PENICILLIN IN VENEREAL DISEASES—1*

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Penicillin is a substance produced by a mould, *Penicillium notatum*. Culture fluid of some kind is put into a bottle and then mould spores are put on the top of it. Growth takes place, not in a hot incubator, but in the temperature of a rather uncomfortably hot room. The mould forms a thick felt on the top of the clear fluid, which turns yellow. (All the penicillin which we use is yellow, but the pure material has no colour at all.) After a week or a fortnight the liquid is poured off, and this contains the penicillin. The treatment of this fluid for the purpose of extraction of the active principle varies with different manufacturers, and also keeps on varying with the same manufacturer, because they have not yet agreed on the best method. The fluid is finally dried. In the course of purification a great many things are taken away from it which might on injection cause fever of some kind, and one is left with a yellow powder, perhaps from 10 to 30 per cent pure. The culture medium varies and so does the method of extraction and therefore the impurities vary.

Bacteriostatic effects of penicillin

Penicillin has a very selective action in inhibiting the growth of some bacteria whereas it has no effect on others. The more sensitive organisms are staphylococcus, streptococcus, pneumococcus, gonococcus, meningococcus and *Bacillus diphtheriae*. *B. coli*, *B. influenzae* and many others are not sensitive. If we take a culture which contains a large number of penicillin-sensitive and penicillin-insensitive organisms, it will be found that the former do not grow whereas the latter do. As a preliminary titration of the potency of penicillin we take an agar plate, punch out some discs, remove them with the point of the knife, put penicillin into each cup thus made and spread the surface with staphylococcus, which is a suitable test organism. The plate is put into the incubator and the staphylococcus grows except round about the cup. The area of inhibition varies with the strength of the penicillin. This is an easy method of titration whereby anybody who is using penicillin can obtain a fairly good idea as to whether or not the material is as active as it should be.

Years ago we had an idea that this material was going to be useful for treatment, but in those days we were not good enough chemists to be able to concentrate it. The reason why we thought it was going to be good for treatment was that all the antiseptics in use up to that time—say 1930—had the disadvantage that whereas they killed the invading organisms they had a much more lethal effect on the leucocytes. Take carbolic as an example. With this substance in infected blood you may get more and more colonies developing as the strength of carbolic acid increases up to a concentration of 1 in 640, because the leucocytes are killed by concentrations too weak to have any effect on the microbes. All the old antiseptics were much more active against leucocytes than against bacteria. Penicillin was the first chemical I had ever encountered which acted far more strongly on the bacteria than on the leucocytes. Indeed, we could not find that it had any harmful influence on the leucocytes at all, whereas on certain bacteria the crude culture fluid was more than twice as inhibitory as was carbolic acid. Table 1 illustrates the strength of certain antiseptics in human blood.

From this comparison it appeared that penicillin would be good for the treatment of infections, but there was a great practical difficulty owing to its instability. As the action of penicillin is very selective, it has first to be discovered whether one is dealing with a sensitive or an insensitive infection. It is of no use to treat a patient with penicillin when the infection is one which is insensitive. If there is any doubt whether the organism is sensitive or not a simple test should

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be carried out on a "gutter" or "ditch" plate. With some organisms, such as the staphylococcus or the gonococcus, sensitivity is the general rule, but there are others in which it is not quite so safe to rely upon their sensitiveness.

Methods of treatment with penicillin

In using penicillin in the body we have sometimes employed the sodium salt and sometimes the calcium salt. To begin with, all the penicillin for injection was in the form of sodium salt, but latterly we have been using the calcium salt for injection intramuscularly, intravenously or subcutaneously and we have found that it is as suitable as the sodium salt. It has certain advantages in manufacture, so that it may be that we shall change over some day to the calcium salt for general use.

TABLE 1.—EFFECT OF CERTAIN ANTISEPTICS IN HUMAN BLOOD

ANTISEPTIC	CONCENTRATION WHICH INHIBITS		RATIO
	STAPHYLOCOCCI	LEUCOCYTES (5 hours contact)	
Carbolic Acid	$\frac{1}{400}$	$\frac{1}{800}$	1 : 2
T.C.P. (Amyl salicylate)	$\frac{1}{2}$	$\frac{1}{2}$	1 : 4
Proflavine	$\frac{1}{200,000}$	$\frac{1}{800,000}$	1 : 4
Sulphanilamide	$\frac{1}{10,000}$	$\frac{1}{200}$	50 : 1
Penicillin	$\frac{1}{80,000,000}$	? $\frac{1}{100}$	? 800,000 : 1

The salt can be applied locally so that the penicillin comes into contact with the organisms. This calls for a certain ingenuity on the part of the surgeon. Consider, however, what happens with the systemic use of penicillin. It cannot be taken by the mouth because it is destroyed by the stomach juices. It cannot be given by the rectum because it is destroyed by the organisms in the rectum. Therefore we must confine ourselves to injection—intramuscular, intravenous or subcutaneous.

In order to test the concentration in the blood, the power of the serum to inhibit a test microbe is estimated. We use a slide cell or capillary tubes about 2 inches long. Serial dilutions of the serum are made and to these are added blood infected with haemolytic streptococci. When there is sufficient penicillin to inhibit the streptococci, we get the blood cells still undissolved. The unit of penicillin is an arbitrary quantity but, if we take one unit per cubic centimetre strength of penicillin, we can dilute it just 50 times and it then inhibits the ordinary staphylococcus. The rate of disappearance of penicillin from the blood is very rapid, especially with intravenous injection, and the absorption with either the subcutaneous or the intramuscular injection is also very rapid. If it is desired to keep a constant level in the blood, the only way is by constantly supplying the penicillin in the form of a continuous drip. This drip was formerly always intravenous, but an intramuscular drip, for which we use a bent needle and as little as 100 cubic centimetres of fluid in 24 hours, is a very satisfactory method. The fluid is rapidly absorbed and there is no thrombosis of veins, as there may be with the intravenous drip.

In treating another patient, instead of the drip, we injected fresh doses of 15,000 units every 15 minutes. After the fourth dose the blood content remained stationary and half an hour after the last dose it started coming down and came down rapidly. In all, this patient had 105,000 units in $1\frac{1}{2}$ hours. Sometimes we have used larger doses—100,000 units, intramuscularly. Within 15 minutes the

blood content was at the maximum, remained there for about an hour, and came down almost to nothing in 5 hours. Then we split that dosage, giving 2 doses of 50,000 units at 4-hour intervals, and we got the same picture; after the first dose penicillin was just perceptible after 4 hours, and after the second was apparent for a further 4 hours. These curves describe what is happening in the blood in whatever dosage the penicillin is given. By the aid of curves such as these we are able to work out an effective system of dosage which is convenient to the patient. In an ordinary clinic, to have injections every 3 hours, which is the common practice, is perhaps not really the most suitable procedure, for it means that the patient has to come up every 3 hours over a period of 12 hours in order to get 100,000 units.

Local treatment does not at present come very much into the treatment of venereal disease; or at least I should be glad to hear whether local irrigations have been used successfully. But in surgery it is very prominent, because it is an extremely economical way of using penicillin. It can be put on raw surfaces and can be injected into abscesses, boils and the like. It stays in the abscess cavity in appreciable concentration for 48 hours or longer.

Penicillinase is a substance which is elaborated by many bacteria and which destroys the penicillin. The destruction of the penicillin by penicillinase has happened quite frequently when people have not used enough care in making up their solution to ensure its sterility.

Treatment of venereal disease

Gonorrhoea.—We are not allowed to have penicillin for the treatment of venereal disease, but we have managed to treat some cases of gonorrhoea, although we have not treated them systematically, by combining the treatment with some pharmacological experiment with penicillin. A good many of the patients were treated in order that we might ascertain whether we could inject the calcium salt with safety. We have used a great variety of doses. In the case of a first patient we employed the same method as had been used in the United States of America—105,000 units split up into 3-hourly doses of 15,000 units—and that was successful. We have carried out the treatment in 7 cases with one single dose of 100,000 units and succeeded in every case except one. Therefore it looks as if with one injection success can be achieved in most cases. Then we tried 2 injections of 50,000 units, but that also did not give 100 per cent success. (Dr. Suchet's communication (see p. 136) gives some details of these cases.)

We thought it better to have an injection of 50,000 units to begin with and then 2 of 25,000 units. That is possible in a clinic, but it again has not been absolutely successful. I am not wanting to claim success or failure with any system of dosage, first because we have not enough cases to justify us in so doing, and secondly because some of the penicillin we have used is not material issued for actual treatment, but is material which we received from manufacturers in order to make sure whether or not it was toxic. Nevertheless almost all of the patients have got well with one, 2 or 3 doses. Two patients received 15,000 units every quarter of an hour for an hour and a half. Some were treated with intravenous drip; we gave 60,000 units, and 2 out of 3 patients got well; the other one turned up at the clinic again 12 days afterwards, but we found that 2 days previously he had run the risk of a fresh infection. Among the patients we treated were 3 women, all of them successful cases. One of them might be called a failure or a success. She was treated with 100,000 units in 12 hours and a few days afterwards the gonococci appeared again in the cervix and a few days later in the urethra. Fortunately we did nothing and the organism went away and stayed away: the woman cured herself.

The gonococci which appear in pus films two hours or more after treatment has been commenced are usually swollen and curiously misshapen.

Syphilis.—Accounts of some cases have been published which show extraordinary results in the treatment of syphilis by penicillin. We treated one case of chancre, which had a positive Wassermann and a positive Kahn reaction, with 1,200,000

units spread over 10 days. The chancre healed up and the Wassermann and Kahn reactions both became negative after rather more than 5 weeks and have remained negative for several months. This agrees with the results published in the United States of America in a small series of cases and there are now many cases in which the results are apparently excellent, but no final conclusions can be drawn until sufficient time has elapsed to show that there are no recurrences. It looks as if penicillin were going to prove effective with both the chief venereal diseases; it may take the place not only of the sulphonamides for gonorrhoea but of the arsenicals for syphilis.

PENICILLIN IN VENEREAL DISEASES—2*

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The use of penicillin, of which Sir Alexander Fleming is the discoverer, in the treatment of venereal diseases has not been systematic. We have used it, rather, during a research programme; we have, however, treated all sorts of venereal diseases from the chancroidal type of lesion on the vulva in the female to acute gonorrhoea in the male. We have treated one case of primary syphilis and one of tabes dorsalis. We have also tried penicillin in non-specific urethritis. We have thus gone through the whole range of venereal conditions. Our cases are much too small in total number to provide any definite conclusions and the results are clinical "impressions" only. Altogether we have treated 70 cases in the venereal diseases department.

Gonorrhoea

Taking first acute gonorrhoea in males, our treatments have varied from single injections at 10-minute intervals to multiple injections at intervals of a varying number of hours. We have also used the continuous drip. No matter what the dosage has been, our results have been surprisingly good. Nevertheless in some cases there have been relapses which we did not anticipate. Of the patients who were treated by the single injection method, there was only one failure among 7 cases. In these patients the discharge cleared up completely within 24 hours, the gonococci having disappeared within 2 hours. In the one case, however, the patient relapsed 2 days later but finally responded to treatment with a different dosage.

The suitable amount to be used for the treatment of gonorrhoea appears to be between 100,000 and 120,000 units. What seems to be important is the time factor. In those people to whom we have given 120,000 units over a long interval—giving them perhaps 15,000 unit doses at 3-hourly intervals for 8 doses—our results have been better than they would have been if the whole total dose had been given straight off. Both the calcium and the sodium salts were used. At first we were wary of using the former, but some patients were given 100,000 units in a single injection and there was very little local reaction after the intramuscular injection. Some patients did have a little pain, ranging from a local numbness to a cramp, but it did not last long nor did it upset the patient even when a large dosage of 100,000 units was used. There was no ill effect—no general toxic effect—no matter what dosage of penicillin was employed. When it was given intravenously the only noticeable effect was that the patient complained of a burning sensation at the site of the infection. In the case of a gonococcal arthritis, for example, there was a sense of warmth in the joint.

In one case an application in ointment form into the urethra was tried but the result was not a success. This man, however, was eventually cured without further treatment, although he was sulphonamide-resistant.

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