

DIETHYL DITHIOLISOPHTHALATE IN THE TREATMENT OF LEPROSY. (ETIP or 'Etisul'); A PROGRESS REPORT

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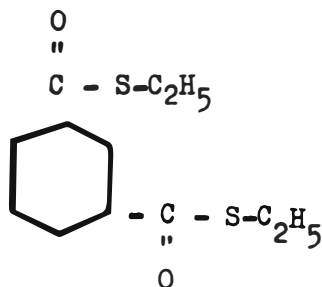
Introduction

In 1950 Del Pianto stated that a mixture of certain thiol compounds prevented the development of tuberculosis in infected guinea-pigs. Although his original statement had later to be modified, it attracted the attention of other workers to the thiol compounds as a possible source of anti-tuberculous substances, and some interesting facts soon emerged. Davies, Driver, Hoggarth, Martin, Paige, Rose and Wilson (1956) traced the active principle to ethyl mercaptan and compounds capable of breakdown or metabolism to it, and found that this property was limited to the ethyl homologue only. Furthermore, it was evident only *in vivo*, the mercaptan having only a slight action *in vitro*, and it was concluded that a metabolite of ethyl mercaptan was the ultimate active agent. They suggested thiol esters as the most promising group of compounds for the treatment of human disease.

After examining many such compounds, Davies and Driver (1957) ultimately chose diethyl dithiolisophthalate as the most promising for therapeutic use. They found this substance to have an anti-tuberculous effect in mice comparable to that of isoniazid and streptomycin, effective when given in single doses, and against isoniazid resistant strains. It was most effective when injected subcutaneously or applied to the skin. Drug resistance was demonstrated. The effects of this and other thiol esters were antagonised by their methyl homologues. Its toxic qualities were of a very low order. These findings prompted the trial of this substance both in tuberculosis and in leprosy.

Notes on Physical and Chemical Qualities

Diethyl dithiolisophthalate is the ester formed from isophthalic acid and ethyl mercaptan. For convenience we shall call it ETIP in this paper. It is also known as Etisul. Its chemical structure is as follows.



The mercaptans or thiolalcohols are mostly colourless volatile liquids with disagreeable smells. Chemically they resemble alcohols in many ways, but differ in their behaviour towards oxidising agents.

Esters formed from them are aesthetically much more pleasant than the corresponding thiol alcohols. ETIP is a bland pale yellow oily liquid with a smell suggestive of garlic, and very similar to the smell of decaying neem fruits. Although decidedly less unpleasant than that of ethyl mercaptan, and indeed quite tolerable when first encountered, its odour is persistent, and we have found that tolerance to it tends to diminish with increasing acquaintance. When given by injection, the odour of ethyl mercaptan can be detected in the breath within fifteen minutes.

Clinical Trial in Leprosy

Italian workers have continued to study sodium ethyl-thio-sulphate, one of the two thiol compounds used by Del Pianto in the work referred to above. Bertaccini (1957) described a trial of this substance in a total of thirty-one leprosy patients, to whom it was given orally in a dose rising from 0.8g daily to 1.6g daily. All the patients were classified as lepromatous, but twenty-six had had previous sulphone treatment, and only fourteen were stated to present overt and active lepromatous lesions. They were treated for periods up to nine months. It was considered that sodium ethyl-thiosulphate had a chemotherapeutic action not inferior to that of other drugs, and deserved further study. Reference was made to a lack of toxicity, and to the smell of garlic in the breath. (See also in this issue a report of the contribution of Del Pianto, page 22).

This substance was one of those examined by Davies, Driver, and their colleagues, but as has already been mentioned, their choice for a drug of greatest practical usefulness finally fell on ETIP. This compound has now been subjected to clinical trial both in tuberculosis and leprosy. We here describe a pilot trial in leprosy, which has so far covered sixty-five patients, all with their disease in an active condition, and nearly all of them without previous chemotherapy. They have received treatment with ETIP at various times during the past eighteen months, mostly for short periods.

Standards

Although clinical appearances, photography and histology have all contributed to our judgment in estimating the progress of patients in this trial, reliance has been placed primarily on changes in the numbers and morphology of *M. leprae* as observed in routine smears. The Bacterial Index with a maximum reading of 4.0, based on the average of findings at multiple sites, has been used as a register of quantity, and its variation during the course of treatment has provided a measure of progress which experience has shown to be the least subject to criticism, while detailed records of the condition of the bacilli at all sites tested have given much useful additional information.

The practice, formerly routine, of selecting individual controls in drug trials, has been superseded at this unit by the use of a standard graph showing average decline in Bacterial Index during DDS treatment. This has gradually been built up during the past five years and represents the average decline in Bacterial Index of 150 patients who have had DDS treatment alone and continuously for four years. It is considered that this yields a more reliable standard

than can be provided by individual controls. It offers a means of comparing one new drug with another, and enables the progress of individual patients or of groups of patients to be compared with the average for the unit. This standard is used in this trial.

Toxicity

Very frequent examinations of blood and urine were undertaken as routine on all patients receiving ETIP. In the dosages used it has been impossible to demonstrate any significant toxic action of any kind.

Progress of the Trial

The nature of ETIP, the manner of its administration, and its effects have introduced unusual features into this trial and necessitated its development in four stages. These will be described in turn.

First Group

The original trial group of patients consisted of nine lepromatous and nine tuberculoid cases, all unselected apart from the criteria of good general health, active leprosy, and no previous chemotherapy. It so happened that the lepromatous cases were all relatively recent infections, the majority representing a degeneration from a previous borderline form of the disease. In them all the disease was active and progressing, the high proportion of normal bacilli in routine smears confirming the lack of previous chemotherapy.

At that time the ETIP preparation consisted of a 70% cream lacking a perfume strong enough to mask the smell of ETIP. This cream was administered by inunction in a dose of 3 cc. weekly, with vigorous massage over a wide area of the body surface.

The trial soon proved self-limiting. After a few weeks patients found the persistent odour of ETIP (and ethyl mercaptan in their breath) increasingly offensive both to themselves and their neighbours. Although all did their best to persevere, gradually one by one they asked to stop the treatment, until by the fourth month it became necessary to abandon the trial for the time being, and patients with two exceptions were transferred to standard oral treatment with DDS, DPT, or DDSO. The arrival of a second preparation more strongly perfumed than the first failed to affect the outcome, but did enable four patients to take combined treatment for a further three months. The two exceptions did continue with the treatment, and more is said of them later.

Results. (a) Lepromatous cases

Even in the short period of trial some surprising results were obtained. Without exception all lepromatous cases showed a marked change in the state of their bacilli within eight weeks, with diminution in numbers and a considerable increase in the proportion of degenerate forms, not only locally at the site of inunction, but generally at all sites tested. In some of them change was evident in the first month. Later, progress tended to slow down, and at the conclusion of the experiment had become erratic.

There was here a reversal of the usual sequence in the chemotherapy of leprosy, for bacteriological progress preceded clinical progress instead of following it, and patients themselves, although feeling well, did not appreciate from the appearance of their lesions the change that had occurred. Clinical improvement became obvious later, in most cases after oral treatment with DDS or CIBA 1906 had been instituted, and with the passage of time it became evident that clinical and bacteriological improvement was continuing at a rate decidedly above average. This was not an individual finding but was common to the group as a whole, as is evident from Figure 1, in which the average progress of the Bacterial Index of the group is compared with the DDS standard. The two exceptions who continued ETIP treatment after the others are excluded.

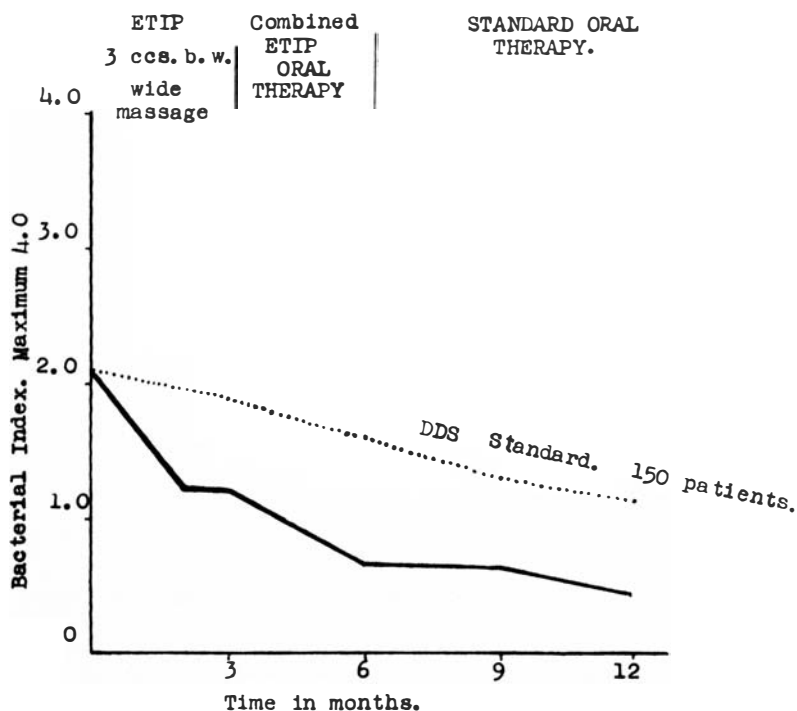


FIGURE 1
Variation in Bacterial Index in patients receiving ETIP followed by standard oral chemotherapy.

The following case notes on three of the patients in this group illustrate the general trend.

1. Ref. No. 9815. Male aged 14. Early but very active diffuse, nodular and macular leproma of two years duration. No previous chemotherapy. Bacterial Index 2.6 on admission, with bacilli almost all in normal form. ETIP was given in a dose of 3 ccs. twice weekly for ten weeks. During the first month the B.I. fell from 2.6 to 1.6, with the development of degenerative changes in a large majority of bacilli. This progress was not maintained, and at the tenth week the B.I. was tending to rise. DDS treatment was then instituted, when progress was resumed. Six months later the B.I. had fallen to 0.9 with all bacilli in a degenerate condition. Clinically and bacteriologically the improvement shown by this patient in nine months was well above the average shown by patients on DDS alone.

2. Ref. No. 1160. Male aged 28. An early infection with symptoms of five months duration. Borderline leprosy now rapidly degenerating to leproma with severe nerve involvement. Bacterial Index 2.5 with 100% bacilli in normal form. ETIP was administered in a dose of 3 ccs. twice weekly for ten weeks. Six weeks after treatment had started the Bacterial Index had fallen to 1.5 with a majority of bacilli now degenerate. Four weeks later it was still 1.5, though at some sites further degeneration of bacilli had taken place. Treatment was now changed to DDS, and progress continued. Six months later the B.I. had fallen to 0.8 with all bacilli degenerate and the condition of the patient excellent. In this patient an unusual decline in Bacterial Index in the first weeks of treatment was succeeded by improvement during DDS treatment which continued to be above average.
3. Ref. No. 865. Male aged 28. Very active nodular, diffuse and macular lepromatous leprosy of only two months duration, a relapse four years after discharge in a previously indeterminate case who had had hydno-carpus and sulphone treatment. Bacterial Index 3.3 with bacilli almost all in normal form. ETIP was given for seven weeks in a dose of 3 ccs. weekly. At the end of this time the B.I. had fallen to 2.7. At this point DDSO 100 mg. daily was given in addition to the ETIP for a further three months. During this period the B.I. remained steady, but the proportion of degenerate bacilli continued to rise. Thereafter treatment continued with DDSO only. Six months later the B.I. had fallen to 1.1, with all bacilli in a granular condition. Clinical improvement was also excellent. After one year progress was definitely better than would have been expected with either DDS, DPT, or DDSO alone.

(b) Tuberculoid cases

During the period of trial, three of the nine cases showed rapid clinical improvement, the others exhibiting nothing outstanding. Subsequently on oral treatment all have made very good progress.

Comment

Here was a drug of obvious interest. All the lepromatous cases appear to have received in the first weeks of treatment an impetus to recovery which later stood them in good stead, so that by the end of a year their progress was at least six months ahead of that expected with standard oral treatment. It was impossible to explain this and the rapid change in the condition of bacilli in the first weeks of treatment on any other grounds than chemotherapy. Unfortunately in the presentations then available ETIP had no future. Our patients possess in high degree, a willingness to co-operate which would go far to overcome their squeamishness where an odoriferous compound was concerned. If they reached the limits of their tolerance after a few weeks it seemed most unlikely that others would find the drug more tolerable. The manufacturers were advised accordingly.

Second Group

Three months later a fresh preparation of the drug was received, this time much more effectively perfumed. In order to make it still more acceptable to patients the suggestion was offered that it should be applied to a limited area of the body only, avoiding hairy parts, and at a site not normally covered with clothing if possible.

A fresh group of twenty-two patients volunteered for trial with this preparation. They consisted of fourteen lepromatous and eight tuberculoid cases. Some of the lepromatous cases were severe, and the whole group represented a heavier level of infection than obtained in the first group. In addition two of the first group volunteered to join the second and were allowed to do so.

These patients received a dose of 6 ccs. ETIP twice weekly, i.e., double the dose administered to the first group. It was rubbed into the legs from above the knees downwards, an area of the body usually kept free from clothing. It quickly became apparent that although this third preparation was aesthetically a considerable advance on the first, the perfume in it effectively masking the ETIP when first applied to the skin, it was still by no means perfect, as the perfume tended to disperse before the smell of ETIP disappeared. With some difficulty patients were persuaded to continue with this preparation for periods up to five months. The lepromatous cases were divided into two sub-groups, one of which received INH orally in addition to their ETIP, as it had been suggested that this might be beneficial. In actual fact the INH appears to have had no perceptible effect on the outcome, and can be ignored.

Results. (a) Lepromatous cases

Progress with this group was in distinct contrast to that observed with group 1. During the first two months of treatment bacteriological improvement comparable with that observed in group 1 was witnessed in only four out of the fourteen cases. Three others showed some progress, but the remaining seven showed little if any change apart from some diminution in the proportion of normal bacilli in routine smears. During the third month failure to improve became almost general, except in two cases in whom some change in leprosy type was developing. From the fourth month onwards the reappearance of normal bacilli in increasing numbers in the ears and nose was noted in six patients, followed by a rise in Bacterial Index and heightened clinical activity of the disease. Here was evidence that *drug resistance* had begun to develop, and this was strengthened by the fact that both the group 1 patients who continued taking ETIP exhibited exacerbation of their disease with considerable increases in Bacterial Index after six months treatment with ETIP. The following notes on one of these may be of interest.

Ref. No. 5660. Male aged 33. Two years history of leprosy, evidently borderline, now becoming frankly lepromatous. B.I. 2.0 with strongly positive smears in ears and face, and macules on the body with varying bacillary concentration. ETIP was first given in doses of 3 ccs. twice weekly for four months, then raised to 6 ccs. twice weekly. Six weeks after the onset of treatment the B.I. had fallen to 1.0, with a majority of bacilli degenerate. Subsequently the B.I. rose again, the proportion of normal bacilli increased, until in spite of increased dosage the B.I. at the end of seven months was 3.2 with 100% normal bacilli in the nose, and the clinical condition of the patient obviously degenerating. Treatment was then changed to DDS, with subsequent rapid clinical and bacteriological improvement. The movement of the Bacterial Index in this patient is compared with the DDS standard in Figure 2.

(b) Tuberculoid cases

Irregularity of resolution was also witnessed among the group of eight tuberculoid cases. One made very good progress, five made progress that was not outstanding, one remained stationary, and after some resolution the eighth showed fresh spread of the disease.

When transferred to standard oral chemotherapy, all these patients made very satisfactory progress within three months.

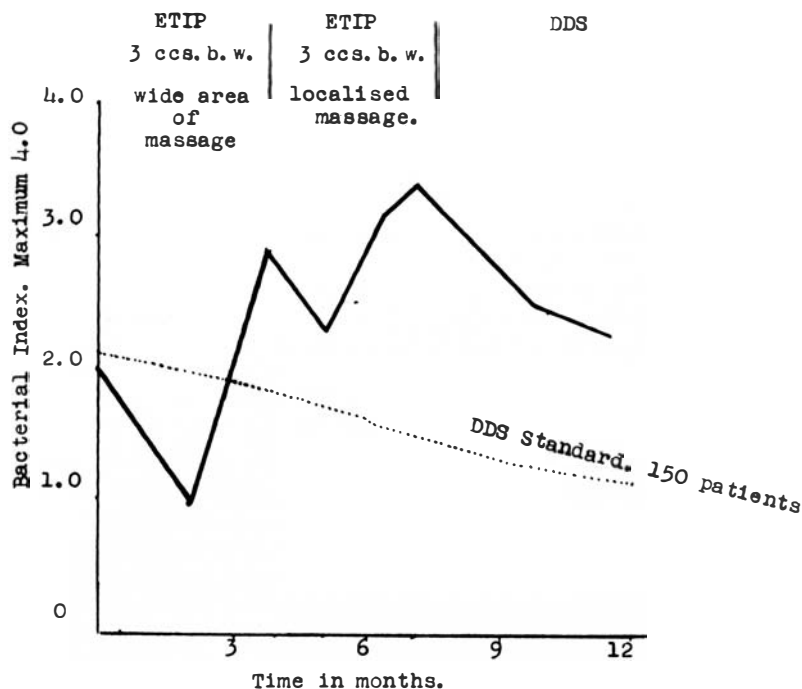


FIGURE 2

Variation of Bacterial Index in a patient developing drug resistance to ETIP.

Comment

Thus in spite of an increase in dose ETIP appeared on the whole to have had considerably less therapeutic effect in this group than in the first group of patients, with strong evidence of drug resistance developing if treatment was continued for more than four months.

When considering possible causes for the discrepancy between the findings in Groups 1 and 2, attention was directed first to *the method of inunction*. Close observation of the patients soon made it highly probable that absorption of the cream from the limited area of the body to which it was applied by Group 2 was defective. Patients quickly tired of rubbing just one area of the body, and it seemed likely that any virtue there may have been in increased dosage was more than counterbalanced by inadequate absorption from a relatively small area of skin, and that one not the best, adapted for the purpose.

It became necessary therefore, to test the drug once again in a third group, in whom the larger dose would be combined with inunction over a wide surface of the body.

Third Group

This group consisted of ten lepromatous and five non-lepromatous cases. The lepromatous cases were a very representative selection of this type of the disease. One was a very serious reactivation after TB₁ treatment. The others with one exception had had no previous chemotherapy.

These all received a dose of 6 ccs. ETIP administered twice weekly by inunction over a wide area of the body. All were submitted to very close observation, several being biopsied, with routine smears being taken at intervals of two or three weeks in all cases. The course of treatment was deliberately limited to eight to twelve weeks, after which standard chemotherapy was initiated.

Results

Improvement was general in these patients during the period of trial, the pattern observed in group 1 being resumed. During the first eight weeks in eight out of ten lepromatous cases a decline in Bacterial Index was seen, varying from 0.3 to 1.5 and averaging 0.8. It was accompanied in all cases by a marked diminution in the proportion of normal bacilli, strangely enough least evident in the nose. A considerable change in the state of the bacilli was also seen in the two patients in whom the Bacterial Index remained steady, and these subsequently made good progress.

During the third month progress once again became variable, five showing continued progress, the other five remaining stationary. By the end of this month ETIP was either joined or replaced by DDS in all the patients. Their progress during the period of trial is well illustrated by the following case notes on two patients, both heavy infections of unquestioned lepromatous leprosy, both previously untreated.

1. Ref. No. 5692. Male aged 30. Very severe diffuse, nodular and macular leproma, diffuse on face and ears, nodular elsewhere, particularly involving buttocks, arms and legs. Two years history. No previous chemotherapy. B.I. 3.2. ETIP 6 ccs. twice weekly. Eight weeks after starting treatment the B.I. had fallen to 2.9 with a diminution in the proportion of normal bacilli from 70% to 25%. At the eleventh week DDS was added. By the thirteenth week the patient was well and happy. Clinically there was by now an obvious change in his condition, with infiltration of the face much less, and increased localisation and diminution in size of nodules generally. B.I. still 2.9 but now only 15% normal.
2. Ref. No. 5697. Male aged 23. Early but widespread nodular leproma, with six months history of symptoms but only two months history of eruption. Now presenting innumerable nodules on all parts of the body, relatively well localised. B.I. 3.7. ETIP given, 6 ccs. twice weekly. During the first month the B.I. remained steady, but during the second month it declined to 3.0. By the tenth week clinical improvement was evident and the patient very well. Biopsy of this patient at the third week showed a typical and quite extensive foamy leproma on histological section. Biopsy at the twelfth week from a site adjacent to the first indicated a considerable reduction in the area of leproma, most marked in the more superficial layers, but evident throughout the corium.

Comment

It is impossible to envisage changes of this nature, occurring so quickly in patients of this type, apart from effective chemotherapy.

Reviewing the three series of patients up to this point, two interesting facts emerged. The first was the advantageous course taken by the patient when ETIP was associated in some way with DDS. Reference has already been made to the excellent progress of those who received DDS after their course of ETIP. In Group 3 the greatest progress of all was made by the one patient who had had some previous chemotherapy, namely five months of DDS treatment.

He was a patient with quite severe diffuse lepromatous leprosy. During the first *eight weeks* of the trial his Bacterial Index fell from 3.0 to 1.5, a fact that speaks for itself. In a patient of his type such a change would have been incredible on DDS treatment alone. The second observation made was that progress was also good in patients in whom there was a macular element in their clinical picture.

The first of these observations prompted the trial of ETIP in conjunction with DDS in a fourth group of patients. This trial is still in progress and will be reported more fully later. Here it can be said that in the ten lepromatous and borderline cases at present included in it, obvious bacteriological improvement has taken place within six weeks of starting the combined treatment.

Discussion

From the facts elicited so far it may be said that ETIP is a drug of considerable interest to the leprosy worker. The possibility that drug resistance may develop quite quickly if the drug is used alone is itself sufficient to remove ETIP from the select group of basic leprosy remedies, but it already appears to have a place as an adjunct to oral chemotherapy, and if drug resistance can be delayed by combination with other drugs, its future influence in leprosy treatment may be considerable. It has not been an easy drug to study. This report is only a beginning, for many points of interest arise in connection with it which as yet are not clear. The following call for further comment.

Speed of action

The main action of ETIP appears to be concentrated in the first two or three months of therapy, and during this time the speed with which it may influence leprosy bacilli is something new in our experience. Although some borderline cases and the occasional lepromatous case do respond very quickly to oral chemotherapy, the effects of DDS are usually more evident in the second three months than in the first. CIBA 1906 (DPT) approaches most closely to ETIP in its influence during the first three months, but with it a fall of Bacterial Index by 1.0 in this period would be exceptional, whereas with ETIP it was by no means rare.

Administration by inunction

The method of administration by inunction is a novelty, but one that is psychologically sound. Provided the preparation is aesthetically acceptable to patients there is every thing to be said for supplementing oral treatment with skin massage, particularly if thereby a further therapeutic effect can be obtained. In our patients the cream itself has had a useful effect in improving the general condition of the skin. It remains to be seen whether the perfumed preparation now in use will prove generally acceptable.

The technique of inunction is obviously important. The similarity of findings in groups 1 and 3 and their difference from those in group 2 are sufficient to demonstrate this. The cream needs to be rubbed in until it is no longer visible as such. We have found the following general method of treatment the most acceptable to our patients.

Loose garments, the minimum necessary, need to be reserved for the period of treatment. On arrival the patient changes into these, and inunction is then undertaken, avoiding hairy parts, other patients assisting as necessary in applying the cream to the back. The inunction is given with good massage, the treatment occupying about fifteen to twenty minutes for a 6 ccs. dose. The patient thereafter rests for three hours, keeping the inuncted area exposed to the air as far as is possible, and then takes a warm bath using scented soap, after which normal clothes are resumed.

Irregularity of results

One of the curious findings in the trial has been *the difference in effect produced by ETIP as between one patient and another*. Whereas one patient may show a phenomenal change in the state of his bacilli in a few weeks, another of apparently identical type shows nothing comparable. The cause of this is obscure. It does not appear to be directly related to the vigour with which inunction is undertaken. Within the limited range studied, dosage is not the factor responsible. Duration of the disease and the state of nutrition may be involved.

Mode of action

Known peculiarities in the mode of action of ETIP are of interest here. The difference found by Davies and Driver between its activity *in vitro* and *in vivo* strongly suggest that the action of ethyl mercaptan is not directly on *M. tuberculosis*, but is mediated through physiological processes in the body of the host. The same authors (1958) have recently shown that ethyl mercaptan exerts its action intracellularly on tubercle bacilli in tissue cultures of both human and guinea-pig monocytes, and it is evident that no product of metabolism formed elsewhere in the body is required. Rose (1958) suggests that the effect of ethyl mercaptan in the tuberculous animal is to stimulate its natural defences perhaps by inducing a measure of anti-bacterial activity in the macrophages.

If this applies also in the case of leprosy, the effects of ETIP could be expected to be most pronounced in those patients in whom there was already some degree of tissue resistance. It is of interest that a tendency to increased localisation of nodules has been common in our patients, and that macular lesions have tended in several patients to become better defined and closer to tuberculoid in appearance. In these patients there does appear to have developed a heightened immune response, but in all of them a decline in Bacterial Index took place before any clinical change of this nature was evident. It remains to be seen whether these findings were fortuitous or not.

Drug resistance

ETIP is the fourth drug in our experience with which signs highly suggestive of drug resistance have arisen. In all cases the first signs of this have shown themselves by the reappearance of normal bacilli at sites, particularly the nose and ears, at which bacilli had become granular. In succeeding smears the numbers of normal bacilli increased rapidly and soon there was clinical evidence of increased activity of the disease. With ETIP treatment these signs, appearing in some patients after four months, were encountered more quickly

than with any other of the drugs concerned. We may note the slow effect of the drug on bacilli in the nasal septum in this connection. It remains to be seen whether drug resistance can be averted or delayed by combined treatment.

It is of interest that in spite of the similarity in chemical structure between ETIP and the thioureas, CIBA 1906 has proved an effective continuing treatment for patients exhibiting signs of drug resistance to ETIP.

Future work

There is immediate need for the study of this drug in combination with basic oral chemotherapy with DDS or CIBA 1906. One of the most promising features of ETIP is indeed the ease with which it can be combined with DDS. If later observation confirms the results obtained hitherto, we may have here a valuable adjunct to DDS, particularly in mass treatment, in which the cheapness and lack of toxicity of ETIP are important virtues.

The possibility may now be entertained that suitably combined with DDS, or DPT, ETIP may lead to a material shortening in the period of treatment now needed. The most serious disadvantage of ETIP is its odour, not yet completely masked. Related compounds deserve study both from the standpoint of activity and also this important aspect of acceptability to patients. In conclusion it is not without significance that for the first time since trials of ETIP began, patients are now coming forward on their own initiative and asking for it.

Summary

A pilot trial of diethyl dithiolisophthalate (ETIP or Etisul) in the treatment of leprosy is described. Administered by inunction in a dose of 3-6 ccs. twice weekly to sixty-five patients with active leprosy, divided into four groups, the drug, provided inunction is adequate, has been found to exert a chemotherapeutic action in the first two to three months of treatment which is variable but in some patients is very marked indeed. When continued for more than four months signs suggestive of drug resistance appeared in several patients, but when after a course of ETIP lasting eight to twelve weeks, standard oral chemotherapy with DDS, CIBA 1906, or DDSO was instituted, progress continued to be better than average, and all those concerned appear to have received an impetus to recovery during the first few weeks the effect of which continued, so that after one year their progress was at least six months ahead of that expected with oral treatment alone. This led to the trial of ETIP in combination with DDS which is still in progress.

No signs of toxicity have as yet appeared. The only disadvantage of ETIP is its rather unpleasant odour not yet perfectly masked by perfume, but the effects of this can be minimised by a suitable inunction technique.

The safety with which it may be used and its low price commend ETIP for use in mass treatment as an adjunct to DDS, with some hope that combined treatment may lead to a shortening in the period of treatment needed.

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