
Cornea	4	4	4	1	1·5	0	0
Anterior sclera ...	1	1	1	0·5	0·6	0·3	0·3
Posterior sclera ...	3	3	1·5	1·5	1·4	0·8	0·4
Anterior uvea ...	2·5	2·5	1·25	0	0	0	0
Posterior uvea ...	5	2·5	2·5	0	0·1	0	0
Extra-ocular muscles	6	6	4	0	0	0	0

Fig. 5 shows graphically the levels reached with adrenalin.

4. *Effect of adrenalin on blood-level.*—From Table II it would appear that where adrenalin is not used, the maximum blood level is reached within half an hour, after which it rapidly declines

to zero by the end of the second hour. Where adrenalin is used (Table III), lower but more persistent levels are reached. The following summary table and the revelant graphs in Figs. 1 and 3 bring out the salient features.

TABLE III

Distribution of Penicillin in Ocular Tissues after Subconjunctival Injection of 50,000 units Pure Penicillin in 0·5 ml. of Adrenalin 1 : 1,000

	Penicillin levels in units per c.c. of fluid or per gm. of tissue						
Hours after injection :	¼ hr.	½ hr.	1 hr.	2 hrs.	3 hrs.	4 hrs.	6 hrs.
INJECTED EYE							
Aqueous	>32	>17	>32	>32	>20	20	1·25
Vitreous	>17	>17	17	5	0·5	13	0·03
Cornea	>860	>200	>1,440	925	450	65	2·5
Anterior sclera ...	>290	>285	>450	295	185	50	4·0
Posterior sclera ...	>400	>240	>520	450	96	19	1·25
Anterior uvea ...	>290	>220	>775	510	60	13·5	0·6
Posterior uvea ...	>550	>200	>750	230	20	6·5	0·6
Extra-ocular muscles	>2,200	1,400	1,200	560	92·5	50	9·0
BLOOD	>2	>3	3	1·5	0·75	0·12	0·12
UNINJECTED EYE							
Aqueous	3·25	0·37	0·25	0·5	0·19	0·12	0·3
Vitreous	0·06	0·3	0·06	0·06	0·25	0	0·05
Cornea	2·75	3·75	1·25	0·625	1·2	1·75	0·12
Anterior sclera ...	3·50	1·75	4·4	2·1	0·58	0·75	0·65
Posterior sclera ...	3·8	2·8	3·75	2·1	0 85	0·6	0·7
Anterior uvea ...	5·7	2·25	5·65	0·8	0·33	1·5	0·1
Posterior uvea ...	9·0	3·50	1·25	0·62	1·4	0	0·3
Extra-ocular muscles	9·0	2·65	3·0	3·5	0	0·6	0·25

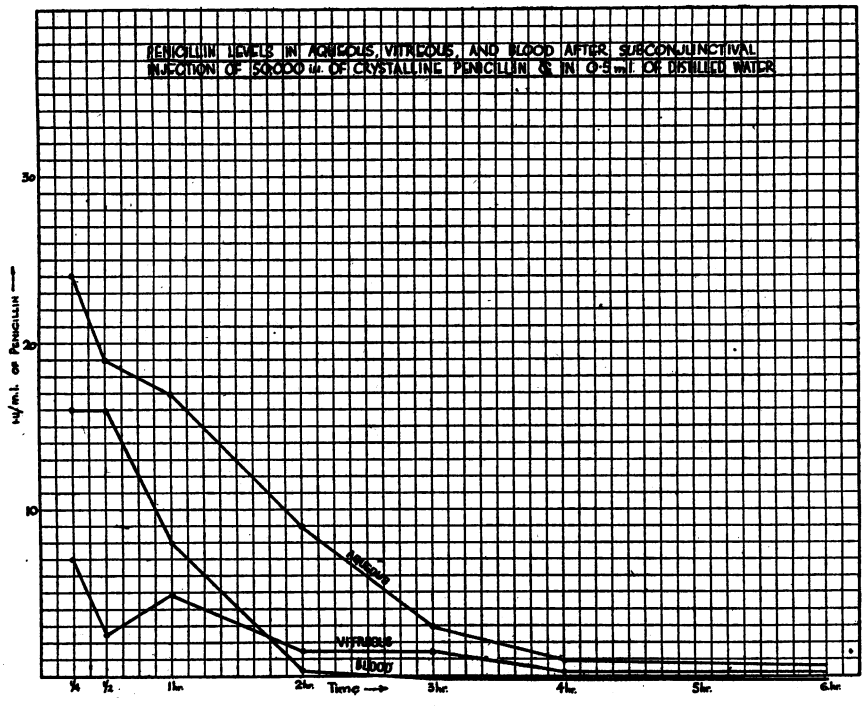
PENICILLIN LEVELS IN AQUEOUS, VITREOUS, AND BLOOD AFTER SUBCONJUNCTIVAL INJECTION OF 50,000 iu. OF CRYSTALLINE PENICILLIN & IN 0·5 ml. OF DISTILLED WATER
30
20
10
μg/m.l. of Penicillin
AQUEOUS
VITREOUS
BLOOD
½ hr
½
1 hr
2 hr
Time
3 hr
4 hr
5 hr
6 hr

FIG. 1.

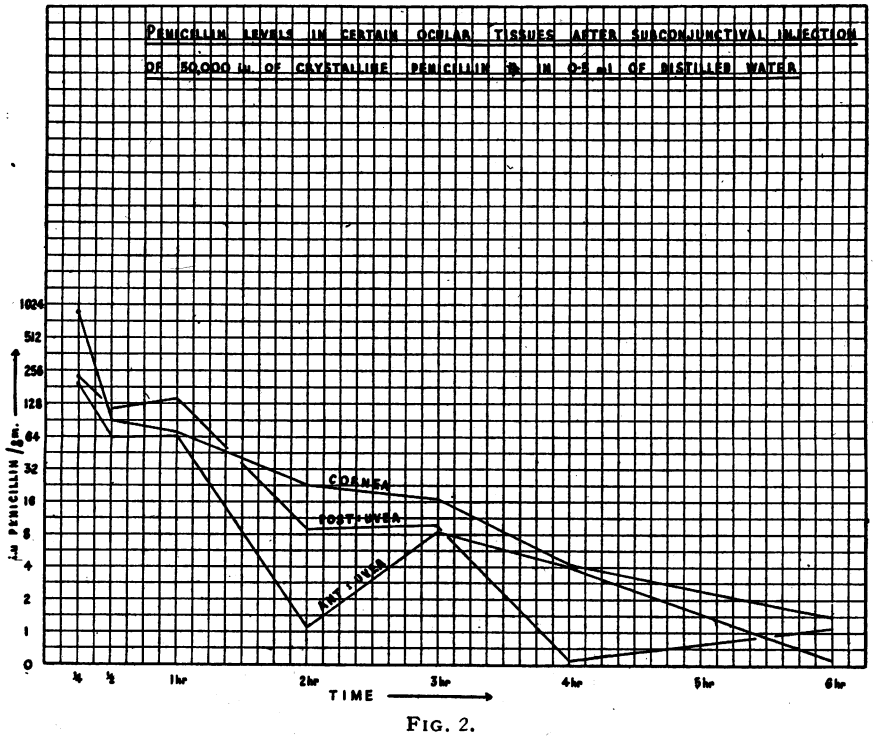
PENICILLIN LEVELS IN CERTAIN OCULAR TISSUES AFTER SUBCONJUNCTIVAL INJECTION OF 50,000 iu. OF CRYSTALLINE PENICILLIN IN 0·5 ml. OF DISTILLED WATER
1024
512
256
128
64
32
16
8
4
2
1
0
μg PENICILLIN/gm.
CORNEA
POST-UVEA
ANT-UVEA
½ hr
½
1 hr
2 hr
TIME
3 hr
4 hr
5 hr
6 hr

FIG. 2.

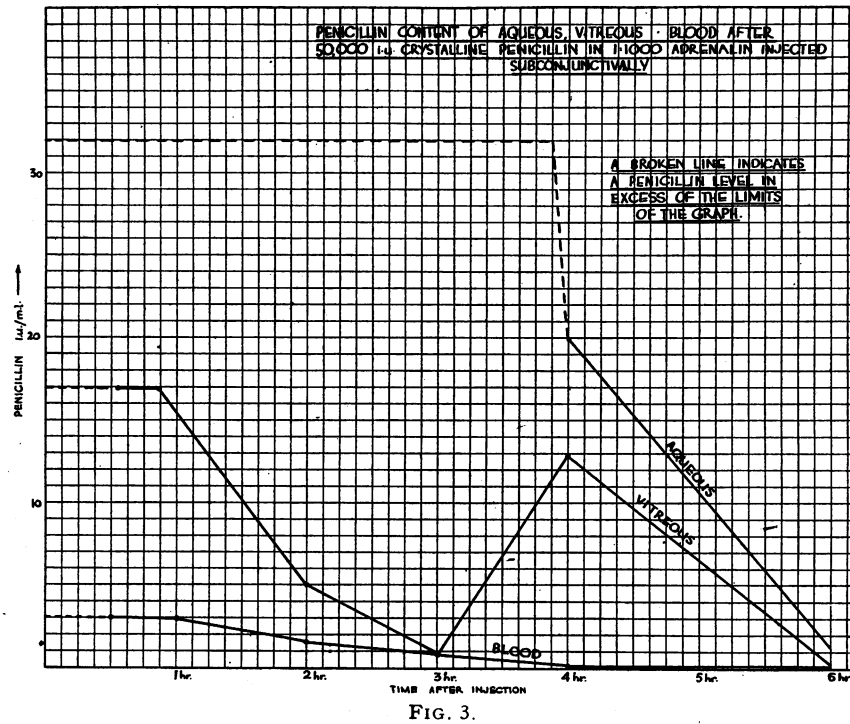
PENICILLIN CONTENT OF AQUEOUS, VITREOUS & BLOOD AFTER 50,000 I.u. CRYSTALLINE PENICILLIN IN 1:1000 ADRENALIN INJECTED SUBCONJUNCTIVALLY
A BROKEN LINE INDICATES A PENICILLIN LEVEL IN EXCESS OF THE LIMITS OF THE GRAPH.
PENICILLIN I.u./ml.
30
20
10
AQUEOUS
VITREOUS
BLOOD
1 hr.
2 hr.
3 hr.
4 hr.
5 hr.
6 hr.
TIME AFTER INJECTION

FIG. 3.

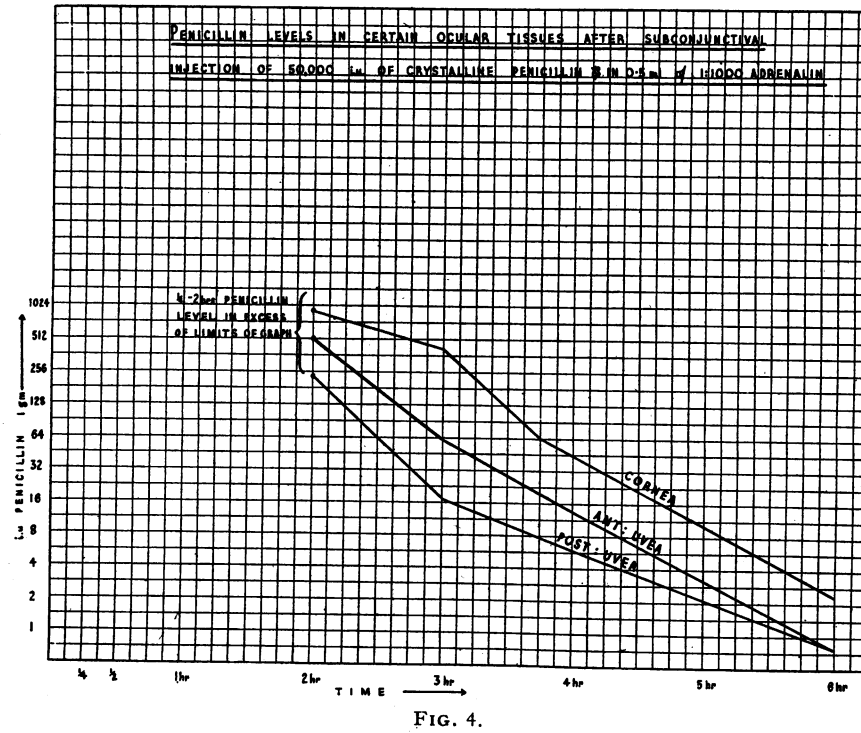
PENICILLIN LEVELS IN CERTAIN OCULAR TISSUES AFTER SUBCONJUNCTIVAL INJECTION OF 50,000 I.u. OF CRYSTALLINE PENICILLIN G IN 0·5 ml. of 1:1000 ADRENALIN
½-2hrs PENICILLIN LEVEL IN EXCESS OF LIMITS OF GRAPH
I.u. PENICILLIN I gm.
1024
512
256
128
64
32
16
8
4
2
1
CORNEA
ANT. UVEA
POST. UVEA
½
½
1 hr
2 hr
3 hr
4 hr
5 hr
6 hr
TIME

FIG. 4.

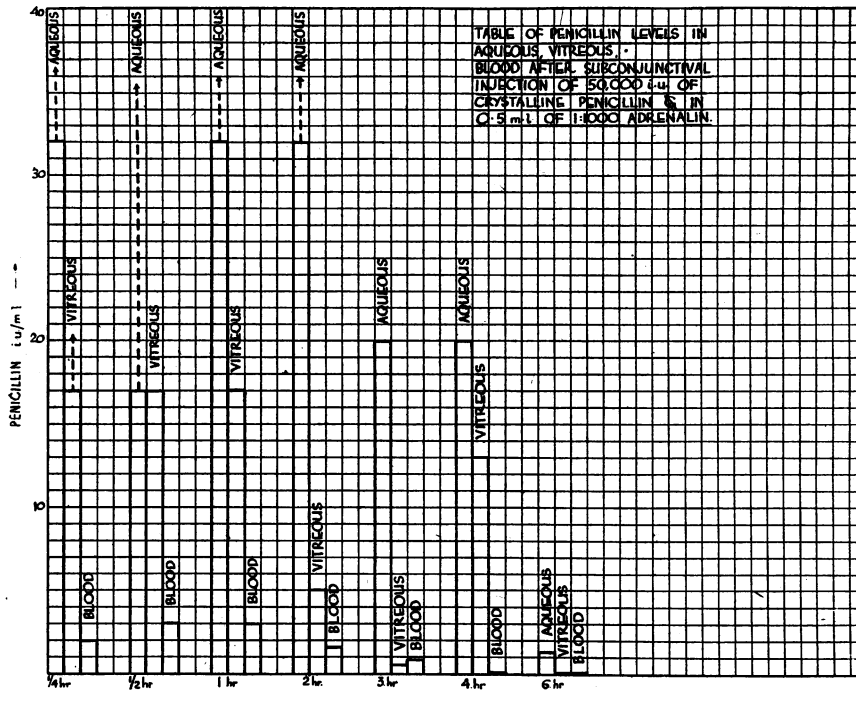

FIG. 5.

Subconjunctival injections of 50,000 units of penicillin	Blood-levels at				
	¼ hr.	1 hr.	2 hrs.	3 hrs.	6 hrs.
Without adrenalin ...	16	8	0·35	0	0
With adrenalin ...	>2	3	1·5	0·75	0·12

5. *Effect of adrenalin on the levels reached in the uninjected eye.*—As can be seen from Tables II and III there is a considerable intra-ocular level of penicillin in the uninjected eye after a massive dose subconjunctivally in the fellow eye. Comparison between the levels reached on the injection of penicillin with and without adrenalin is difficult, as these levels are generally low and rather bizarre. It is, however, clear that intra-ocular levels tend to persist longer when adrenalin is used. When injections are made without adrenalin all the ocular tissues except the sclera are free from penicillin at 4 and 6 hours, whilst fairly substantial levels are still present where adrenalin has been used.

6. *Observations in man.*—When eyes of patients came to excision the opportunity was taken to inject penicillin subconjunctivally at variable intervals before excision. The level of penicillin in the aqueous and vitreous was determined by assay of some aspirated fluid. The following table gives the results obtained.

Level of penicillin in the aqueous and vitreous of human eye after subconjunctival injection of 50,000 units of penicillin in 0·5 c.c. of 2 per cent. novocaine

Patient's Age	Time injected before enucleation	Concentration in		Clinical Condition	Remarks
		Aqueous	Vitreous		
74	½ hour	16	0	Old irido cyclitis	—
12	1 hour	2	0·25	Old intra-ocular foreign body	—
5	1 hour	4	0·125	Old irido-cyclitis	—
27	2 hours	32	0·5	Intra-ocular foreign body. Panophthalmitis	—
55	4 hours	0·5	16	Old injury. Iris bombé	Fluid vitreous

These limited results are consistent with the experimental findings, in so far as they show that adequate therapeutic levels can be reached in both the aqueous and vitreous, and much more readily in the first than in the second.

Discussion

1. *Comparison with previous data.*—Andrews' data, like our preliminary results, have shown that high intra-ocular levels are reached by subconjunctival injection of 50,000 units of penicillin. Though his actual values are consistently lower, the findings recorded by Andrews agree closely with our own. The significant differences in the two studies are that whilst Andrews found the concentration in the vitreous almost uniformly negligible, the concentrations we obtained were therapeutically significant. In our present investigation we ignored the lens, as in preliminary experiments we found the concentration in the lens consistently negligible. Andrews' readings showed rather more positive values.

2. *Comparison of levels reached by subconjunctival injection with those obtained by ointments and systemic administration.*—The only data available are those recorded in our previous study.

It may be recalled that ointments in concentrations of up to 40,000 units/gm. do not maintain any adequate intra-ocular levels after 2½ hours. To a lesser extent this also applies to massive systemic administration. The following summary table brings out salient comparative data on the use of subconjunctival injections, ointment and systemic administration of penicillin.

Concentration at 2 hours after application

	Aqueous	Vitreous	Cornea	Sclera	Uvea
Subconjunctival injections 50,000 units					
Without adrenalin ...	9	1·5	25	20·5	5·37
With adrenalin ...	>32	5·0	925	372·5	370
0·1 gm. of ointment 50,000 U/gm.	2·75	4	0·75	1	0·3
Intravenous injections * 25,000 units	0·37	1	0·5	2	2·05

* After 2½ hours.

Though the values recorded for intra-ocular levels after the application of ointment and after systemic administration are based on few observations, the overwhelming advantages of subconjunctival injections are beyond question.

3. *Factors in the maintenance of intra-ocular levels of concentration.*— The level of concentration of penicillin intra-ocularly depends on the amount of penicillin that reaches the eye, on the amount eliminated either by excretion or destruction, and on the rate at which these processes take place. Of the many factors involved only the dose of penicillin and the addition of adrenalin to the penicillin have so far been isolated. For adequate control of intra-ocular levels an intensive study of other relevant factors is required.

4. *Clinical applications.*—From the data recorded it is clear that an injection of 50,000 units is preferable to one of 20,000 for two reasons: in the first place it gives considerably and disproportionately higher levels of intra-ocular concentration; and secondly, these levels are maintained for a longer period. It is also clear that the solvent used is a matter of some importance. Normal saline is excluded as any substantial amount of penicillin dissolved in such a solution makes it hypertonic (Ungar and Denston, 1946). The advantages of adrenalin have already been indicated. For repeated injections, particularly in an inflamed eye, 2 per cent. novocaine as a solvent has considerable advantages, and there

would seem to be no reason why equal quantities of adrenalin and novocaine should not be used as a solvent for routine purposes. As for the frequency of application, results in the rabbit suggest that when 50,000 units are used injections should be given at intervals of 6 hours.

Summary

1. Substantial concentrations of penicillin in the ocular tissues, many times the usual therapeutic level, can be obtained by the subconjunctival injection of crystalline penicillin in a dose of 50,000 units. Adequate levels persist for 6 hours.

2. The concentrations are distinctly higher if adrenalin 1:1,000 is used as the solvent for the penicillin.

3. Observations on 5 human eyes support the findings obtained experimentally.

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LOCAL PENICILLIN THERAPY OF HYPOPYON FORMATION: WITH SPECIAL REFERENCE TO THE USE OF SUBCONJUNCTIVAL INJECTION*

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INDICATIONS for the use of penicillin and optimal methods for its employment locally have still to be determined. Drops require to be instilled at frequent intervals; lamellae have not proved satisfactory and ointments have presented difficulties as to the best base to be employed. For hypopyon ulcer Juler and Young (1945) have found penicillin effective and have advocated the application of solid penicillin to the infected ulcer. The present study on the

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