offer to provide funds for the construction of three leprosy clinics on condition that the suggested amendment of the law was made. In 1923 the only known cases were 267 advanced ones in the Manaica Leper Institution. When the three clinics (later increased to 15) were opened and surveys made, so many infective cases were discovered or came forward voluntarily for admission to Manaica that by 1932 747 were in residence. At the end of 15 years' work Dr. Rose recorded that 71.2% of regularly treated cases had had their disease arrested, but only 16.7% of those not submitting to regular treatment showed improvement. In 1941 there were 400 cases in the settlement—a decline of 46% since 1932—and 500 more were attending clinics, out of an estimated total of 1,000 in the colony. As the number of yearly discovered new cases had fallen, Dr. Muir reported that "there is good reason to believe that this decline in notifications is the result of an actual decrease of leprosy in the colony."

Ceylon

In 1921 there were 577 advanced leprosy cases under compulsory segregation. In 1930 our medical secretary, Dr. Cochrane, was consulted by the Government, and on his advice modern methods of control were introduced and the rigid provisions of the 1910 Leprosy Ordinance suspended. During the next two years surveys and propaganda and the establishment of clinics for early cases were carried out and new settlements on modern lines provided. Arrangements were also made for the repeated examination of contacts of all known cases to detect infections from them in an early amenable stage of the disease. By 1939 the known cases had risen to 3,618, 70% of which had been discovered by surveys. The number of isolated infective cases had risen to 1,031, but from 1941 onwards the yearly number of new cases declined and a start had been made in reducing the disease in the island.

Nigeria

Nigeria has the largest number of lepers in our Empire except India, with a high proportion of infective cases, and so presents a very difficult problem, on which the home committee of B.E.L.R.A. has largely concentrated its efforts. After Mr. Oldrieve's visit in 1926 a special leprosy officer was appointed, but the slump caused him to be axed in 1931, when nearly 6,000 cases were already under treatment. In 1926 Dr. Macdonald opened a large settlement at Itu, which in 1943 had some 2,400 inmates. Another, under Dr. Money, was opened in 1936 at Old River, which recently had 1,187 resident cases, and over 13,000 were being treated at a large number of satellite clinics. A third settlement, at Uzuakold under Dr. Davey, recently had 1,255 resident cases and 11,548 being treated at 43 outlying clinics. More important still, in this area a large proportion of the advanced infective cases were voluntarily isolated, with treatment, in 34 leper villages built at the cost of the chiefs. That these measures are already proving effective is shown by the fact that during a third house-to-house survey of 7,000 people of one tribe not a single unisolated advanced case was found; but 40 very early ones were detected, which should nearly all clear up with out-patient treatment. With continued frequent surveys, followed by treatment of all discovered early cases, there should be a rapid decline of the disease in such an area. Sir Bernard Bourdillon, when Governor of Nigeria, visited the Old River and Uzuakold leprosy settlements, and was so struck with the promising results already obtained that he procured a grant of £258,000 from the Colonial Development Fund, spread over five years, to enable the Nigerian Government to take over the work from the medical missionaries in charge and to extend it to other tribes, who were clamouring for similar help. This will allow B.E.L.R.A. to extend its pioneer work to other African colonies, until they too are educated up to taking over the control of leprosy in their territories.

B.E.L.R.A. may therefore fairly claim to have demonstrated the value of the recently introduced methods of treatment and prevention of leprosy under very varying conditions in widely separated portions of the British Empire. The more efficiently and extensively they can be put into operation the more rapid will be the decline in the incidence of the disease during the next two or three decades, imperfect though they may still be.

Need for Further Research on Treatment

It only remains to point out the need for continued research with a view to finding a treatment which will be effective in advanced lepromatous cases of leprosy. The triumphs of chemotherapy in recent years in discovering such potent remedies as the sulphonamides and penicillin encourage the hope of a real cure for leprosy being found before very long. Penicillin has so far shown no promise in this disease, but the intravenous use of the sulphone compounds promin and diasone in leprosy by Americans in Louisiana and by Muir in Trinidad has already yielded improved though still inadequate results

in lepromatous cases. Other such drugs are already available for trial—a slow and difficult operation on account of the long and variable course of the disease. It is hoped shortly to provide for an experienced whole-time research worker, who will have unlimited clinical material: success will greatly facilitate and hasten the eradication of leprosy from our Empire.

THERAPEUTIC ACTION OF DIFFERENT PENICILLINS ON SPIROCHAETA RECURRENTIS INFECTIONS IN MICE

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It is now well established that there are a number of distinct but very similar penicillins, all characterized by a high degree of activity against certain pathogenic bacteria, combined with remarkable freedom from toxic effect on the host. Penicillins I, II, and III of Great Britain are recognized to be the same as penicillins F, G, and X, respectively, of the United States,^{1,2} and still further types have been identified. Preparations normally issued for therapeutic purposes contain a considerably higher proportion of penicillin II than of the other forms; yields from deep vat cultures are said to consist almost entirely of penicillin II, while those obtained from shallow surface cultures in flasks, although mainly comprising penicillin II, generally include moderate but varying proportions of penicillin III.³

Chemically these penicillins all have the same central structure, differing only in a side group,² and they vary somewhat in their selective potency against bacteria. For example, measured in Oxford units, although penicillin III is equally as effective as penicillin II against strains of *Staphylococcus aureus* and *Bacillus subtilis*, it was found to be two to eight times more effective than penicillin II against strains of streptococcus, pneumococcus, meningococcus, and gonococcus *in vitro*.^{4,5} This superiority seemed to be borne out in the treatment of gonorrhoea with penicillin III and II respectively.^{3,4} We refer to this work again below.

Crystalline penicillin II has a potency of about 1,650 units per mg., and crystalline penicillin III about 900 units per mg. Preparations normally issued for parenteral injection in clinical practice have fallen far short of these concentrations, and the Therapeutic Substances Act allows a potency as low as 150 units of undifferentiated penicillin per mg.,⁶ although earlier batches released by British producers contained two to four times this amount. More recently, some batches have been of the order of 1,000 units per mg., and it is expected that this standard of potency will become general.

An important contribution by Dunham and Rake⁷ has suggested that crystalline penicillin II is considerably less effective than partially purified preparations against *Spirochaeta pallida*. They worked with the Nichols strain of rabbit syphilis, and found that the spirochaetes were immobilized *in vitro* much more readily by impure preparations than by crystalline penicillin II; in fact, they were able to remove from the penicillin of partially purified samples a substance capable of immobilizing spirochaetes and resistant to the influence of penicillinase for eleven days at 37° C. Spirochaetes exposed to 1,100 units per ml. of certain partially purified preparations were non-infectious on intratesticular injection in rabbits, while spirochaetes exposed under similar conditions to 8,800 units per ml. of crystalline penicillin II gave rise to a specific orchitis.

In the experiments summarized below we have compared (a) partially purified penicillin as issued for parenteral injection, (b) crystalline penicillin II, and (c) crystalline penicillin III, in respect of their therapeutic action on *Spirochaeta recurrentis* infections in mice. It was trials against such infections (and those of *Spirillum minus*) which had previously led us to suggest that penicillin might be effective against human syphilis,⁸ as was in fact substantiated by Mahoney *et al.*⁹

Present Experiments

Mice were infected with *Spirochaeta recurrentis* by intra-peritoneal inoculation, and were then treated subcutaneously two days later, when wet blood films showed about 1 to 20 parasites per microscope field (oc. 4, obj. 1/6). The preparations of penicillin used were: (a) samples from eight batches of partially purified sodium penicillin of British manufacture, potency varying from 258 to 475 units per mg., as issued for parenteral use clinically, obtained through the Penicillin Clinical Trials Committee of the Medical Research Council; (b) two batches of crystalline sodium penicillin II, each of potency 1,600 units per mg., kindly supplied by Glaxo Laboratories Ltd.; and (c) two small quantities of crystalline sodium penicillin III, potency 680 and 635 units per mg. respectively, also supplied by Glaxo Laboratories. The penicillin preparations were dissolved in normal saline in concentrations such that treatment should be by 0.2 ml. per 20 g. of body weight.

Results and Discussion

Treatment was regarded as effective if the blood was cleared of parasites 24 hours later. The results obtained from individual batches did not differ significantly from one another.

Results of Treating *Spirochaeta recurrentis* Infections in Mice with Different Penicillin Preparations

Oxford Units per 20-g. Mouse, Subcutaneously	Partially Purified Penicillin, as for Clinical Use	Crystalline Penicillin II	Crystalline Penicillin III
2,500	$\left\{ \begin{array}{l} 105 \\ 112 \end{array} \right. (94\%)$	$\left\{ \begin{array}{l} 57 \\ 60 \end{array} \right. (95\%)$	$\left\{ \begin{array}{l} 17 \\ 35 \end{array} \right. (49\%)$
1,000	$\left\{ \begin{array}{l} 51 \\ 91 \end{array} \right. (56\%)$	$\left\{ \begin{array}{l} 12 \\ 23 \end{array} \right. (52\%)$	$\left\{ \begin{array}{l} 1 \\ 33 \end{array} \right. (3\%)$
500	$\left\{ \begin{array}{l} 35 \\ 118 \end{array} \right. (30\%)$	$\left\{ \begin{array}{l} 15 \\ 54 \end{array} \right. (28\%)$	$\left\{ \begin{array}{l} 0 \\ 27 \end{array} \right. (0\%)$
250	$\left\{ \begin{array}{l} 0 \\ 20 \end{array} \right. (0\%)$	$\left\{ \begin{array}{l} 0 \\ 8 \end{array} \right. (0\%)$	$\left\{ \begin{array}{l} 0 \\ 7 \end{array} \right. (0\%)$

The denominator shows the number of mice treated, the numerator the number in which the blood was clear of parasites 24 hours later.

within each of the three categories of penicillin preparations under trial, and aggregate findings for each of these three types of preparation are therefore summarized in the accompanying Table, from which the following arises:

Crystalline Penicillin II.—The partially purified preparations were not found to be more effective than the specimens of crystalline penicillin II, since the proportions of mice which responded to treatment, in these two groups, did not differ significantly at respective dose-levels. This is in line with the findings of Richardson *et al.*,¹⁰ working also with *S. recurrentis* (*Borrelia novyi*) infections in mice, but adopting somewhat different criteria of therapeutic efficacy. They also found no significant differences between the action of crystalline penicillin II and partially purified preparations (about 900 units per mg.—i.e., containing much less impurity than ours).

If Dunham and Rake's conclusions, quoted above, be applicable to human syphilis, the status of penicillin in the treatment of that disease will tend to deteriorate in the future as methods of purification become more and more refined and as batches released for clinical use accordingly become more and more free from impurities. It will then become increasingly necessary to investigate the antispirochaetal properties of by-products in the manufacture of penicillin. If, on the other hand, the results of the experiments here recorded are a reliable index to the position in human syphilis, then the release of penicillin preparations of a higher and higher grade of purity presents no threat to the position of penicillin as a remedy for syphilis.

Crystalline Penicillin III.—This preparation proved to be substantially less effective than the other forms of penicillin tested. Thus, only 49% of 35 mice treated with 2,500 units of penicillin III responded favourably, as compared with 94% of 172 mice treated with the same dose of the other preparations. Applying the formula $\sqrt{(p_1 \times q_1)/n_1 + (p_2 \times q_2)/n_2}$ (see Bradford Hill¹¹), the difference between these proportions (45%) is 5.2 times its standard error (8.6). This means that, other factors being equal, the chances of such a difference arising merely through errors of random sampling are as little as 1 in several millions. The

difference is therefore highly significant statistically, and this is reinforced by the fact that at lower doses—1,000 and 500 units—penicillin III was practically ineffective whilst the other preparations produced a favourable response in a fair proportion of cases.

Again assuming that these results afford an index to the position in human syphilis, certain implications follow. As mentioned above, penicillin III has been found to exercise greater activity than the more easily obtainable penicillin II, or than partially purified preparations, against a number of bacteria, including the gonococcus.^{4,5} It is stated to have the additional advantages of giving rise to higher and more sustained blood levels than these other forms of penicillin, after intramuscular injection of comparable doses.³ If these claims are fully confirmed it is likely that much effort will be directed towards improving methods of production and increasing supplies of penicillin III. While this will favour the campaign against gonorrhoea it will not have the same effect in regard to syphilis.

It will be fortunate if it can be substantiated that, as the present work suggests, the more easily and more copiously produced form of penicillin—i.e., penicillin II—is also the more active against syphilis, since this disease demands such high aggregate dosage—perhaps twenty times or more for the average case of early syphilis than for the average case of uncomplicated gonococcal urethritis.

Summary

Of the various identified forms of penicillin, that known as penicillin II in Great Britain (i.e., penicillin G in U.S.A.) appears in much greater proportion than any of the others, in batches ordinarily prepared for therapeutic use. Reports of other workers have suggested that crystalline samples of this form of penicillin may be less effective against syphilis than partially purified preparations, such as are normally issued for parenteral injection in clinical practice. If this be the case, then the status of penicillin in the treatment of syphilis stands in danger of deteriorating as production methods improve, with consequent release of batches of a higher and higher grade of purity. However, in so far as trials against *Spirochaeta recurrentis* infections in mice may be an index to the situation, the present experiments do not reveal any superiority of partially purified preparations over crystalline penicillin II.

Penicillin III (penicillin X of U.S.A.) is stated to be significantly more active than penicillin II, or than ordinary partially purified preparations of penicillin, against certain strains of streptococcus, pneumococcus, meningococcus, and gonococcus *in vitro*. It is also believed to have given better results than these other forms of penicillin in the treatment of gonorrhoea. The present experiments show, however, that it is substantially less effective than the other forms in the treatment of *Spirochaeta recurrentis* infections in mice.

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The National Association for the Prevention of Tuberculosis has started a new quarterly magazine, *Health Horizon*, for the average reader. This periodical, edited by Dr. Harley Williams, will be by no means confined to tuberculosis. Its emphasis is upon ideas potentially useful in improving the health of the individual; and its aim is to give authoritative information, readably presented, to lay people not only in Great Britain but throughout the Empire, particularly the smaller Colonies. The price is 5s. a year or 1s. 6d. a copy, and it is published by N.A.P.T., Tavistock House, Tavistock Square, London, W.C.1. The April number includes an article by Sir Harold Scott, F.R.S., on "Risks from our Animal Friends"; another on "D.D.T. and Health in the Tropics," by Mr. V. B. Wigglesworth, F.R.S.; and another on "Food Yeast," by Mr. L. D. Galloway. Dr. Douglas Guthrie writes on Arabian medicine; and there are also unsigned articles on paludrine (the new drug for malaria) and on mass miniature radiography.