favourable evidence must also be obtained from studies of toxicity, absorption, and distribution and actual therapeutic effect in animals. These matters are outside the scope of the present work, but in fact some such evidence has been obtained for all of these antibiotics, and indeed several of them have been used clinically.

It is a matter for much regret that those two whose discovery was made by independent investigators in this country should appear to be unpromising. Cephalosporin P suffers from the defect that resistance to it is rapidly acquired, especially in a dense bacterial population: the results of a test of bactericidal action with a large inoculum show that this change can make considerable progress overnight. Ritchie *et al.* (1951) did not observe increased resistance *in vivo*, although therapeutic effect was poor: this point perhaps deserves to be further explored. Micrococcin P suffers from the same defect to perhaps an even greater degree, and has the further disadvantage of very low solubility, which would render administration difficult. It was on these two grounds that micrococcin, to which micrococcin P is very closely related, was decided some years ago to be therapeutically unpromising (Florey, 1956). By far the least potentially useful of all those studied is albomycin, and the present findings seem irreconcilable, so far as antistaphylococcal action is concerned, with the claims of Gause (1955). Many strains were initially highly resistant to it, and those which were not became so with unexampled rapidity.

Of those in the erythromycin group, spiramycin has the disadvantage of lesser activity, both bacteriostatic and bactericidal. Whether it possesses any countervailing advantage of a kind outside the scope of these studies remains to be seen. The only infection in which there is adequate evidence of its therapeutic usefulness is pneumonia, and the pneumococcus is more sensitive to it than any other organism. Antibiotic E129, and Factor B derived from it, are in a different category. They greatly exceed spiramycin and approach erythromycin in activity, and resistance to them is much more slowly acquired; moreover, strains resistant to erythromycin remain relatively sensitive to them. This is a property which could be of much consequence in therapeutic use.

Novobiocin possesses a high degree of *in vitro* activity: resistance to it develops slowly but reaches a high level. Whether the very high concentrations attained by this antibiotic in the blood and tissues will prevent such a change *in vivo* has yet to be seen. Vancomycin has about one-eighth of the bacteriostatic activity of novobiocin, but is more rapidly bactericidal in the higher concentration used for that test, and has the unique advantage that resistance to it of such a degree as to preclude therapeutic effect apparently cannot develop in staphylococci at all.

Summary

The following antibiotics have been examined for antistaphylococcal activity by several *in vitro* methods, a few tests being also done with other organisms: (1) erythromycin, (2) spiramycin, (3) antibiotic E129 and Factor B derived from it, (4) cephalosporin P₁, (5) micrococcin P, (6) albomycin, (7) novobiocin, (8) vancomycin. Their approximate order of merit for antistaphylococcal activity is:

Bacteriostatic action—5, 1, 7, 3, 4, 8, 2, 6.

Bactericidal action—8, 3, 1, 7, 2 (4, 5, 6 not bactericidal under conditions of test).

Degree of bacterial resistance developed—8, 3, 2, 7, 1 (4, 5, 6 limits not reached).

Cross-resistance studies show a relationship between erythromycin, spiramycin, and E129; otherwise there is no relationship between these antibiotics, or between them and penicillin, streptomycin, chloramphenicol, or tetracycline.

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LEPROSY: A CHANGING SITUATION IN EASTERN NIGERIA

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From the Nigeria Leprosy Service

Little is known of the extent of leprosy in Nigeria before 1920. Leprosy patients in a few of the main townships had made themselves evident enough to provoke the Leprosy Ordinance in 1917, but this did not relate at all to the wide rural areas where most of the people live, and did not even refer to Eastern Nigeria, then a little-known region of forest and savanna only recently brought under effective British administration.

During the next two decades extremely rapid development took place in this region. Literally hundreds of roads were built, and for the first time in history people began to move about freely. As the size of the population became evident, so did the extent and variety of the tropical diseases which abounded, and by 1930 sufficient evidence had accumulated to enable Mayer (1930) to produce a map of the country indicating the prevalence of leprosy. Interest and concern had been aroused by the appearance in newly developing townships of leprosy patients in significant numbers, and also by the opening of the Church of Scotland Leprosy Colony at Itu in 1927, where in a short time several hundred patients had been admitted.

Prevalence of Leprosy

The 1930's witnessed the rapid build-up of evidence that the incidence of leprosy in Eastern Nigeria was not only generally high but in some localities phenomenal. At new settlements at Uzuakoli and Oji River experience at Itu was repeated, and far more patients sought admission than could be accommodated. In 1937 detailed information about specific localities began to be available. In that year a survey of the Abua clan by one of us (T. F. D.) revealed

492 patients with active leprosy among a population of 14,515 (34 per 1,000). That one small group, and one unusually health-conscious, could have so high an incidence was as surprising as it was disconcerting. This survey was quickly followed by many others, and, although lower figures were sometimes recorded, in a number of instances the incidence was far higher, figures of 50, 100, and even 150 per 1,000 being recorded. By 1942 it was evident that a formidable amount of leprosy existed in the region. By then the vigorous efforts of missionary societies were evolving methods of leprosy control which aroused Government interest, and led directly to the creation in 1945 of the Nigeria Leprosy Service, which has cared for many thousands of patients and undertaken very intense and extensive leprosy control measures.

Unusual Features of the Disease

Leprosy in Eastern Nigeria, especially as encountered on surveys between 1937 and 1948, has certain unusual features. In comparison with its manifestations in some other parts of the world, it is a relatively mild disease. The patient with mutilations and serious complications is generally rare. Even though severe and moderately severe infections have been more than sufficient to fill settlements to capacity, they represent only a minority of the total. Often more than 50% of patients in a locality have shown only one or very few lesions, which involve little physical discomfort and no disability.

The relative distribution of the various types of the disease is also of interest. Frank lepromatous cases rarely represent more than 10% of the total. The proportion is often smaller. The more flamboyant forms of tuberculoid leprosy are also uncommon, the bulk of infections consisting of tuberculoid leprosy of low intensity, and a smaller but considerable group of indeterminate character.

Furthermore, the disease is not particularly selective where sex and age are concerned. There is often little difference in incidence between the sexes. Infection is not by any means confined to childhood and youth; indeed, the frequency of apparently recent infections in the later age groups has attracted the attention of those familiar with leprosy elsewhere (Lowe and Smith, 1949).

Finally, the generally good response to treatment is also noteworthy. It was apparent before the days of sulphone therapy.

Decline in Leprosy Incidence

These features of the disease are interesting pointers to its natural history in Nigeria. They become even more interesting in the light of events during recent years. From 1948 onwards evidence began to appear that in some heavily infected localities the incidence of leprosy was declining. The following are two examples of this.

Ndi Oji Abam, Owerri Province

At one isolated group of villages (Ndi Oji Abam, Owerri Province) a careful survey early in 1941 brought to light 369 cases of active leprosy in a population of 3,057, an incidence of 121 per 1,000. Excessive though it was, this amount of leprosy represented by no means the whole story. In addition to those who showed unmistakable signs of active disease there were others who displayed suspicious but uncertain lesions, and yet another group who presented scars and ulcers from the application of caustics to what they themselves regarded as leprosy lesions. The people here were extremely co-operative, and it proved possible to maintain a relatively close watch on events after the survey. During subsequent years new cases of active leprosy among the resident population became evident, as follows:

1941	..	..	37	1946	..	12	1951	..	..	9
1942	..	..	45	1947	..	20	1952	..	..	8
1943	..	..	71	1948	..	13	1953	..	..	10
1944	..	..	19	1949	..	16	1954	..	..	8
1945	..	..	26	1950	..	5				

In a few instances these cases were discovered by the examination of contacts, but most came forward for treat-

ment on their own initiative, presenting extremely early lesions. The high degree of co-operation given by the people is attested by two further intensive surveys, undertaken in 1947 and 1955. The former of these brought to light only 18 persons who had developed leprosy since 1941 and had not bothered to seek treatment on their own. In all cases the infection was slight. They are included in the figures for 1946 and 1947. The most recent survey, in January, 1955, revealed only 8 cases previously unknown. Four are included in the total for 1954.

Thus the stream of new infections evident between 1941 and 1943 then began to decline and had become a trickle by 1950, since when it has remained at low level. As a result of this and the symptom-free discharge from treatment of many patients, the amount of active leprosy in this area has declined enormously—522 cases at the end of 1943 comparing with 216 in 1947 and 49 at the end of 1954, a fall of over 90%.

Bende Clan, Owerri Province

This is a very different area from Ndi Oji Abam, although they are separated by less than 20 miles. It was the first administrative centre of British rule in the area, and has had flourishing contacts with surrounding clans for over half a century. The people are mainly traders and so are often away from home, sometimes travelling long distances. They also have a relatively high standard of living.

Survey work in such an area is necessarily less certain than in an isolated community, but in two surveys, in 1943 and 1951, a high level of accuracy was in fact achieved. During this period, in a population of 3,500, the incidence of leprosy declined from 31 to 5 per 1,000. In the second survey only three previously unknown cases were found. It was possible to transfer the three remaining lepromatous cases to the central settlement. In this clan leprosy has almost completely died out in a period of ten years.

These are examples of a process that has in fact been going on in many areas to a greater or less degree, and during the past six years a mass of evidence has accumulated of a decline in the incidence of the disease that is widespread and is gaining in momentum each year. Its scale is indicated by the fact that, whereas in the three provinces of Onitsha, Owerri, and Rivers 30,630 patients with active leprosy were taking treatment in December, 1948, by the end of 1954 the number had dropped to 14,770, a decline of over 50%.

Causes of the Decline

In the community, as in the individual, leprosy usually takes a very chronic course, and with one exception, to which reference is made later, the few examples of a decline in the disease have taken decades to develop. A decline in incidence on the scale now apparent in Eastern Nigeria, occurring in so short a period, is a most unusual phenomenon. When one comes to examine the influences that may be responsible, it becomes evident that several are at work, and that they are operating in a most complex manner, so that what has probably been decisive at one time and place does not apply at another. The subject is a very large one, and it is possible here to examine very briefly only a few of its main features.

Has There Been a Leprosy Epidemic?

The rather curious association of a very high incidence, an essentially mild disease, and a rapid decline over a short period of years has been reported before—namely, in the case of the epidemic of leprosy in the island of Nauru in the early years of this century (Bray, 1930). The question immediately arises whether what has been witnessed in Eastern Nigeria is a similar outbreak, but on a far larger scale, and in particular whether the very high incidence recorded around 1940 was the result of an epidemic that had developed during the preceding 20 to 30 years and was then not far from its peak. However reluctant one may be to accept such a hypothesis, there is a great deal of evidence in favour of it.

1. Conditions were extremely favourable for a leprosy epidemic to develop. It is well known that leprosy is most likely to spread not among entirely primitive communities but among communities in which the social and economic changes of civilization have begun to operate. Even as recently as the early years of this century, each of the multitudes of villages in the Region was very much an isolated unit, with neighbouring villages probably hostile. Travel was not to be undertaken lightly. There was no central African authority, and, although leprosy was known and was often dealt with ruthlessly, in some places there was greater laxity. Then with bewildering rapidity the country was opened up. The fear of travel disappeared. Education spread rapidly, but hygiene and standards of living lagged far behind, especially during the years of depression in the 1930's. It is impossible to imagine a situation more likely to encourage the spread of leprosy.

2. The people are themselves of the opinion that leprosy did spread very greatly during this period. Personal opinion is of course highly unreliable as evidence, but in this case it does deserve some respect, for the Ibo is a very efficient diagnostician where leprosy is concerned, and, as generally very little clothing was worn during the years concerned, there was ample opportunity to observe the disease.

3. The relative rarity of the patient bearing the stigmata of a long-standing infection calls for explanation. Either many patients died before this stage was reached or the disease was formerly much less common.

4. It is customary to gauge the activity of leprosy in a community by its incidence among children as compared with that among adults. This simple and obvious method is reliable enough when conditions affecting the immunological status of the community are relatively stable, but it breaks down under unstable epidemic conditions. Here in parts of Eastern Nigeria leprosy is very common both in children and in adults, and the frequency of the unstable indeterminate and borderline varieties of leprosy among the higher age groups is particularly suggestive. It is what one would expect in the earlier stages of an epidemic with all age groups susceptible.

Taken together, these strands of evidence are weighty, and receive added strength from experience during the past 10 years. If an epidemic of leprosy did develop in many areas during the third and fourth decades of this century, it is not to be expected that the excessive incidence found in a number of surveys could in fact continue at that level. Some decline would be expected with the development of resistance to *Mycobacterium leprae* in the population, and would be accompanied by an increasing tendency for the disease to exhibit the tuberculoid form, with a corresponding decrease in the indeterminate group. A total decline with a relative increase in tuberculoid leprosy has been noted in certain areas.

Even if it is true that an acute epidemic of leprosy has appeared in parts of Eastern Nigeria, its inevitable decline offers only a partial and very inadequate explanation for the observed facts. Leprosy may decline naturally, but in this case the process has undoubtedly been hastened by other influences.

Influence of Tuberculosis

Lowe, working in Eastern Nigeria, drew attention to the immunological relationship between leprosy and tuberculosis (Lowe and McNulty, 1953). There seems to be little doubt that tuberculosis is also a factor in the situation. The opening up of the country which facilitated the spread of leprosy also encouraged the spread of tuberculosis inland from coastal areas. It is significant that the areas of highest leprosy incidence have never been found in close relationship to ports and townships on the main routes of communication. Tuberculosis of the lungs is still a relatively uncommon disease in many rural areas, but its spread, followed by the development of allergy to tuberculin, has probably influenced the natural course of leprosy through the production of a concomitant allergy to lepromin in a proportion of those infected. It is very difficult to

assess the importance of tuberculosis as a factor in the general decline of leprosy. A positive reaction to tuberculin is often found in leprosy patients who are negative to lepromin. Pseudo-reactions to tuberculin are not uncommon. It has even been suggested that *M. leprae* may be one of the agents responsible for them (Lowe, 1955). The impression remains that, even if tuberculosis is having a limiting effect on leprosy in and around ports and townships, its effects in remoter rural areas are not yet sufficient to have contributed much to the decline of leprosy already observed in such areas.

Improved Living Conditions

Another, and very welcome, factor in the situation is the considerable rise in the standard of living of the people, which began towards the end of the war and has steadily gained in impetus. Far more clothing is worn and opportunities for contact are thereby lessened. Standards of housing have improved, sometimes greatly, though it may be doubted whether this is as yet sufficient to have had any significant influence. Of greater importance is the advance in child health that has undoubtedly occurred, and the spread of medical facilities, which have reduced the incidence of diseases causing abrasion of the skin—for example, yaws and scabies. Opportunities for the spread of *M. leprae* by contact are certainly fewer than they were, and the healthier population is better able to withstand infections of all kinds.

Influence of Leprosy Control Measures

Finally, it is necessary to consider the influence of leprosy control measures on the natural course of the disease. In doing so it is first worthy of note that in many localities there was no need to stimulate an awareness of the infectivity of leprosy. This already existed, enshrined in taboos relating to contact with patients and demonstrated in efforts to expel patients from the community and, in one or two instances, in the provision of segregation villages for them. The original requests for leprosy surveys came because these efforts had broken down and the disease had got out of hand. Although in some places prejudice against leprosy was so strong that the very idea of doing anything to help patients was abhorrent, this did not apply in areas of very high incidence, and here it was not difficult to establish treatment centres and local segregation villages and organize preventive work, often at negligible cost and with the co-operation of the entire community, both patients and non-patients. The fact that the entire community often participated needs to be stressed. Once started, the idea of local anti-leprosy schemes spread, and between 1938 and 1943 many centres were established, which have continued up to the present, their number growing each year, and together dealing with many thousands of patients. The effect of all this effort may be reviewed from the two standpoints of treatment and isolation.

In Eastern Nigeria leprosy has been particularly amenable to treatment, and good results were achieved with hydnocarpus oil during the years when it was the mainstay of treatment. The resolution of tuberculoid lesions was generally hastened, and large numbers of patients with this type of leprosy were discharged in an inactive condition. On lepromatous cases its effect was very much slower, and, although some did gradually resolve, in other cases it succeeded in doing little more than keep the patient alive. Judged by its action on the two stable forms of the disease, it may be concluded that hydnocarpus oil had very little effect on the spread of leprosy, for the non-infective tuberculoid cases resolved and the infective lepromatous cases continued to stay infective for a long time. Where, however, patients displaying the unstable indeterminate varieties of leprosy are concerned its action may very well have been of importance. It is thought by many workers that these varieties of leprosy play an important part in the evolution of lepromatous leprosy (Lowe and Chatterji, 1941). In Nigeria our experience has been similar. In such patients the virtue of hydnocarpus oil was evident, for, once under

treatment, they rarely degenerated into the lepromatous type of the disease. Through its action on such patients in particular, hydnocarpus oil must have contributed to the decline of leprosy.

The virtue of the isolation of open cases is self-evident. Over the past 20 years several thousands of these have been isolated at settlements in Eastern Nigeria, and this must inevitably have had its effect on the disease. In addition, particularly in Owerri and Rivers Provinces, during the past 15 years approximately 10,000 patients have been isolated for longer or shorter periods in local segregation villages, this number including most of the known cases likely to be infective in the localities concerned. Even though this group of patients enjoyed considerable freedom, and visits home were sometimes frequent, they were for a considerable part of their time removed from the compounds where they formerly lived, and many opportunities for infecting others were thereby prevented. The virtue of the system as an anti-leprosy measure was commented on by Cochrane (1953). There seems to be no doubt about its importance.

Since 1949 the most important leprosy control measure of all has come into play with the general adoption of sulphone treatment. This area provided the first large-scale experiment in the use of oral 4:4'-diaminodiphenylsulphone (D.D.S.) in the field, initiated by the enterprise of Drs. Lowe and Bland. In Onitsha Province it has been reported on by Garrett (1951) and Garrett and Corcos (1952). Since 1951 oral D.D.S. has been the standard treatment for leprosy at all centres, and its effects are now manifest. The long-standing lepromatous cases whose infection lingered on under hydnocarpus treatment are for the most part now discharged. Treatment is extremely popular, attracting patients at an earlier stage of the disease than ever before. Early lepromatous cases speedily become bacteriologically negative. The general public is increasingly leprosy-conscious, and prejudice in localities long resistant to local leprosy control measures has finally succumbed. Relapses hitherto have been unimportant, and there have been no grounds for losing the confident outlook that sulphone treatment engendered. Here, then, is a potent anti-leprosy weapon rendered especially powerful because, thanks to an existing organization, it proved possible to apply it at many centres simultaneously.

The only clue to the relative importance of the four influences antagonistic to leprosy, which have been discussed briefly here, lies in the speed with which change has occurred. Circumstances are unusual, but it is extremely unlikely that natural regression of the disease, the spread of tuberculosis, or a rising standard of living can, either singly or collectively, have produced such profound effects in the space of seven years. They have doubtless played their part, but there seems to be little room for doubt that intense and widespread leprosy control work has been of great importance, that the effort of many devoted leprosy workers has borne fruit, and that the cost of the Leprosy Service to the British taxpayer through the Colonial Development Fund has entirely justified itself.

Summary

Leprosy is a disease of major importance in Eastern Nigeria, where it has a number of unusual features: (a) its incidence as encountered in surveys between 1937 and 1948 was generally high, sometimes phenomenally so; (b) its character is usually mild; (c) highly infective lepromatous cases form only a small minority of total infections, and indeterminate cases are common; (d) the disease affects all age groups; and (e) since 1948 signs of a decline in incidence have steadily increased, and a large-scale reduction in the disease is now evident.

The facts suggest that an epidemic of the disease has occurred which is now waning. In its decline the influence of tuberculosis, improved living conditions,

and leprosy-control measures is probable, and the relative importance of these factors antagonistic to the disease is briefly discussed.

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LETTERER-SIWE SYNDROME IN ADULTS

REPORT OF TWO CASES

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Descriptions, from both clinical and pathological aspects, of the commoner lymphatic node tumours are abundant, and their recognition now presents no great difficulty. It is amongst the rarer members of this group of tumours that the greatest difficulty in accurate diagnosis is often encountered. Robb-Smith (1938) has attempted the task of clarifying a most confused group of conditions, and it seems desirable that cases of the rarer types of lymphoid tumours should be recorded, not merely because of their rarity, but in order that the adequate study of such cases may eventually make their clinical and pathological recognition easier.

The cases described below are of the rare Letterer-Siwe syndrome in adult life: they showed several of the clinical features described by Robb-Smith in this condition, with other features not hitherto recorded. The presenting symptoms in each case consisted of a severe macrocytic anaemia with steatorrhea.

Case 1

The patient, a married woman aged 39, was admitted to hospital in January, 1947, for the investigation of a severe anaemia with nausea, anorexia, and rapid loss of weight. A short bout of diarrhoea lasting a few days had occurred

CHART I.—Case 1.