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 surveyed made, so many infective cases were discovered that it 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 reported new cases halved, Dr. Rose 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 seclusion. In 1930 our medical secretary was succeeded 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, 766 of whom had been treated. The yearly 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 and 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 Uzuakol under Dr. Davye, 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 three house-to-house survey of 7,000 people of one tribe not a single case was discovered; but the cases found were almost entirely 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. Since Bernardourdillon, when Governor of Nigeria, visited the Old River and Uzuakol 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 erect the Nigeria Government leper 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.
Present Experiments

Mice were infected with *Spirochaeta recurrentis* by intra- peritoneal inoculation, and were then treated subcutaneously two days later, with the other forms 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 with 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

<table>
<thead>
<tr>
<th>Oxford Units</th>
<th>Partially Purified Penicillin, as for Clinical Use</th>
<th>Crystalline Penicillin II</th>
<th>Crystalline Penicillin III</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,500</td>
<td>105 (94%)</td>
<td>57 (95%)</td>
<td>17 (95%)</td>
</tr>
<tr>
<td>1,000</td>
<td>51 (95%)</td>
<td>60 (95%)</td>
<td>35 (95%)</td>
</tr>
<tr>
<td>500</td>
<td>35 (93%)</td>
<td>23 (92%)</td>
<td>33 (92%)</td>
</tr>
<tr>
<td>250</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

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., 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, are 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 antisyphilitic 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 penicillins 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 \( V(p \times q)/n + (p \times q)/n \) (see Bradford Hill*), 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 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.

When 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. It is stated that this additional advantages of giving rise to higher and more sustained blood levels than these other forms of penicillin, after intraperitoneal injection of the doses. 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 gonorrhea 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 to be much more effective than the other, in batches ordinarily prepared for therapeutic use. Reports of other workers have suggested that crystalline samples of this form of penicillin may be more effective against syphilitic infections, such as are normally used 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 in 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 pneumoniae, meningococcus, and gonococcus in vitro. It is also believed to have given better results than these other forms of penicillin in maintenance and eradication of infection in animals. However, however, that it is substantially less effective than the other forms in the treatment of *Spirochaeta recurrentis* infections in mice.

References

1 Recommendations of the International Conference on Penicillin, Science, 1945, 101, 42.

The National Association for the Prevention of Tuberculosis has started a new quarterly magazine, *Health Horizon*, for the average reader. It is put out by the British Tuberculosis Association, of which D. Harley Wildy will be president. It will be aimed at keeping the public informed of developments in 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, R.C.S., on "The fight from My Young Friends;" another on "D.D.T. and the 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 miniaturization.