

to penicillin on subcultivation in laboratory media. It may be that penicillin-resistant staphylococci are an exception to the general rule, and that, consequently, resistant strains of this organism will not appear in clinical practice after more prolonged use of the drug.

Summary

Two strains of coagulase-positive staphylococci were made penicillin-"fast" by cultivation in increasing quantities of penicillin. They were then subcultured daily in broth without penicillin and, contrary to expectations, a rapid fall in resistance to penicillin was noted. It therefore appears that "fastness" of staphylococci to penicillin is not a permanent characteristic.

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WEIL'S DISEASE IN NORMANDY: ITS TREATMENT WITH PENICILLIN

BY

ERNEST BULMER, O.B.E., M.D., F.R.C.P.

Brigadier; Consulting Physician, 21 Army Group; Honorary Physician, Birmingham Hospitals

In view of the experiences of the last war Weil's disease was not unforeseen in the present campaign in North-West Europe. Sporadic cases have occurred, and the opportunity has been seized of treating cases with penicillin. Such results as have been obtained are presented now, as no further cases have been seen for over two months.

History of Outbreak

Weil's disease is spread by infected rats who pass the spirochaetes in their urine; the organisms can live for some time in stagnant streams, in wells, and in the zoogloea-like substance on the walls of wells and sewers. It has been impossible to make detailed studies of the epidemiology of the disease, nor are these necessary. The source of the infection was almost certainly water which men used for washing. Drinking-water was supplied from water-carts or was sterilized in some way, but the supply was not sufficient for other uses; the men were forced to draw water from wells or streams for washing, shaving, and brushing their teeth. They bathed when they could in any available stream. On some sectors they lived in damp rat-infested ditches. As cases were few it was decided that the risk was worth taking, as the alternative—even if it could have been enforced—would have been that the men remained dirty or unrefreshed by bathing during the dreary and often very hot period on the Normandy beach-head.

Up to date (December, 1944) cases have been met with only in Normandy, and only from the middle of July to the end of September. It is surprising that conditions in the Low Countries have not produced further infections; there is plenty of water, both in canals and in the fields, but the weather has been unattractive for the bather, and organized bathing and ablation facilities are much better. I saw the first recognized case on July 18 with Major C. L. Davidson in a C.C.S. near Caen. The patient had had a febrile illness with severe muscle pains and a leucocytosis; on the tenth day he had a very faint icteric tint in his conjunctivae, but was convalescent. We discussed the possibility of Weil's disease, and a few days later we learnt that the agglutination test was positive. The beach-head was so small then that it was easy to tell all the physicians at C.C.S.s and hospitals to watch for it: its presence made common or garden jaundice an attractive clinical problem. Cases cropped up in many units, and when the outbreak ceased at the end of September I had been informed of 39. It is difficult to compute the extent of the outbreak; my figures must be incomplete, and cases must have been missed, especially those without jaundice. Of the 39 cases only two did not have jaundice, whereas the number should have equalled those with jaundice. I would make an informed guess that about 100 cases occurred altogether.

Some cases were very severe, and supplies of antileptospiral serum at first were scanty; it seemed possible that the leptospira might be penicillin-sensitive, and Col. J. S. K. Boyd, Deputy Director of Pathology, ascertained in a telephone conversation with the War Office that it was moderately sensitive. It was at once decided to investigate the matter. In only one case—the only fatality in the penicillin series—was antileptospiral serum given.

Clinical Features

These will not be recited at length—they are well dealt with in the standard textbooks. Those of us who were little familiar with the disease were struck by its unusual features: a brisk febrile illness with severe muscle pains as the leading symptoms, associated with a leucocytosis and complicated by signs of gross renal damage. In the presence of an outbreak this picture is highly suggestive even if jaundice does not follow. In all but two of our cases jaundice developed on or after the fifth day; in sharp contrast to "infective hepatitis," the temperature did not subside when jaundice appeared; it usually increased, and the urine still showed the signs of renal damage. In most cases there was some haemorrhagic incident—conjunctival ecchymosis, epistaxis, haemoptysis, haematemeses, purpura.

The disease if at all severe ran a longish course, the temperature was maintained for perhaps two weeks, and there were often febrile relapses later. The patients were very debilitated, but as they could not remain in the theatre of war we did not find out how long convalescence was going to take, or whether some would develop a type of cirrhosis within a few months.

Of the special types described the anginal form was rare; there were three examples of the meningeal form, but only one had an abnormal cerebrospinal fluid; lung involvement with haemoptysis, watery sputum, and abnormal signs, both physical and radiological, was not uncommon.

Laboratory Findings.—Spirochaetes were found in the blood in several cases, and in the urine in quite a number—both by dark-ground illumination. Animal inoculation was possible only when a resourceful pathologist was able to procure a guinea-pig by local purchase. In most of the cases positive agglutination tests were obtained by sending blood to the U.K. I am satisfied that the errors in diagnosis of Weil's disease have been negligible.

Penicillin Treatment

The dosage recommended was 40,000 units 3-hourly, with a total of about a million units. The average amount given was 1,125,000 units—some by continuous intramuscular drip, some by intramuscular injection—and there was a certain variation in dosage.

Our difficulties in assessing the results have been great. The disease rapidly inflicts severe damage on liver and kidneys, and to be successful any treatment must be given early enough to anticipate this; in practice this means that treatment must be started before the diagnosis has been firmly established—perhaps at a time when a diagnosis is impossible to make. We were dealing with a disease with which few of us were familiar, and no case was treated in the pre-icteric stage when there was the best chance of rapid resolution. Even if penicillin should prove to be a specific remedy it seems doubtful how often really early treatment will be practicable, unless there is so big an epidemic that everyone becomes very skilled in early diagnosis.

We have been unable to find any satisfactory measurement of progress. The numbers we had were too small to warrant any statistical approach—I have avoided any deduction from the deaths occurring in the treated and the untreated. With an elaborate laboratory service it might be possible to estimate the rate of disappearance of spirochaetes from blood or urine—this would need experimental animals, which we lacked. The most promising indication of progress was the effect of the drug on the temperature and on the number of febrile relapses. As is only too common in medicine, we were left with a clinical impression; this demands a nicety of judgment and an intellectual honesty which the observer may indeed possess but which a critic could be forgiven for doubting.

Most of the severe cases received penicillin and recovered; all observers claimed a dramatic improvement in 36 hours, which was usually reflected in the temperature chart, but with

slow improvement in jaundice and urine. Of the fatal cases, I doubt whether any treatment would have saved the two who died of suppression of urine (one treated, one not treated); the third case was not thought severe enough to need penicillin, and this patient died of auricular flutter on the 21st day: this should have been averted if there had been a specific treatment.

Lieut.-Col. L. H. Howells and Major R. R. Hughes made an intensive study of seven cases, six of which they treated with penicillin. Their conclusions were as follows:

1. Penicillin in adequate doses appeared to shorten the general effects of the disease as assessed by the duration of the fever; it had an effect on the number of febrile relapses, and these results bore a direct relation to the dosage.

2. Penicillin did not seem to influence the degree and duration of the cholaemia as estimated by the icteric index and the van den Bergh test, or to affect the rate of disappearance of icterus from the skin or of bile from the urine.

3. Penicillin did not influence the degree of nitrogen retention as estimated by the blood urea, or the degree or rate of disappearance of albuminuria.

4. Apart from the objective evidence mentioned in paragraph 1 there remains only the very definite clinical impression that cases treated with penicillin, especially with high doses, improved dramatically within 36 hours.

5. It is considered that penicillin should be given in cases of Weil's disease as soon as possible and in high doses. Once liver and kidney damage has occurred penicillin does not appear to minimize the results of this; hence it would be interesting to observe the effects of the drug during the pre-icteric phase.

Results

The results in the present series of cases of Weil's disease are as follows:

Total cases	39
Penicillin-treated	16
8 severe, 7 moderate, 1 mild. (14 confirmed by agglutination tests.) 1 died of uraemia	
Untreated	23
2 died—1 of myocarditis on 21st day, 1 of uraemia soon after admission	

Discussion

I have presented the results of the treatment with penicillin of 16 cases of Weil's disease. It would appear that there has been an effect on the speed with which the temperature falls and on the number of febrile relapses, while all the observers claimed an improvement in the patients' general condition within 36 hours. These are scanty pieces of evidence on which to base definite conclusions.

In another theatre of war penicillin treatment, in my opinion, has been considered as ineffectual, but the dosage used was inadequate—15,000 units 3-hourly. It is known that certain strains of leptospira are penicillin-sensitive *in vitro*.

In view of these facts it is felt that further work on this subject should be pursued; it is essential to give treatment early, and the dosage should be high.

I have followed this work throughout, and have seen most of the patients; nevertheless my part in this paper is that of compiler on behalf of the following physicians of 21 Army Group: Lieut.-Cols. C. L. Cope, G. G. Gillam, L. H. Howells, R. L. Mackay, I. McGolrick, I. Murray, R. E. Tunbridge—all R.A.M.C.; Lieut.-Col. J. H. Geddes, R.C.A.M.C.; and Majors H. A. Dewar, R. R. Hughes, S. B. Karani, and Capt. J. A. Lorimer—all R.A.M.C.

More than 250 hospitals in England and Wales are now using rehabilitation methods—including physiotherapy, remedial exercises, outdoor games, and handicrafts. This is nearly twice as many as a year ago, when the Ministry of Health made a special appeal to civilian hospitals to establish a rehabilitation department as soon as possible. Some hospitals are using local halls; others have been supplied by the Ministry of Health with prefabricated huts for remedial exercises and other activities. The Ministry also lends equipment for gymnastics, sports, and occupational therapy. The majority of some 400 hospitals covered by a Ministry of Health survey have appointed a member of the staff as a rehabilitation medical officer. Many of these doctors have attended special courses at selected rehabilitation centres. Other courses have been provided for physiotherapists, handicraft teachers, and others. To help with the resettlement of disabled persons in industry, large firms in the neighbourhood of certain hospitals have established special workshops in which disabled employees may be restored to working capacity by exercising the affected limbs in suitably adapted work under proper supervision.

LOCAL PENICILLIN THERAPY IN OPHTHALMIA NEONATORUM*

BY

ARNOLD SORSBY, M.D., F.R.C.S.

AND

ELIZABETH HOFFA, L.R.C.P.&S.Ed., D.C.H.

Unlike the sulphonamides, penicillin remains effective in the presence of pus. It therefore has possibilities for the local therapy of ophthalmia neonatorum as an alternative to general sulphonamide treatment of this affection. To investigate this possibility 47 infants at the Ophthalmia Neonatorum Unit at White Oak (L.C.C.) Hospital were treated with penicillin. Table I brings out the salient features in summary form.

TABLE I.—Showing results in 47 Cases of Ophthalmia Neonatorum Treated by Various Concentrations of Penicillin. (+ = Successful Treatment; - = Failure)

Organisms	Concentration of Penicillin: Oxford Units per c.cm.							
	500		1,000		1,500		2,500	
	+	-	+	-	+	-	+	-
Gonococci	2	2*	2	0	2	3*	5	0
Staphylococci	1	1	1	—	1	—	9	—
Diphtheroids	—	—	1	—	1	—	1	—
Staphylococci and bacilli	—	1†	—	1	—	—	3	—
Unidentified diplococci	—	—	—	—	1	—	—	—
No organisms or inclusion bodies found	—	—	—	—	—	—	2	—
Virus: assumed from the presence of inclusion bodies	—	1	—	2‡	—	—	2	—
Total	3	5	4	3	6	4	21	1

* Including one case which relapsed.

† Relapsed after clinical cure in 6 days.

‡ Both initially clear after 8 days and 4 days respectively when relapse occurred.

The Series as a Whole

(a) Initially, penicillin was used in a concentration of 500 Oxford units per c.cm. Eight cases received this treatment, one drop of the solution being instilled hourly during the first 24 hours, and continued two-hourly subsequently. Only three of these eight cases were cured. Two more showed an initial recovery, which, however, was not maintained. The three cured cases required treatment for 2 days, 3 days, and 6 days respectively.

(b) A second series of 7 cases were treated with penicillin in a concentration of 1,000 units per c.cm., the method of application in three cases being as in the first series, and in the remaining four cases the penicillin was instilled at half-hourly intervals for 24 hours and hourly subsequently. Four of this series of 7 cases showed clinical cure in 2, 4, 2, and 5 days respectively; one case did not respond to treatment; while the remaining two cases both relapsed after an initial recovery.

(c) A further 10 cases constituted a third series treated with penicillin, this time in a concentration of 1,500 units per c.cm. (the drops being instilled half-hourly during the first 24 hours and hourly subsequently). Six of these 10 cases showed an excellent response, clinical cure being obtained in 18 hours in one case, in 2 days in four cases, and in 3 days in the remaining case successfully treated. Two cases showed a poor response in spite of treatment for 4½ and 5 days respectively; in one case penicillin treatment was discontinued after 3 days as progress appeared inadequate; in the remaining case of this series an initially satisfactory response which gave a clinical cure within 2 days was followed by a relapse which did not respond to further penicillin therapy.

(d) Twenty-two infants were treated with penicillin in a concentration of 2,500 units per c.cm., the drops being instilled half-hourly for the first 3 hours, then hourly for 24 hours and two-hourly subsequently. In all but one case there was an

* A report to the Penicillin Trials Committee of the Medical Research Council.