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LOCAL TREATMENT OF INTRABULBAR INFECTIONS*†

6. Treatment of Staphylococcuspanophthalmia by Intrabulbar Injection of Penicillin

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As shown in previous articles (Roenne^{1 8}) artificial intrabulbar infections can be cured by injecting chloramine-T into the vitreous body. This treatment has, however, only limited effect, as an inoculum of more than 5,000 microbes is difficult to sterilize. This being the case the testing of other bactericides was desirable, principally the sulphonamides and penicillin. From preliminary experiments it was found that sulphonamides, in conformity with the reports of other workers, have but a very slight effect, whereas penicillin proved to be particularly efficacious. Even with weak concentrations of 1-2 Oxford Units, the effect on infections in the vitreous humour was considerable. The effectivity improved with increasing concentrations of penicillin, even an inoculum of 5,000,000 virulent staphylococci was overcome and the eye preserved. It was also observed, that penicillin injected into the vitreous was extremely durable; it disappears so slowly that a bacteriostatic concentration is preserved for many hours, up to 48, all depending on the original quantity of penicillin (Roenne^{4 7}).

American workers have also taken an interest in the treatment of intrabulbar infections with penicillin. von Sallmann, for instance, tested the effectiveness of treatment of infections induced by pneumococci and staphylococci injected into the anterior chamber.

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Treatment was partly by means of drop instillation and partly by iontophoresis. In the absence of any lesion of the lens both forms of treatment gave good results. In the case of a lens-lesion the result was inferior, though the effect was still apparent. Infections produced by *Clostridium Welchii* did not respond to treatment.

von Sallmann, Meyer and Di Grandi demonstrated that neither iontophoresis nor general treatment had any effect on inflammation in the vitreous body, and therefore they tried injecting penicillin direct into the vitreous, with good results. They observed that intravitreal injections of penicillin produced lesions of the retina at the site of the puncture and opacities and sometimes haemorrhage in the vitreous body. The present author has previously published a short series of experiments on the toxicity of penicillin injected into the vitreous and has shown that penicillin concentrations of 10-100 O.U. do not produce definite pathological changes (Roenne⁴), whereas, the opposite is the case with sulphonamides in the necessary concentrations (Leopold and Scheie). von Sallmann *et al.*, demonstrated that for 24 hours after the injection of penicillin it was possible to detect a bacteriostatic penicillin concentration in the vitreous.

According to Struble and Bellows, demonstrable quantities of penicillin are found in the vitreous after subconjunctival injections. Leopold's investigation gave the opposite result. He found, that only when there was inflammation in the anterior section of the eye, could a therapeutic penicillin concentration be obtained. When penicillin was injected into the anterior chamber, Leopold found a therapeutic concentration in the vitreous, and the concentration became higher if there was inflammation in the anterior chamber or if iridectomy had previously been performed. According to Leopold, intramuscular and intravenous treatment does not lead to therapeutic penicillin concentration in the vitreous. In accordance with this he found that intravenous injection as a means of treating intravitreal infection is of no value. Subconjunctival injection and injection into the anterior chamber could be protective against suppuration, but penicillin injections into the vitreous were most effective. All eyes that were given over 1,000 O.U. in the vitreous were practically normal. With decreasing amounts of penicillin the results became poorer, but even 5 O.U. showed some effect. In all cases Leopold employed an inoculum of about 400 microbes of a haemolytic *Staphylococcus aureus*.

Toxic effect of penicillin on the eye

With the exception of slight opacities, clinically observable toxic phenomena are not occasioned by injection into the vitreous of even very considerable quantities of penicillin viz : 100-500 O.U.

Similar opacities occur after the injection of saline in various concentrations. Whether penicillin in therapeutic concentrations produces histological changes, cannot be decided at the present stage with absolute certainty, particularly because the preparations available to the writer were not in a highly purified state. Nevertheless, it seems justifiable to say now, that even fairly large doses of 100-500 O.U. of penicillin are practically harmless to the eye.

Penicillin treatment of infections in the vitreous body

Technique.—The rabbits employed weighed about 2,000 grammes. They were inoculated with a highly virulent staphylococcus aureus strain, which, with an inoculum of 50 bacteria led to perforation of the eye in less than four days. Even with an inoculum of 5 bacteria there were 100 per cent. takes. (For details, see previous works (Roenne^{2 3 5 6 8})). The penicillin, which was supplied by Professor K. A. Jensen and produced by him, was standardized according to the usual principles. During the course of the investigation, preparations of penicillin purified in various ways were employed. Nevertheless, the various preparations all had identical effects. In every experiment 0.2 c.c. of penicillin was injected into the vitreous.

The inoculation by intravitreal injection with various inocula followed a logarithmic scale, viz: 5, 50, 500, ———, 5,000,000 microbes; after a certain interval, the eyes were treated with penicillin injected into the vitreous.

As will be seen from Table I, there were four experimental groups; treated respectively with 0.2, 2, 20 and 200 O.U. The first column shows the amount of penicillin in O.U., the second column the interval between inoculation and treatment, and the next columns show results of the treatment with increasing inoculum. In these columns, the first cipher gives the number of cured eyes, the second cipher the number of those not cured. For each group the tests in which the number of cures was lower than 100 per cent. but higher than *nil* are circumscribed. The experiments within these limits correspond roughly to 50 per cent. cures. It is significant that an increase in the penicillin concentration improves the results, and greater quantities of bacteria can be destroyed.

To obtain a more concise picture of the effects of the treatment, we must know the quantities of bacteria present in the eye at the moment when the penicillin is injected. The following method was adopted: In a previous paper, (Roenne⁶ Fig. 2) the growth curve of staphylococci in the eye was calculated for two different inocula, 5,000,000 and 50 bacteria respectively. If the ordinate is the logarithm of the concentration of bacteria and the abscissa is the experimental time in hours, we can, by the method of least squares, obtain the following equations for the bacterial growth. With an

TABLE I

Penicillin injected after inoculation

Influence of size of inoculum, penicillin concentration and interval between inoculation and treatment upon the therapeutic result

Groups	Dose of penicillin injected	Interval in hours	Inoculum						
			5	50	500	000'5	000'05	000'005	000'000'5
I	0.2 O.U.	1	2-0	2-0	1-1	0-2	0-2	-	-
		2	3-1	2-2	1-3	0-4	0-2	-	-
		4	2-0	0-2	0-2	-	-	-	-
II	2 O.U.	1	-	-	-	-	2-0	2-0	1-1
		2	-	-	-	2-0	2-0	1-1	0-2
		4	-	-	-	2-0	3-1	2-2	0-2
		8	-	-	2-0	2-0	0-2	0-2	-
		16	2-0	2-0	2-0	0-2	0-2	-	-
		24	1-3	0-4	0-2	-	-	-	-
III	20 O.U.	1	2-0	2-0	2-0	2-0	2-0	2-0	1-1
		2	2-0	2-0	2-0	2-0	2-0	1-1	2-0
		4	2-0	2-0	2-0	2-0	2-0	1-1	0-2
		8	2-0	2-0	2-0	2-0	1-1	0-2	0-2
		16	4-0	4-0	3-1	2-2	0-4	0-2	0-2
		24	4-0	2-2	0-4	0-4	0-2	0-2	0-2
		32	0-4	0-4	-	-	-	-	-
IV	200 O.U.	1	-	-	-	-	-	2-0	2-0
		2	-	-	-	-	-	2-0	2-0
		4	-	-	-	-	2-0	2-0	0-2
		8	-	-	-	2-0	2-0	1-1	1-1
		16	2-0	2-0	2-0	2-0	1-1	0-2	0-2
		24	2-0	2-0	1-1	0-2	0-2	-	-
		32	2-0	1-1	0-2	0-2	0-2	-	-

inoculum of 5,000,000 bacteria : $y = 0.28x + 5.44 \pm 0.21$, and for an inoculum of 50 bacteria : $y = 0.26x + 0.11 \pm 0.31$. This means that the growth velocity in the two experiments is the same (the same coefficient of inclination). As the distance along the ordinate between the growth curves is 5.43 (the theoretical value is 5.00), with a mean error of ± 0.36 , the conformity cannot be much better. Therefore it must be justifiable to interpolate the growth curves for other inocula. The writer chose the experiment with 5,000,000 bacteria to determine the point of intersection with the ordinate-axis, because that experiment embodied the greater number of observations.

TABLE II

Calculated values for the logarithm of the bacteria concentration with various inocula after different times

Inoculum	Hours after inoculation							
	1	2	4	8	16	24	32	48
5	—	0.1	0.6	1.7	3.9	6.2	8.4	—
50	0.7	1.0	1.6	2.7	4.9	7.2	—	—
500	1.7	2.0	2.6	3.7	5.9	8.2	—	—
5,000	2.7	3.0	3.6	4.7	6.9	—	—	—
50,000	3.7	4.0	4.6	5.7	7.9	—	—	—
500,000	4.7	5.0	5.6	6.7	—	—	—	—
5,000,000	5.7	6.0	6.6	7.7	—	—	—	—

Growth curves for all inocula employed in the present experiment having been drawn, the logarithm of the bacterial concentration at the various points of time can be read direct, and the values found are shown in Table II. As the bacterial concentration per c.c. in the eye does not rise beyond 8.5 logarithmic measurement, no values higher than this are included in the table. Then, within each series of experiments (Table I), we determine with which inoculum we have 50 per cent. cured, and by means of Table II we can ascertain directly the corresponding concentration of bacteria. As will be understood, this determination rests on a

rather rough estimate. The calculation is completed for all experimental series and groups and the result is shown in Table III.

TABLE III

The logarithm of the bacterial concentration for 50 per cent. cured at the time of treatment.

Penicillin concentration	Inoculum						
	5	50	500	5000	50000	500000	5000000
0.2 O.U.	0.6	1.0	1.7	—	—	—	—
2 O.U.	5.6	6.0	7.0	5.8	5.1	5.3	5.7
20 O.U.	7.3	7.2	6.5	6.9	5.7	5.6	6.3
200 O.U.	8.5	8.5	8.2	8.0	7.9	6.7	7.7

From this table it will be seen that within each group (penicillin concentration) there is surprising constancy in the bacterial concentration that corresponds to 50 per cent. cured. This implies that it is more or less immaterial whether the quantity of bacteria present has been produced by a large inoculum which has grown within a few hours, or a small one with a long period of growth.

This is rather extraordinary, as one would expect *a priori* that in the case of an infection 16 to 24 hours old, the microbes would have the opportunity of spreading among the tissues of the eye, and in many places they would be well sheltered from the attacking substance. The result we have observed means, presumably, that the penicillin is distributed very readily in the eye tissues and everywhere attains a considerable bactericidal concentration, and that this concentration is maintained for a sufficient length of time.

Velocity of decrease in penicillin

Table IV represents a summary of a number of experiments performed in exactly the same manner as those in Table I, only with the one difference, that the penicillin was injected *before* the eyes were inoculated. The table is in principle similar to Table I, and here again the experiments in which the number of cures was less than 100 per cent. and over *nil* are circumscribed for each group. Even a casual examination shows that these delimited experimental values (except in the case of Group I) form very nearly a straight line within each group, and that the three lines thus arrived at are almost parallel.

TREATMENT OF INTRABULBAR INFECTIONS

TABLE IV

Penicillin injected before inoculation

Influence of size of inoculation, penicillin concentration and interval between inoculation and treatment upon the therapeutic result

Groups	Dose of penicillin injected	Interval in hours	Inoculum							Calculated penicillin concentration in O.U. at time of inoculation
			5	50	500	5,000	50,000	500,000	5,000,000	
I	0.2 O.U.	0	2-0	2-0	1-1	0-2	0-2	0-2	0-2	0.2
		1	4-0	2-2	1-3	0-4	0-4	0-2	0-2	
II	2 O.U.	1	-	-	-	-	-	-	-	1
		2	-	-	-	-	2-0	1-1	1-1	
		4	-	-	-	2-0	1-1	1-1	0-2	
		8	-	2-0	2-0	2-0	1-1	0-2	0-2	
		16	2-0	4-0	3-3	2-4	0-4	0-4	0-2	
		24	0-2	0-2	0-2	-	-	-	-	
III	20 O.U.	1	-	-	-	-	-	-	-	11
		2	-	-	-	-	-	-	-	
		4	-	-	-	-	2-0	2-0	2-0	
		8	-	-	-	2-0	1-3	4-0	3-1	
		16	2-0	2-0	2-0	4-0	3-1	3-1	2-2	
		24	4-0	6-0	4-0	4-2	2-4	0-2	0-2	
		32	4-0	4-0	3-1	0-4	0-4	-	-	
IV	200 O.U.	1	-	-	-	-	-	-	-	64
		2	-	-	-	-	-	-	-	
		4	-	-	-	-	-	-	-	
		8	-	-	-	-	-	2-0	2-0	
		16	-	-	-	-	2-0	2-0	2-0	
		24	2-0	2-0	2-0	2-0	2-0	2-0	1-1	
		32	2-0	2-0	2-0	2-0	4-0	3-1	2-2	
		48	2-0	4-0	3-1	3-1	1-3	0-4	0-2	
		56	1-1	0-2	0-2	-	-	-	-	

This becomes still more obvious if we plot the results in a co-ordinate system in which the axes are the logarithm of the inoculum ($\log c$) and the interval between the penicillin injection and inoculation (t) respectively. Thus, it is obvious that there is a rectilinear relation between the interval between penicillin injection and inoculation (t) on the one hand and the logarithm of the bacterial concentration (the concentration that is cured in 50 per cent. of cases) on the other; briefly expressed: $t = a \log c + \text{constant}$. As, moreover, it is obvious that the quantity of penicillin present at the moment of inoculation must be a function of t (the interval between the penicillin injection and the inoculation), the natural assumption is, that the inclination of the three curves is an expression of the relation between the penicillin concentration at the moment of inoculation and the bacterial dose (50 per cent. cured).

Furthermore, according to the laws of diffusion and osmosis, we must assume that the disappearance of the penicillin from the eye owing to diffusion, absorption and destruction, proceeds logarithmically, *i.e.*, that a certain percentage of the penicillin disappears per time unit; the result of these processes must be that the relation penicillin-concentration—bacteria-concentration is reproducible by a straight line in a double logarithmic coordinate system.

Returning to Table IV, we find that the distance between the two pairs of the three parallel lines along the Y-axis (the interval between penicillin injection and inoculation) is 16 hours. (As stated, in the first experimental group, the material is too small for the calculation of a line analogous to the other groups, but the one point in this group, which we can make use of, agrees with the other observations). The difference in the penicillin concentration between each experimental group is 1:10. This signifies that in the course of 16 hours, the original penicillin concentration has fallen to 1/10, in the course of 32 hours to 1/100 and in 48 hours to 1/1,000, which again shows the correctness of the previous assumption, that the penicillin in the eye disappears according to a logarithmic curve.

On this basis, for each experimental group, we can calculate the penicillin concentration present at any moment. The values found are shown in the last column of the table. (*)

Ratio of penicillin concentration and bacteria concentration

We now proceed to compare the calculated penicillin concentrations with the appropriate inocula ($\log c$) and plot the values

* Naturally, this determination is easier to carry out by a direct analysis of the penicillin content of the eye at various times after injection. An analysis of this kind was made and it was found that the halving time, *i.e.*, the time at which half of the penicillin has disappeared, is just over 5 hours. The method described above gives a halving time of just under 5 hours, so that there is a satisfactory agreement between the two.

found in a coordinate system in which the axes are the logarithm of the bacteria concentration and the logarithm of the penicillin concentration.

TABLE V

The number of bacteria destroyed in 100 and 50 per cent of cases with various penicillin concentration

Calculated penicillin concentration	Group	Cured	
		100% cured	50% cured
0.06 O.U.	II	—	—
	IV	—	— 5
0.2 O.U.	I	50	500
	II	50	500
	III	50	500
	IV	50	5,000
0.6 O.U.	II	5,000	50,000
	IV	500	5,000
1 O.U.	II	5,000	500,000
2 O.U.	III	5,000	5,000,000
	IV	50,000	5,000,000
6 O.U.	III	500,000	50,000,000
	IV	500,000	5,000,000
11 O.U.	III	5,000,000	—
20 O.U.	IV	5,000,000	—

On the surface, it might seem that we are here begging the question. Actually, of course, this is not the case. Really, all we have done is to replace the original ordinate values in each experimental group (for each line in the coordinate system) with new values, *i.e.*, the time with the logarithm of the penicillin concentration and this does not alter the shape of the curves. Let the unit of the new coordinate system correspond to 16 hours in the old system and the inclination of the lines is exactly the same.

With Table IV as basis, Table V is formed by comparing the calculated penicillin concentrations with the inocula which can be overcome in respectively 100 and 50 per cent. of cases. The first column gives the concentration of penicillin at the time of inoculation and the second column the respective experimental groups. The third and fourth columns give the quantity of bacteria destroyed for 100 and 50 per cent. respectively. An interpolation has been made because, as stated, we have not exactly 50 per cent. cures in all experiments, but sometimes more and sometimes less. The correlative values thus arrived at are plotted in a coordinate system (Fig. 1) for 100 and 50 per cent. cures. It appears from the figure that they are very nearly linear functions, as was to be expected from the theoretical considerations. From the curves, we can now read directly how high a concentration of penicillin is necessary to destroy or sterilize a certain quantity of bacteria in 100 and 50 per cent. of the experiments. It is of great importance in the practical therapeutic employment of penicillin, that ten times the concentration of the bacteria requires only about twice the penicillin concentration, or conversely, that ten times the penicillin concentration increases the number of bacteria that can be destroyed a thousandfold.

However, the numbers in the figure representing the penicillin concentration are not absolute, but merely relative values. For example, if the quantity injected into the eye in a given case is

2 O.U., the concentration per c.c. will not be 2 O.U. but somewhat lower, because the volume of the rabbit eye is more than 1 c.c. As a rule we must reckon with a dilution of about 2-3 times, so that with this quantity of penicillin the concentration in the eye is 0.5-1 O.U. This, of course, involves a parallel displacement of the curve, but no change in its inclination.

In addition, Table III shows quite distinctly, that an increase of the penicillin dose involves an increase in the number of bacteria that can be affected by the treatment. On the basis of Table III, we can calculate the mean value of the bacterial concentration capable of being killed in 50 per cent. of cases by the penicillin concentrations employed, and we find the values shown in Table VI, column 2. In column 3 are the numbers of bacteria which similar doses of penicillin, according to Fig. 1 (Table IV) can deal with. As appears from Table VI, there is a rather considerable difference between the two main experiments. Penicillin treatment undertaken *after* the inoculation gives a much inferior therapeutic result to that obtained from treatment *before* the inoculation. Table III showed that primarily the result of the treatment depends only on the concentration of bacteria, and is independent of the interval between inoculation and treatment. It might perhaps be natural to assume that this would also be the case when the interval was "negative," i.e., when the penicillin treatment was undertaken before the inoculation in which case the figures in column 2 and 3 would be similar. As Table VI shows, this is not the case, and must be due to special circumstances. In the first place we must bear in mind the radical change that takes place in the biology of the bacteria when they are transferred from the nutritive media to the eye, and it is a natural assumption that by this means the vitality of the microbes is lowered very considerably for a time, that many of them die and that the survivors become acclimatized to their new conditions of life only after a certain time has passed. Indeed, it is a fact, that quantitative tests of bacterial growth in the eye show a heavy initial fall in the number of bacteria immediately after inoculation, and only reaches its original size after some hours (Roenne⁴). Thus, the difference in the results of the treatment in the two experimental groups may be explained by the decrease in vitality of the bacteria at the moment of inoculation.

If the relation penicillin concentration—bacteria concentration for the experiments in Table IV can be expressed by a linear function in a double logarithmic co-ordinate system, this, of course, should also apply to the experiments in Table I. It appears, however, from Table VI, column 2 that these experimental data only with difficulty compare favourably with this hypothesis. However, it must be borne in mind that even if the figures in Table III, column 2 are based upon a fairly considerable material, in contrast to

TABLE VI

* Comparison between treatment before and after inoculation.
Logarithm of the number of bacteria destroyed in 50 per cent. of cases.

Penicillin concentration	Data from Table 3	Data from 50% graph in Fig 1
0.2 O.U.	1.1	3.1
2 O.U.	5.8	5.9
20 O.U.	6.5	8.7
200 O.U.	7.9	11.5

* It should be noted that the last two values in Table 6 col. 3 are extrapolations and it is therefore uncertain whether we can reckon with these values as true. It is not impossible that the linear function does not apply to extremes.

Table IV there are so many more approximations and interpolations that they are encumbered with very considerable uncertainty. Without embarking upon an exposition of the error of these values (indeed, it cannot be calculated exactly), it may be stated that within the bounds of probability, the error is of such an order that these experiments also follow the general relation for the penicillin-concentration—bacteria concentration.

With these reservations, it is nevertheless possible, with only four values, to draw the straight line representing the function penicillin-concentration—bacteria concentration for the experiments in Table I. This line is also plotted on Fig. 1 and is practically parallel with the two already referred to. Of course, here again we must remember the dilution that takes place in the eye.

Discussion

Although several approximations and interpolations have been used in the arrangement of the basic experimental data, the parallelism of the graphs in Fig. 1 can hardly be accidental, but must be the expression of a biological law. Besides, the experiments are a further example of the remarkable bactericidal property of penicillin and show, moreover, that it is practically unlimited how intense infections it is possible to cure when sufficiently large doses are employed.

Finally, on going into the question of how this relation between

quantity of bacteria and penicillin concentration compares with our experience in other directions, we find that there is reasonable conformity. With general penicillin treatment of, for example, septicaemia, the penicillin concentration obtained in blood and tissues fluid is of a maximum average of one-fifth to one-third O.U. per c.c. On looking at the curve (the one based on the experiment in Table I), we find that it corresponds to a bacterial dose of about 10-200 microbes per c.c. On correcting for the aforesaid dilution error, the quantity of bacteria susceptible to treatment turns out to be 100-1,000 per c.c. This of course is much higher than the concentration of bacteria in the blood of sepsis patients, but the difference does not seem to be greater than is permissible, especially when we realize that direct comparison is impossible. The explanation is that the time factor, *i.e.*, the time during which the microbes are exposed to a penicillin concentration that will injure or inhibit them, undoubtedly differs in the clinic and in these experiments. In the clinic, the effective penicillin concentration is maintained from for many hours to several days, whereas in the experiments it was presumably maintained only some few hours, at any rate when the quantities of penicillin were small.

Unfortunately, in these experiments it is impossible to derive any direct information as to the time factor and its importance to the result of the treatment, because both this and the penicillin dose enter into the experiments in such a manner, that the effects of the two different factors defy analysis. But it is obvious that investigations into the importance of the influence of the time factor on the result of the treatment is a question of great interest, not only theoretically but also clinically. For example, it is possible that in the case of penicillin too, the protracted continuous treatment with the appertaining low blood concentrations can—and will—be replaced by a therapy which brings the blood and tissue concentrations up to high values for a short time.

Although these investigations have been concerned only with a single form of bacterium, it is reasonable to suppose that the same laws will apply to the action of penicillin on other microbes, even if in that case the constants of the equation will be altered. For the present it is justifiable to assume that in penicillin we possess the best weapon so far at our disposal for combating intra-ocular infections, and that by local treatment we obtain a number of advantages not possible with general treatment *viz*: (1) the maintenance of a bactericidal concentration of penicillin for a long period, 16-24 hours; (2) only small quantities of penicillin are necessary; (3) Leopold and Struble and Bellows have shown that general penicillin treatment does not lead to any demonstrable concentration in the vitreous or at any rate only in very small quantities. The present author has made a series of similar experiments and can verify

the results. With very large doses of 5,000 O.U. per kg. one can obtain concentrations of about 0.05-0.10 O.U. per c.c. in the vitreous.

Thus, there can hardly be any doubt, that for the moment local treatment— injection of penicillin in the vitreous humour—is the most rational therapy for intra-ocular and especially intra-vitreous infections. Chloramine-T previously employed by the writer (Roenne^{1, 8}) is much less effective, partly because of its toxic action when in large concentrations, partly because the bactericidal effect is maintained only a few hours.

The only drawback of penicillin is its specificity. Fortunately it attacks most of the microbes we encounter in infected perforating lesions in human pathology.

Conclusions

(1) In therapeutic concentrations of 100-500 O.U. the injection of penicillin into the vitreous body is practically harmless.

(2) Intra-vitreous penicillin treatment of infections in the vitreous body is extraordinarily effective compared with other forms of application and other substances.

(3) The effectivity of the treatment is directly proportional to the concentration of penicillin.

(4) Within fairly wide limits the result of the treatment is dependent only on the number of bacteria in the eye and not on the interval between inoculation and treatment.

(5) The method employed provides indirect information as to the velocity of the absorption of the penicillin from the vitreous body. The values found agree very well with the results gained by direct bio analysis.

(6) The velocity of the absorption of penicillin from the vitreous body is expressed by the halving time, about 6 hours.

(7) The function: $\log \text{ bacteria-concentration} - \log \text{ therapeutic penicillin-concentration}$, is of first degree.

(8) For intrabulbar, especially intravitreal inflammation, the injection of penicillin into the vitreous body is the best therapy at the moment.

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RETINAL DETACHMENT DUE TO WAR TRAUMA

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THIS enquiry was made to find out the incidence of retinal detachment directly attributable to the effects of war missiles, the relation of this incidence to other types of retinal detachment occurring in soldiers serving in a field force, and the comparative results of treatment and prognosis.

In the 1914-18 war Gonin's principle of locating a retinal tear or tears accurately and sealing these by diathermy with subsequent drainage of the inter-retinal fluid was not known or practised and so in the 1939-45 war an opportunity arose to try out modern surgical treatment in such cases as seemed to offer a reasonable chance of effecting some improvement.

This work was done in the M.E.F. 1941-43 and the B.L.A. 1944-45 where to the 15th (Scottish) General Hospital in Egypt, the 102nd Field Hospital in Normandy and the 108th General Hospital in Belgium the majority of retinal detachment cases and serious ocular and orbital wounds with retained foreign bodies were referred.