THE USE OF "ETISUL" (DIETHYL-DITHIOLISOPHTHALATE) IN THE TREATMENT OF LEPROSY IN AFRICANS

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Stimulated by the work of Davey in Nigeria, we carried out a trial of diethyl-dithiolisophthalate ("Etisul") cream in in-patients at the Yonda Leprosarium.

The immediate aim of this first trial was not to determine the therapeutic efficacy of the drug, but to assess its local tolerance in Africans. The clinical and bacteriological progress of the patients was only recorded incidentally.

1. History

Del Pianto must be credited with having drawn attention, in 1950, to the fact that a mixture of two mercaptans, i.e. mercaptobenzothiazol-5-sodium sulphonate and ethylthiosulphate, inhibits the development of tuberculosis in infected guinea-pigs.

After various authors (Brown, Solotorovsky, Mathewson, Chang, etc.) had carried out numerous investigations into the action of various mercaptans in tubercular infections in mice, in infections with *Mycobacterium leprae*, and in human tuberculosis, Davies discovered diethyl-dithiolisophthalate (ETIP, ET, "Etisul", Ditophal). The review by Chang and Doull (1959) of the development of these investigations should be consulted for details.

As regards human leprosy, Bertaccini in 1957 treated 37 lepromatous cases with ethyl thiosulphate *by mouth*, in a dosage of 0.8–1.6/g.day, for a maximum of nine months, with interesting results.

Davey in Nigeria used diethyl-dithiolisophthalate in the form of a cream ("Etisul"). At the Tokyo Congress he showed photographs of patients treated with this drug and reported having obtained remarkable improvement with it. In two recent papers he reported the results achieved in 133 patients. The most outstanding aspect was a spectacular drop in the bacterial index: in certain groups of patients studied by Davey this fell by half in 4, 8 and 12 weeks, respectively.

"Etisul" shows remarkable activity, particularly in fresh cases. "Etisul" is thus of interest only in the early stages of treatment. In older cases, where scanty bacilli persist after several years of treatment (with other drugs), it is said to be ineffective.

When it is used alone, its effect subsides after two or three months. We do not yet know whether and under what conditions the drug may recover its efficacy, when a second course is applied. Combination with parent sulphone is highly effective, but where the two products are administered together from the beginning, i.e. where the maintenance dose of DDS has not yet been reached by the time the action of "Etisul" has subsided, the emergence of resistance cannot be prevented. Starting the parent sulphone some weeks in advance, on the other hand—and this is of particular importance—decidedly prevents the appearance of such resistance. It is said that the same results can also be obtained by beginning with three types of treatment, i.e. "Etisul", DDS and DPT, simultaneously. In this case DPT, in a daily dosage of 2 g., is intended to prevent resistance from emerging towards the third month, while waiting for the standard dose of DDS to be attained.

2. Choice of Patients and Method of Administration

It seemed as if the odour of "Etisul", generally considered as extremely unpleasant, might present a major obstacle to its extensive use.

The object of our trial was to study the acceptance of this new type of product by African patients.

We chose 28 patients, all males, including two children. 26 were of the lepromatous type, including eight fresh cases and had never previously received organised treatment, one reactional tuberculoid case and one borderline case. Four subjects did not finish the treatment: two of these experienced a severe lepra reaction (one with oedema of the hands and one a straightforward reaction, without erythema nodosum), and two left the leprosarium.

"Etisul" was administered for a period of 8 to 15 weeks, twice weekly to seven of the subjects ,and three times weekly to the remainder, in a dosage of one tube (=3 g. of the drug) per session.

Following the advice of Davey, who had noted that application of the cream to the legs was without effect, we caused the product to be massaged into the skin of the back, over a wide area extending from the belt to the shoulders. This type of application is rapid and requires no nursing personnel. The patients are arranged in a circle, either sitting on stools or, better, standing up, each massaging the back of the one in front of him, and the first member of the group massaging the back of the last. The patients spontaneously took up the habit of singing a work song during inunction sessions, which seems to encourage them. The advantage of this method lies in the fact that each patient demands to be massaged as vigorously by the one behind him as he is massaging the one in front of him.

Each session lasts 20 minutes. In spite of vigorous massage, the back is still covered with cream at the end of that period. The patient

then waits 2–3 hours before covering his back, attends to his jobs and then has a wash.

Care is necessary in ensuring that patients, particularly children, do not wash as soon as the drug has been applied.

3. Local Tolerance

Cooperation by the patients was excellent.

By not using any constraint on those treated with "Etisul", by not threatening penalties against those who might shirk the treatment, and by simply stating that this is a costly and probably very effective drug, we obtained an attendance of 90.5% at the sessions, a proportion which is usual at the beginning of any new therapeutic trial, but is only exceptionally seen to persist for several months, as in this case. In our group this level of attendance was kept up until the end of the course.

While this trial was in progress, many patients asked to be treated with "Etisul", and these were invariably men. Up to the present we have not succeeded in persuading women to let themselves be inuncted, since, due to the shortage of covered accommodation, the sessions take place in the open air and the women absolutely reject any attempt to convince them.

Contrary to our initial fears, the odour of the product, either when applied to the skin or when excreted via the lungs, did not give rise to any objection. Not a single complaint was made either by the patient himself or by those surrounding him. According to those involved, only the first two sessions are objectionable, and then they become used to it.

We questioned the treated patients both separately and as a group, and some of them, being former clerks, policemen, etc. did let us have a little report. Some of these have certain jobs in the leprosarium, such as: teacher of French in the social centre, registrar in charge of administrative reports, foreman carpenter, lorry driver, etc.; it seems that they prefer to avoid coming into contact with the public on the evening after their inunction with "Etisul" (the sessions took place about 3 p.m.), but they all feel that, if they were to be treated with this cream on an out-patient basis, they could all go back to their work the next morning without any difficulty. On several occasions, when we were receiving visitors shortly after an "Etisul" session, we had cause to call in our shorthand typist, who was receiving the drug and who still had his back bare and covered with cream, in order to give him some task or other. While it is true that the odour was powerful, we never heard the slightest remark from the visitors. The odour of "Etisul" is certainly much less disagreeable than that of certain chaulmoogra esters, which was at one time a feature of any leprosarium, and which still persists today in certain buildings.

The reason for our discussing this subject at length is that the odour of the product is at present a subject for comment and is often considered to be an obstacle to its use.

Two complaints, on the other hand, were expressed by almost all the patients:

1. Excretion in the sweat.—Wherever heavy physical work is involved, the sweat, for at least two days after an "Etisul" inunction, carries a marked odour of the drug and imparts it to the clothing. As regards the laundering of the latter, they can be washed with other clothing without transmitting the odour to it. The patients, however, said categorically that certain soaps immediately remove the odour from the clothing, while others are without effect. The same remark applies to the bath they take after inunction. No more detailed information could be obtained from them.
2. Odour from the soil and withering of grass after contamination with "Etisul".—In the beginning the patients used to wash behind their houses, after having rolled in the grass for the purpose of rubbing their back, which was still covered with cream. Some hours later the grass appeared withered, and the soil upon which the washing water had been emptied gave off the typical odour for several days, particularly after each rainfall.

A last point regarding this odour: we became forced to store "Etisul" in a separate place outside the hospital, since the cardboard boxes containing the tubes were not airtight.

To sum up: we do not believe that the odour of "Etisul" presents an obstacle to its use in Africans. Some easy precautions are all that is required, and it is as well not to dwell excessively on this problem. The odour is certainly less unpleasant for the patients than that of chaulmoogra and that of vitamin B complex, both of which either have been, or are still being, extensively used in leprosaria.

At present we are testing the tolerance of "Etisul" on an out-patient basis in intelligent patients.

4. Results of Treatment

As a secondary consideration we studied the progress of patients treated with "Etisul". Naturally our results, which were obtained in a small number of leprosy patients, lack any statistical value.

It is, however, of interest to compare them with those published by Davey, and we feel they are worth recording.

We have divided the patients into two groups, according to the time at which treatment was begun.

A.—First Group (March 1959)

Seven patients were chosen, including:

(*a*) Four severe fresh lepromatous cases (two of them children)

and one adult borderline case, all previously treated with sulphones for 1 to 7 months.

(*b*) Two severe lepromatous patients, who had started "Diasone" treatment in 1949, had disappeared in 1951, and had remained without treatment until they were re-admitted in 1956 and 1958, respectively; at that time the patients presented with very severe and florid lepromatous leprosy, with generalised infiltrations and lepromata. At the time they were incorporated into the "Etisul" group they had been receiving DDS for 29 and 3 months, respectively.

The nature of the skin lesions in the lepromatous patients can be summarised as follows:—

Patient No.	*Lepromata*	*Infiltration*	*Macules*	*Previous Reactions*
M.L. 0937	+	+	—	in 1957
N.C. 1350	+	+	—	—
L.G. 2899	—	+	—	—
A.J. 2904	+	+	—	—
I.P. 2914	+	—	—	—
E.E. 2921	+	+	+	—

Clearly, these patients were selected, since all but one were either fresh or relapsing lepromatous cases. They were not chosen by virtue of any possible intolerance to sulphones or of any lack of improvement with ordinary treatment.

"Etisul" cream was administered twice weekly and later, during the last two weeks of the course, three times weekly, at the rate of one tube per session per adult patient, and half a tube in children, which was vigorously massaged into the skin of the back for 20 minutes (the first application consisted of one tube for five patients).

All patients were treated simultaneously with DDS tablets in a dosage rising from 400 to 600 mg. of parent sulphone per week, given in three parts.

Patient No.	*Duration of Treatment (weeks)*	*Total Dose of "Etisul" (tubes)*	*Total Dose of DDS (during "Etisul" treatment)*
M.L. 0397	12	27.5	6.70
N.C. 1350	14	32.2	6.90
L.G. 2899	12	14.5	Regular, but record lost at school (child)
A.J. 2904	14	32.2	6.80
K.J. 2910	14	32.2	6.80
I.P. 2914	14	31.2	8.50
E.E.2921	14	16.2	1.45 (child)

The following is a brief summary of the clinical results in each case:—

1. 0937—M.L.: 1.4.1959	Numerous lobster-shell-like infiltrations over the whole body. Lepromata still persist on the ears, chin and forehead, but have clearly shrunk as a result of two years' sulphone treatment. Diffuse coarsening of the face.
8.6.1959	Infiltrations flattened and scarring; lepromata flattened; coarsening of the face reduced.
2. 1350—N.C. 10.2.1959	Generalised infiltration over the whole body; confluent lepromata on the ears; nasal fossae blocked.
8.6.1959	Continues to show infiltrations and lepromata, but these are smaller and less turgid; nasal fossae patent.
3. 2899—L.G. 1.4.1959	Pigmy child showing diffuse coarsening of the face, some beginnings of infiltration, and markedly coarsened ears.
8.6.1959	Coarsening reduced, but infiltration persists, with shiny appearance of skin; lepromata flattened, almost scarring.
4. 2904—A.G. 20.2.1959	Beginnings of infiltration on the chest, back and arms; clusters of small lepromata on face and ears; nasal fossae blocked.
8.6.1959	Slight infiltration persists on the chest, back and arms. The lepromata have completely cleared up, except on the ears where they are much reduced in size; nasal fossae patent.
5. 2910—A.J. 20.2.1959	Previous clinical course unknown. Shows numerous borderline macules over the whole body, including two on the left arm and abdomen, having some micropapules near their borders, which are slightly raised and show a deeper copper colouring at that level.
8.6.1959	No change from the first examination.
6. 2914—I.P.	Very slight incipient infiltration on the chest; thick and florid lepromata on the upper lip, chin, ears, extensor aspects of the arms, and back.
8.6.1959	A very slight infiltration persists on the arms and the chest; all lepromata have disappeared without trace.
7. 2921—E.E.	Incipient lepromata on the ears, diffuse coarsening of the face, tawny macules of greasy and infiltrated appearance on the back.
8.6.1959	Lepromata, infiltrations, coarsening and macules have disappeared without trace.

For bacteriological purposes biopsies were obtained at the beginning, during and at the end of the treatment from six different sites: apparently healthy skin, skin of forehead and chin, apparent infiltration or macule, ear lobes and nasal mucus (scrapings).

The tests were carried out by a laboratory technician who had no access to clinical data that might have influenced his findings.

In order to illustrate the progress we calculated the bacteriological index according to Davey's method, allocating a coefficient ranging from 1 to 4, according to the density of the bacilli for each sampling site, grouped for all sites and then divided by the number of biopsies. We did, however, take six biopsies instead of four and calculated no average, contenting ourselves to add the various coefficients together, thus obtaining a maximum of 24.

We are listing below the results obtained in the most representative patients, compared with those obtained in lepromatous patients who were chosen at random from those presenting the same bacteriological index.

Patient No.	*"Etisul" Treatment*	
	Onset	*End*
1350	16	10
Control	16	14
2904	14	8
Control	14	10
2914	20	6
Control	20	16
2921	18	5
Control	18	16

Patients not shown above were not excluded because their results differed, but as a result of discrepancies between the dates of the biopsies, as between controls and treated subjects, the reason being that patients are highly reluctant to undergo repeated biopsies.

Biopsies taken three months after the end of "Etisul" treatment, when patients had continued to take DDS in a dosage of 600 mg. per week, indicate that the bacteriological improvement still persists.

B.—Second Group (June 1959)

Among 21 patients chosen, four were excluded (by reason of either departure or lepra reaction), two were added to the group during treatment and will not be considered here, since their period of observation was too short. Two patients were residual lepromatous cases with very marked lesions, with scanty bacilli appearing only intermittently.

Here we are concerned only with the 13 patients showing bacilli, including 12 lepromatous cases and one with a reactional tuberculoid form.

Remarkable clinical progress was made by all the lepromatous cases: the lepromata resolved and infiltrations were clearly reduced to scar proportions. This progress was followed by means of clinical photography and biopsies.

We feel the bacteriological progress is interesting (see Table).

Eleven of these patients were treated with "Etisul" plus DDS in a dosage of 600 mg. per week. Four received only "Etisul" (these are marked + in the Table).

The fluctuations in the bacteriological index from one week to the next are of no importance, since the bacilli are not distributed uniformly throughout the skin, and it is clearly impossible always to take a biopsy from exactly the same spot.

Bacteriological Progress

	Weeks of "Etisul" Treatment																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1349+	13	—	—	5	2	3	3	9	4	4	—	4	3	3	2	5	—
1395+	7	—	—	5	2	2	2	—	1	2	—	2	—	2	—	1	—
1920+	8	—	—	3	2	2	2	—	2	4	—	2	2	0	—	0	—
2003	14	—	—	—	—	5	7	2	—	—	3	2	5	—	3	—	—
2463	—	5	—	—	5	4	2	1	4	2	1	—	—	—	1	5	6
2591+	6	—	—	2	1	1	1	1	0	—	—	0	—	0	—	0	—
2744	—	—	6	—	—	3	4	1	0	—	2	—	1	5	4	—	—
2795	7	—	—	2	2	2	0	1	0	—	—	—	2	0	0	1	—
2875	14	—	—	4	—	2	3	3	1	0	—	1	0	3	1	4	—
2882	6	—	—	2	2	1	3	2	1	1	—	2	1	2	4	3	—
2884	11	—	—	—	2	1	1	4	0	2	—	0	0	2	1	1	—
2888	7	—	—	2	3	—		2	2	0	—	—	2	3	—	—	—
2925	8	—	—	5	8	1		3	1	2	—	1	2	2	0	1	—

Be that as it may, it seems that the changes produced by "Etisul" in the bacteriological index of leprosy patients are, at worst, unexpected and out of the ordinary.

Our results are comparable with those obtained by Davey in the groups he designated as 1A (9 cases) and Cb (14 cases). It should be noted, however, that, judging by the bacteriological index, the patients studied by Davey appear to have had a more severe stage of the disease. Actually, our bacteriological index tends to be lower, overall, than that of Davey, due to the fact that we introduced in our series two additional biopsies (six instead of the four carried out by Davey), which were taken from sites that generally become negative right at the beginning of sulphone treatment (apparently healthy skin and skin of the forehead).

It would be of great interest to compare these results with those obtained by using sulphones alone. But the progress of each patient, whether treated with sulphones or not, varies too greatly, and the error inherent in repeated bacteriological examinations is too high, to allow us to set much store by such a comparison. We might confine ourselves to noting that such a rapid fall in the bacteriological index is only exceptionally seen in patients treated with DDS, particularly at a time when, after marked improvement during the first two years of treatment, the bacteriological index becomes stable and often remains at the same level without marked fluctuations for several years.

5. Conclusions

In the form of cream ("Etisul") diethyl-dithiolisophthalate is fully accepted by African patients, is perfectly tolerated topically, and its slight odour does not form an obstacle to its use.

Lepromata are resolved with such speed that a patient with lepromata and infiltrations may fail to present any visible lesions after two months' treatment. This improvement is maintained wherever the patient is changed over to final treatment with sulphones.

The most remarkable aspect of the drug is its effect on *M. leprae*. In the majority of patients who show bacilli, the bacteriological index drops in the space of a few weeks; it may even happen that the patient suddenly becomes bacteriologically negative while still presenting clinical lesions.

The small number of patients studied here does not allow statistical conclusions to be drawn, but the individual results obtained, which are hardly ever seen at all in our sulphone-treated patients, can be regarded as really surprising.

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