the endemic areas of Bengal and Orissa; but even in these the incidence was less than in 1945. In the remaining seven provinces the incidence was very low, and in the Madras Presidency the 753 deaths were the lowest recorded for 65 years. This was no doubt due to previous good north-east monsoon rains in the last quarter of 1945; for in 1943 no fewer than 117,039 cholera deaths in this province followed "failure of the monsoon rain and consequent water scarcity, coupled with extreme inadequacy of protected water."

It is also recorded in this report that "in some provinces compulsory inoculation was enforced in gatherings in connexion with fairs and festivals, and thus the usual outbreak of the disease was avoided. . . . The practicability and advisability of enforcing inoculations in big gatherings, which are known to cause epidemics, should be the rule rather than the exception." This important finding is confirmed by very similar statements with regard to other provinces with any material prevalence of cholera.

A word of caution is, however, necessary, for in my paper of 1944 I included a table to show the average number of cholera deaths per 1,000 for all India, and for each province, for six decades from 1880 to 1939, together with the data for every year with rates, above and below the average for each decade, in relation to high or low previous monsoon rains and the incidence of the dangerous 12-yearly specially large fairs at Allahabad and Hardwar. These data so clearly illustrate the influence of deficient antecedent monsoon rains in increasing, and of good such rains in decreasing, cholera incidence, that the exceptionally low rates in nearly all the non-endemic areas of India in 1946 must have been mainly due to very favourable preceding rains having provided exceptionally good drinking-water supplies over a large proportion of India. On the other hand, it is of interest to note that in the case of the Samaria Ghat fair in Bihar (which was an unexpected one recurring at long and irregular intervals) neither the usual sanitary precautions nor anti-cholera inoculations were carried out, with the result that a smart outbreak of cholera followed this fair only.

A Sheet-anchor of Defence

A great increase in the yearly total anti-cholera inoculations in India, with the widespread adoption of compulsory inoculation of pilgrims, may be illustrated by the following data. In 1928–33 the average total anti-cholera inoculations in India numbered 2,700,000, and in 1934 they averaged 6,649,000 (Rogers, 1944). On the other hand, in 1946, when the inoculation of pilgrims was in general use, the total figure for eight provinces for which they were recorded (some new provinces having in the meantime been organized) was 19,858,000. But the data of three provinces, containing over one-sixth of the total population, are not given in the report, and if they had a similar proportion (in two of them either "extensive" or "mass inoculations" are mentioned) the yearly total must have amounted to 24,000,000.

Further, on the efficacy of the vaccines used the 1946 report recorded that an evaluation of anti-cholera inoculation by a director of public health, Madras, and a supplementary statistical analysis by the professor of statistics at the All-India Institute of Hygiene and Public Health, Calcutta, concluded that "anti-cholera inoculation affords a significant degree of protection against cholera."

Once more, the 1949 Madras State Health Report states that "anti-cholera inoculations had to be resorted to as *the sheet-anchor* in the defence against cholera, as the environmental hygiene conditions of the villages were far from satisfactory. About 4,600,000 anti-cholera inoculations were performed during the year." It is satisfactory to note that the Cauvery delta main endemic area of Southern Madras has been chosen by the World Health Organization for the implementation of a cholera eradication demonstration, so a well-controlled trial of anti-cholera inoculations should soon be forthcoming (Report on Health Conditions in Madras, 1949).

Conclusion

The ultimate control of outbreaks of cholera in rural India is likely to be obtained only by the gradual extension throughout the million or so of unhygienic villages of India, inhabited by 85% of the total population, of the provision of adequate supplies of safe drinking-water—such as have in the last two or three decades materially reduced the incidence of cholera in the much smaller urban population. As this will require several decades at least, in the meantime the increasingly successful adoption of inoculation of pilgrims all over India appears to be the most effective method of controlling cholera outbreaks under present conditions in India, and, if political conditions allow, also in the other great endemic cholera centre, China.

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THE CHEMOTHERAPY OF LEPROSY*

BY

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As leprosy is one of the oldest diseases known to mankind, and because in its more advanced stages it causes mutilations and deformities, it has had a special place in history. The person suffering from leprosy has all too often been under a stigma, and been ostracized from the community. It is hoped, however, that, as a result of a more enlightened attitude, sufferers will no longer be branded as "lepers"—the word "leper" has by international consent been banned from scientific usage—but be accepted in society as victims of disease in the same way as sufferers from tuberculosis are to-day.

Historical

The story of the treatment of leprosy is one of absorbing interest, but in view of the modern advances in the chemotherapy only passing mention can be made to previous history.

Up to the time of the discovery of the more active therapeutic remedies the sheet anchor of treatment was hydnocarpus (chaulmoogra) oil. This traditional Indian remedy—known to indigenous physicians for many centuries—has had a chequered career. Because of the difficulty of giving the oil by mouth it became largely discarded until the pioneer work of Mercado (1914) and of Heiser (1914) in the Philippine Islands, and of Rogers (1921) and Muir (1922) in India, re-established its claim as an effective remedy for leprosy. For the sake of historical accuracy Dr. Mercado must be given due credit, for his work is apt to be forgotten. While many authorities were sceptical whether hydnocarpus (chaulmoogra) oil had any specific effect, it is of significance to note that in the long history of leprosy therapy, until the discovery of the sulphones, this ancient Eastern remedy retained its place as the most reliable treatment for that disease.

*Read in the Section of Tropical Medicine at the Joint Annual Meeting of the British Medical Association and Irish Medical Association, Dublin, 1952.

There is little point in discussing the mode of action of chaulmoogra oil. Rogers believed that the active principle was contained in the higher-melting-point fatty acids. Be that as it may, in the hands of those who were prepared to give massive doses (15–20 ml. a week) by the subcutaneous and intradermal route, the results in the early lepromatous cases, particularly in those races which responded better to treatment (Indians and Africans), were not unsatisfactory. Unfortunately, however, the relapse rate was high, and it had to be admitted that over a 6- to 12-year period most lepromatous patients relapsed and died or the disease became arrested, with severe and crippling deformity

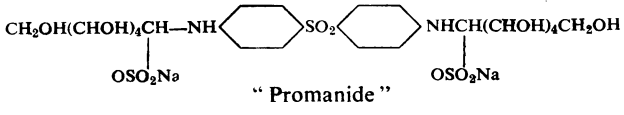
In 1935 Domagk demonstrated that sulphonamides had a chemotherapeutic activity against pathogenic cocci. These drugs were given extensive trials in diseases other than the acute "coccal" infections, and so far as tuberculosis was concerned were found to be inactive, and therefore were not seriously considered in the treatment of leprosy. It is interesting to note that in 1936 a trial of sulphapyridine was undertaken in South India (Cochrane, 1947). The general conclusions of this trial may be of interest. They were as follows: (*a*) The remedy is apt to produce acute lepra reaction, and in some cases this is exceptionally severe. (*b*) There is no evidence that the patient's leprosy condition is benefited by sulphapyridine. (*c*) There seems to be a greater tendency for nausea, alterations in pulse rate, and drug dermatitis to occur in leprosy patients than in persons suffering from other diseases. (*d*) The sulphonamide preparations in the form of pastes have a decided place in the treatment of certain types of trophic ulcers. (*e*) The sulphonamides seem to have no influence on leprosy and should not be used unless there are specific indications for their use.

As the original trial was undertaken with sulphapyridine, it cannot be said that the less toxic sulphonamides may not be more effective, but because of the development of the sulphone group of drugs it would probably be uneconomical to reinvestigate the activity of the more complex sulphonamides.

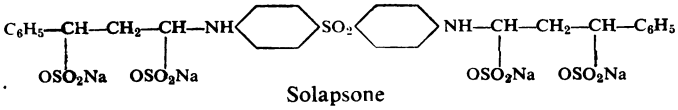
The Sulphones

When the sulphonamides were rejected in the therapy of leprosy, workers turned their attention to a substance which was synthesized by Fromm and Wittmann (1908)—namely, diaminodiphenyl sulphone (D.D.S.). While D.D.S. was found effective against *Mycobacterium tuberculosis*, experimentally it was discarded because of its relatively high toxicity, and, further, the advent of more powerful antituberculosis drugs—for example, streptomycin and *para*-aminosalicylic acid (P.A.S.)—rendered D.D.S. of little value in the treatment of this disease.

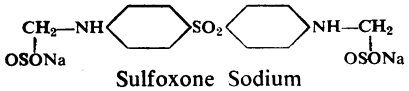
The next step in the chemotherapy of leprosy was the synthesis of three derivatives of the parent substance—namely, "promanide" (1935; "promin" in U.S.A.), solapsone ("sulphetrone") (1936), and sulfoxone sodium ("diasone") (1938). The structural formulae of these compounds are as follows:



"Promanide"

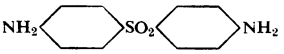


Solapsone



Sulfoxone Sodium

It will be seen that all these substances are disubstituted derivatives of the parent substance, diaminodiphenyl sulphone, the formula of which is

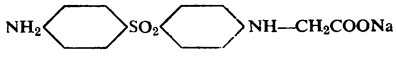


In other words, in the disubstituted sulphones both the amino groups have been blocked. As a result of further work, particularly by Francis and Spinks (1950), Lowe and Smith (1949), Floch and Destombes (1949), and Lowe (1952), evidence was brought forward to show that, orally, these disubstituted sulphones were hydrolysed by the acids in the stomach to the parent sulphone, and therefore it was argued that it was illogical to give disubstituted sulphones when they merely acted as D.D.S. by breakdown in the gut to the parent substance. It was contended that the toxicity of the parent substance could be overcome by giving it in much smaller dosages.

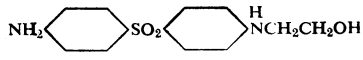
Monosubstituted Sulphones

It has, however, been suggested by Payne (1951, personal communication) that the monosubstituted sulphones are active. If this conclusion is correct we have now to discuss three other points: (1) the evidence that monosubstituted sulphones are active in themselves; (2) the evidence that certain disubstituted sulphones—for example, solapsone—when given parenterally, are broken down to the monosubstituted form; and (3) the chemical changes which the parent sulphone undergoes when it is given orally or parenterally.

With regard to the first point, very limited work has been done on the monosubstituted sulphones. These are difficult to make and tend to be unstable. In our trial of fairly numerous derivatives of D.D.S. we have undertaken limited experiments with two substances which, according to their chemical structure, appear to be monosubstituted derivatives of D.D.S. These are as follows:



Sulphone cilag



Hydroxyethylsulphone

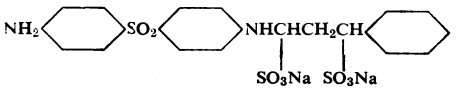
Because the quantities of these drugs which we received were limited, and because of the closure of the Research Unit in South India, our general conclusions have to be tentative. Both these monosubstituted compounds were found to have some activity in leprosy. The activity of hydroxyethylsulphone appeared to be less than that of sulphone cilag, but the latter had an activity apparently as effective as the parent sulphone.

With regard to side-reactions, sulphone cilag produced lepra reaction (erythema nodosum phenomena) in a significant number of patients (38%), and in 38% of cases there was some depression of the haemoglobin value. Apart from one case of mild jaundice, there was no evidence that sulphone cilag showed other signs of toxicity—for example, hepatic damage, dermatitis, or effects on the central nervous system (psychosis). With regard to hydroxyethylsulphone, there was a higher percentage of cases showing signs of hepatic damage (two with enlarged liver—one accompanied by jaundice—and two with urobilin in the urine). In three cases the haemoglobin level was slightly depressed. The total number of cases, however, was only seven.

Biochemistry of Solapsone

Secondly, much work has recently been done on the biochemistry of solapsone, and it is generally admitted that solapsone parenterally is not significantly broken down to the parent sulphone. Lowe contends that as disubstituted sulphones are inactive,

the action of solapsone is due to the D.D.S. being present as an impurity in sufficient quantities to act in a therapeutic dose. We have recently had several samples of a 50% aqueous solution of solapsone analysed, and have found less than 12 mg. of the parent sulphone per gramme of the solution. The parent sulphone, therefore, either as a breakdown product through autoclaving or as an impurity, is present in such small quantities that it cannot be therapeutically active, for it is hardly likely that as small a dose as 24–36 mg. a week is clinically effective. Recent work shows that not only does solapsone contain a monosubstituted derivative of D.D.S., but it dissociates to form this monosubstituted compound. It apparently does not, in fact, break down in any appreciable quantity to D.D.S. when given parenterally. The probable formula of this substance is as follows:



It is therefore seen that this substance is a monosubstituted derivative, and this may explain the effectiveness and lack of toxicity of solapsone when administered parenterally. It must therefore be concluded that there is, up to now, no valid evidence to assume that solapsone in a 50% solution—the more diluted solutions are unstable—contains enough of D.D.S. to explain its activity in terms of the parent sulphone.

Chemical Changes

We now turn to our third point—How is the parent sulphone disposed of in the body? Several workers have shown that D.D.S. is excreted partly as a water-soluble derivative, and a recent interesting and informative article by Lowe indicates that when given parenterally as much as 80% is excreted in this form in the urine. According to Bushby and Woiwod (unpublished) it is a monosubstituted derivative. Thus D.D.S. in the body is converted into one of the monosubstituted derivatives, but where this conversion takes place is surmise, though it is suggested that D.D.S. may be detoxicated in the liver.

If one examines the urine of patients on D.D.S. in a proportion of cases urobilin can be demonstrated in the urine; the percentage of persons showing this depends partly on the dosage and partly on the individual. For instance, in areas where there is a relatively high lepromatous rate (30–50% of the total cases of leprosy) there seem to be a number of cases showing urobilin in the urine (3–5% on the bi-weekly dosage of 300–400 mg.). This means constant but mild hepatic damage. One has to admit that in order to treat effectively a disease of such chronicity as leprosy there will always be cases which will show signs of toxicity to so powerful a drug as D.D.S. Those who advocate the use of the parent sulphone state that this is a price worth paying. Nevertheless, if it is confirmed that the monosubstituted compounds are active in leprosy, and that the body detoxicates the relatively poisonous parent substance by conversion to a monosubstituted derivative, then the argument that it is more logical to give the parent substance cannot be maintained.

Other Chemotherapeutic Agents Used in Leprosy

Of these substances the thiosemicarbazones have had the widest trial. Unfortunately the original claims of Ryrie (1950) that they are as effective as the sulphones have not been substantiated. It, however, has been shown that thiosemicarbazone has some activity in leprosy, and where there is intolerance to the sulphones thiosemicarbazone can be substituted. In other words, this group of drugs should be looked upon as a second line of attack. So far as is known, the thiosemicarbazones have two drawbacks: (1) the drug has to be given by the oral route daily; and (2) it is not free from toxic signs. Lowe (1952) recently has had three cases of agranulocytosis.

Both P.A.S. and streptomycin have been used in leprosy. These drugs show some activity against the *Mycobacterium leprae*, but it is much less than that of the sulphones, and the long duration of treatment (two to five years) would preclude their use, both on the score that such prolonged treatment would not be practicable, and because streptomycin could not be continued for so long a period without toxic signs.

The discovery of the anti-tuberculosis action of *iso*nicotinic acid hydrazide has raised hopes that this may be effective in leprosy. While it is reasonable to assume that if a drug is effective either *in vitro* or *in vivo* against *M. tuberculosis* it may also be an effective therapeutic agent in leprosy, this assumption may not be correct. Streptomycin and P.A.S. are excellent drugs for the treatment of tuberculosis, but of much less value in leprosy. The sulphones are the most potent anti-leprosy drugs we have at present, but they have a very limited place in the treatment of tuberculosis.

Criteria of Cure

The question now arises regarding the criteria of an effective therapeutic remedy in leprosy. Recent histopathological investigation in the follow-up of lepromatous cases of leprosy under sulphone treatment indicates that there are four stages in the progress of the disease towards "clinical cure." (1) A change in the morphology of the *M. leprae*; (2) a phase in which the *M. leprae* appears to be stimulated into activity; (3) a phase when the bacilli begin to diminish and presumably reproductive capacity is affected, and (4) when *M. leprae* cease to multiply the process of disintegration continues until the bacilli are reduced to acid-fast dust, and the macrophages ultimately dispose—in a large number of cases—of these degenerate forms, thus curing the disease.

If the tissues of the body are able to destroy the bacilli completely, then a relapse is unlikely. It is known, however, that bacilli in the granular form, in a large proportion of cases, are often found in the small nerves of the skin when they are no longer detectable in the tissues by standard methods of examination. I am of the opinion that so long as there is detectable acid-fast material one has to conclude that this constitutes a potential source from which a relapse can take place, and treatment should therefore be continued. It may be that these granular forms are the resistant phase of the *M. leprae*, but it appears that while sulphones are being given the bacillus is unable to multiply. It evidently takes at least two years, and in many cases probably much longer, for these acid-fast granules to revert back to active acid-fast rods after sulphones have been stopped. In other words, the leprosy process reverts back to the pre-lepromatous stage, and I believe it is logical to conclude that, because a pre-leproma may take anything from a few months to ten years or more to develop into a full-blown leproma, we may have to wait ten or fifteen years before we can come to any conclusion on the permanency of sulphone "cures" in leprosy.

Discussion

Let us review the chemotherapeutic remedies in the light of the above remarks and endeavour to suggest on what criteria we should base our conclusion on the likelihood of a drug being effective in the treatment of leprosy. It is an expensive matter to make enough of a drug to undertake a large-scale clinical trial in leprosy. Therefore is it not possible to come to some tentative conclusion on a small-scale experiment before embarking on large-scale ones, which may take years to complete and be very time-consuming? I believe it is, and would suggest that a drug can be considered active against *M. leprae* if the following observations are noted: (1) marked change of morphology of the *M. leprae*; (2) precipitation of the erythema nodosum syndrome—this is an indication of activity of the *M. leprae*; (3) marked clinical improvement, with early relief of nasal obstruction; and (4) characteristic changes in the histopathological picture.

Some workers believe that the most rapid method by which to test the bacteriostatic or bactericidal properties of a drug is to select the tuberculoid cases. I am of the opinion that this may lead to erroneous conclusions, because, as I have stated, I believe that if a drug is effective then a phase is experienced in which there is evidence that the *M. leprae* is stimulated into activity. In tuberculoid leprosy such a process, because the tissues are sensitized, would be manifested in an acute tissue response; the more marked this tissue response the quicker the subsidence of the disease. Hence a trial in tuberculoid leprosy will only indicate whether a drug has the property of stimulating the bacillus. I believe a very good example of this is a drug which was first prepared by Barry in Dublin, which has been reported on by Barnes (1951), and which has been given the code number of B.283. I recently had the privilege of examining patients taking this drug in Ogoja, Western Region of Nigeria. The majority of tuberculoid cases showed much improvement, whereas the results in the lepromatous cases were disappointing. In other words, this drug has some activity, but is not powerful enough to interfere with the multiplication of the bacilli and produce any great clinical improvement in lepromatous leprosy within a reasonable time. There are many drugs of this nature.

Conclusion

I trust I have given enough evidence to indicate that the therapy of leprosy is at present at a most interesting phase. If we have not reached the stage when we can claim to have achieved complete chemotherapeutic victory, we at least can look forward to the day, perhaps not too distant, when as a result of the combined efforts of the chemists, the pathologists, and the clinicians it can confidently be asserted that leprosy as an active process can be stopped and the long-awaited cure of this disease be realized.

Even though this satisfactory result be achieved, let us ever bear in mind that our conquest is not complete so long as stigmata and sequelae of leprosy, resulting in gross deformities, remain. The time has now come for the plastic and orthopaedic surgeon to step in and complete the cure, by repairing the ravages and damage which the disease has produced and our chemotherapeutic agents have stopped.

Summary

Evidence is given that before the discovery of the sulphone preparations hydnocarpus (chaulmoogra) oil was used effectively in the early lepromatous case, but the more advanced lepromatous cases showed little response.

A review is given of the sulphone drugs most commonly used, and the drawbacks of the parent sulphone are mentioned. The reasons why aqueous solapsone is not broken down to diaminodiphenyl sulphone are discussed, and there is evidence to show that D.D.S. may be detoxicated in the body to a substituted form.

The opinion of Payne is cited that the monosubstituted sulphones may be active *per se*, and that there are sound reasons for advocating the parenteral use of solapsone ("sulphetrone") in a 50% aqueous solution as an alternative treatment.

The possible mode of action of the sulphone drugs is outlined. In cases of toxicity or intolerance to sulphone therapy, thiosemicarbazone is held to be a good substitute, although not so active as the sulphones.

While streptomycin and P.A.S. are active in leprosy, these drugs are not effective enough to warrant their use. The hope is expressed that *iso*nicotinic acid hydrazide may be found effective.

The criteria of activity of a given drug in leprosy are mentioned, and tests for a critical assessment of any drug likely to be effective in leprosy are detailed.

Finally, orthopaedic and plastic surgeons are reminded of the opportunities opened up to them in this field.

I should like to express my gratitude to Dr. S. R. M. Bushby, of the Wellcome Research Laboratories, Beckenham, for kindly reading this paper, and for his valuable help and advice in its preparation.

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AETIOLOGY AND INVESTIGATION OF VAGINAL DISCHARGE*

BY

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Vaginal discharge is a common symptom and is often accompanied by fears that may be more distressing than the complaint itself, and thoughts of venereal disease or of cancer, for example, loom large, while feelings of guilt or uncleanness are reinforced by the patient's own repeated observations. The information is not, as a rule, volunteered, and to prescribe treatment, however impressive, without a convincing examination is to ignore a large part of the patient's real need. If a discharge is bad enough to treat it is bad enough to investigate; furthermore, empirical treatment prejudices accurate diagnosis later.

The Leucorrhoea Clinic

The busy gynaecological out-patient session is not suitable for properly assessing vaginal discharge, and there is a strong case, in any large unit, for segregating these cases, after preliminary examination, into a special clinic for the following reasons. (1) Investigation and treatment can be more deliberately carried out. All the necessary equipment is readily to hand and efficient organization becomes possible. (2) Most of the treatment involves repeated out-patient attendances only, and the other diagnostic clinics are relieved of a considerable load. (3) Better facilities are afforded for clinical research.

Such a clinic, known as the "D" clinic, has been in operation at the Chelsea Hospital for Women during the past five years, and the cases investigated to date number approximately 600. It is from these that the following figures are collected.

The patients are first seen in the out-patient department before being referred, and those in whom the discharge is found to be due to surgically amenable causes, such as gross degrees of chronic cervicitis, sloughing fibroid polyp, or neoplasm, etc., are of course admitted for appropriate treatment and do not reach the "D" clinic. If diabetes

*Read in the Section of Obstetrics and Gynaecology at the Joint Annual Meeting of the British Medical Association and Irish Medical Association, Dublin, 1952.