SHORT AND LONG ACTING SULPHONES BY INTRAMUSCULAR INJECTION

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A preliminary report is presented of a clinical trial of dapsone (DDS) therapy by fortnightly intramuscular injection over a period of one year.

Material. We selected 60 patients with advanced lepromatous leprosy and divided them into four groups of 15 patients each. Only four patients failed to complete the course (two because of severity of reactions and two absconding) and it has been possible to compare 13 patients from each group. All of these had received oral dapsone therapy for four to eight months prior to the experiment enabling each patient to make a personal comparison of the effects of the parenteral therapy later instituted. Great care was taken to exclude macular lepromatous cases or any showing tissue reactivity suggesting an inclination towards the borderline state.

Restricting the sample to lepromatous cases has several advantages. One avoids the varying levels of resistance encountered in tuberculoid cases and the immunological chaos of the borderline varieties. The clinical picture is not complicated by those factors of immunity which are evidenced by delayed (tuberculin type) sensitivity, and the ability to respond to the bacillus with a tuberculoid granuloma, as all cases are reduced to a common denominator of complete anergy. The rate of bacteriological improvement in lepromatous leprosy on sulphone therapy is remarkably constant. RIDLEY[1] (1959) using serial biopsy technique demonstrated a standard rate of 25% improvement in the bacillary count per six month in Europeans with lepromatous leprosy. Furthermore the variety of reactions encountered is considerably reduced and the reactions are easier to interpret.

Groups. The original intention was to compare the results of a fixed dose (1.2 g.) of dapsone per fortnight administered by differing routes and vehicles. This was modified as the experiment developed. The following preparations were compared:

Group I Oral dapsone in dosage of 300 mg. twice a week, equivalent to 1.2 g. dapsone per fortnight.

Group II Dapsone (1.25 g.) suspended in ethyl esters of hydnocarpus oil (5.0 ml.) administered once every two weeks by intramuscular injection.

Group III 'Avlosulfon' Aqueous Suspension (ICI) administered by intramuscular injection in dosage of 3 ml. containing 0.6 g. of dapsone at intervals of two weeks.

Group IV 'Avlosulfon' Soluble (ICI) administered by intramuscular injection once every two weeks in dosage of 6 ml. liberating in the tissues 1.2 g. of dapsone on decomposition.

Review of Literature. Deep subcutaneous injection was the route selected by COCHRANE[2] (1949) when he pioneered the use of dapsone in human leprosy. In the following year LOWE[3] (1950) published his work on oral dapsone therapy which established this route as the method of choice. Although the optimum blood level of dapsone cannot be precisely stated, LOWE[4] (1952) considered that a safe blood level lay between 1.0 and 0.2 mg.%. The figure of 0.1 mg.% appears to be generally accepted as the lowest satisfactory level for therapeutic benefit.

Fearing the abuses which have occurred when mass oral therapy has been organised in primitive communities, several workers have continued to explore the possibilities of parenteral therapy. MOLESWORTH[5] (1949) for example used subcutaneous injections of dapsone (0.3 g.) suspended in pure cocoanut oil (1.5 ml.) at weekly intervals. Blood levels varied between 0.1 and 0.15 mg.% and reactions were few. MUIR[6] (1951) used arachis oil as the vehicle but there was a tendency to the occurrence of painful subcutaneous depots of unabsorbed dapsone and cocoanut oil was preferred. Neither method gave adequate blood levels for longer than one week.

Interest in injection therapy increased when FLOCH[7] (1951) produced evidence that parenteral dapsone may be less toxic than oral dapsone therapy. He showed that when dapsone is given by injection the drug is recovered unaltered from the blood and urine. When the same drug is given by mouth 20% of the dapsone is changed into an unstable derivative. Among his patients the parenteral route was accompanied by 8% of 'lepra' reactions whereas the oral route was accompanied by 47% of 'lepra' reactions. It was suggested that the dapsone may have been altered by the action of intestinal secretions, by bacteria, or by passage through the liver. Several workers have repeated the claim that sulphones administered by injection give rise to fewer undesirable reactions than the same drug given by mouth, attributing reactions to toxic derivatives. This is discussed later.

Because of the inconvenience of weekly injections, LAVIRON[8] (1953) experimented with fortnightly injections of dapsone (1.25 g.) in oily suspension. When arachis oil was used blood levels rose to a peak of 0.54 mg.% but fell to 0.06 mg.% before the end of the second week. The first figure was considered excessive, the second inadequate; but, when hydnocarpus oil was used as the vehicle, a maximum blood level of 0.29 mg.% occurred and the blood level at the end of the second week was still 0.13 mg.%. It was suggested that irritation by the fatty acids of hydnocarpus oil slowed the rate of absorption of the dapsone. In practice a mixture of the oil and its ethyl esters

proved to be the most suitable vehicle, being less viscous than the oil alone and less irritant than the ethyl esters alone. Guaiacol 4% was added as an antiseptic and for its anaesthetic action.

LAVIRON (1954) reported a three year trial of this preparation on 1,225 patients in French West Africa. Excellent therapeutic results were claimed with very few reactions. His earlier claim of synergic action by the hydnocarpus oil was not repeated in this paper. His work was confirmed by MONTESTRUC[10] (1955) who found that hydnocarpus oil suspensions gave more constant blood levels than those achieved with arachis oil.

A depot effect was also achieved by FLOCH[11] (1954) who studied the influence of particle size on the rate of absorption. Using larger crystals (200 to 500 microns) a single injection of 1.8 g. dapsone suspended in 12 ml. of physiological saline containing 0.2% agar given *once a month* produced satisfactory blood levels. In the first week the concentration averaged 0.194 mg.% and in the last ten days of the month 0.098 mg.%. Satisfactory clinical results and freedom from reactions were claimed. LAVIRON[12] (1955) combined large crystal size with an oily vehicle giving 2.5 g. of dapsone (crystal size 120 to 190 microns) suspended in 8.5 ml. of ethyl esters of hydnocarpus oil at *monthly* intervals. The series involved 20 patients. In the ten patients tested blood levels were very variable and a peak as high as 1.95 mg.% occurred in one patient. In some cases the blood level fell below 0.1 mg.% after the second week but two cases showed no peak and still had a blood level of 0.25 mg.% by the 20th day. In both experiments the bulk of the injection and the large-bore needle required were disadvantages. The internal diameter of a No. 3 (gauge 20) serum needle is 0.9 mm. and if three or more crystals of 200 microns or two crystals of 500 microns were to clump blockage would occur. MONTESTRUC[10] (1955) also used saline agar suspensions giving 1.5 g. of dapsone (crystal size 150 to 180 microns) at fortnightly intervals. Blood levels varied between 0.25 and 0.1 mg.% and injections were well tolerated and less painful than hydnocarpus oil injections, but the comment was made that a larger bore needle was required.

Attempts to produce a retard effect were not confined to the parent sulphone. FLOCH[13] (1954) extended the period of effective sulphonaemia obtained with 'Avlosulfon' Soluble ICI by giving it in a depot vehicle. 3 ml. of a 25% solution of polyvinylpyrrolidone were added to 6 ml. of 'Avlosulfon' Soluble (equivalent to 1.2 g. of dapsone). The 9 ml. injection was given at weekly intervals producing a total sulphonaemia of 7.72 mg.% at the fourth hour falling to 0.06 mg.% on the seventh day. As dapsone can be given orally at weekly intervals in dosage up to 600 mg. little advantage was gained apart from the claim of reduced toxicity by the parenteral route.

The Trial. Facilities for estimation of blood sulphone levels do not exist at Kochira Leprosarium. Fortunately these have been worked out for the various preparations used at other research centres.

Group I The Control

Dapsone tablets were given in oral dosage of 300 mg. twice a week, equivalent to 1.2 g. per fortnight. Dapsone by mouth is moderately rapidly absorbed and slowly excreted and in this dosage the limits of safety and effectiveness suggested by LOWE[4] (1952) namely 1.0 mg.% maximum and 0.1 mg.% minimum are not transgressed. As already stated a proportion of the circulating sulphone is in the form of unstable derivatives of dapsone following oral dosage.

Group II

Dapsone (1.25 g.) suspended in ethyl esters of hydnocarpus oil (5 ml.) with 4% guaiacol administered by intramuscular injection at fortnightly intervals. In the preparations used 90% of the particles were between 3–5 microns in diameter and 10% between 5–15 microns. Blood sulphone levels may be expected to lie between 0.29 and 0.13 mg.% (LAVIRON[8] 1953) and are thus well within the limits set by Lowe.

Group III

'Avlosulfon' Aqueous Suspension (ICI Compound 20, 177) containing 20% dapsone per 1 ml. was used in this group. In the development of this preparation, Imperial Chemical Industries, Ltd. have attempted to provide a relatively painless injection of small bulk achieving a sustained blood level by depot action. Because oil tends to produce pain and tissue damage at the injection site, water has been substituted as a vehicle. A small particle size varying from 1 to 15 microns with the majority of particles falling between 2.5 to 8 microns permits the use of fine needles and ensures that the suspension will 'stand up' well. The retard effect has been achieved by a novel agent which maintains dapsone in watery suspension.

Our original intention was to give fortnightly injections containing 1.2 g. of dapsone in 6 ml. From experiments in monkeys (private communication, ICI Research Laboratories) using a single dose of 20 mg./kg. body weight it was estimated that an injection of 1.2 g. would be necessary to maintain a blood level greater than 0.05/0.1 mg.% for 10 to 14 days. Shortly after the commencement of the trial DAVEY[14] (1958) established that a single injection of 3 ml. intramuscularly gives a maximum blood level of 0.8 mg.% falling to 0.1 mg.% on day 13. Thus a dosage of 0.6 g. fortnightly, which is half the quantity required by oral dosage, gives a blood level which is within the conventionally accepted limits of safety and effectiveness. In the experiment therefore 3 ml. of 'Avlosulfon' Aqueous Suspension containing 0.6 g. of dapsone were given by intramuscular injection at fortnightly intervals.

Group IV

'Avlosulfon' Soluble (ICI Compound M21916), being a 41% aqueous solution of acetaldehyde sodium bisulphite complex of dapsone which breaks down rapidly in the body to release half its weight of dapsone. The dosage was 6 ml. by intramuscular injection at fortnightly intervals which is equivalent to 1.2 g. of dapsone. The drug has been studied by TOUZIN[15] (1953) and DAVEY[16] (1956) who drew attention to the similarity of its chemical structure and behaviour to that of Sulphetrone. Indeed the use of 'Avlosulfon' Soluble in this experiment was suggested by a misunderstanding in 1954 whereby sulphetrone injections were instituted in error at fortnightly intervals (3.0 g.) in the Mlanje district of Nyasaland instead of twice weekly in the treatment of leprosy out-patients. Records were not adequate for analysis but the medical staff of the Mlanje clinic formed a strong impression after one year of treatment that the patients receiving sulphetrone had made better progress, had fewer reactions, and had attended more regularly than those on oral treatment with dapsone.

The dosage selected is high. TOUZIN[15] (1953) demonstrated that 5 ml. of 'Avlosulfon' Soluble equivalent to 1.0 g. of dapsone, by intramuscular injection gave peak blood sulphone levels up to 9.85 mg.% (average 7.53 mg.%) within one hour but that the level at 48 hours was less than 0.5 mg.%. DAVEY[16] (1956) using up to 4 ml. equivalent to 0.8 g. of dapsone, in general confirmed these figures. An extremely high level is attained within two hours declining to about 0.1 mg.% after 72 hours regardless whether the initial dose was 1, 2, or 4 ml. The dosage in the present trial (6 ml., equivalent to 1.2 g. of dapsone) is higher still and may therefore be expected to produce a peak level exceeding Lowe's 'safe' maximum ten fold but sustaining his 'effective' blood level for only three days out of the fortnight. Grosser fluctuation to our knowledge has not been used in sulphone therapy. It must be stated however that most of the circulating sulphone at the peak period is a water soluble form and therefore either 'Avlosulfon' Soluble itself or a metabolite other than dapsone. At 72 hours however the bulk of the sulphone circulating consists of the fraction extractable by benzene which is presumed to be the parent sulphone (dapsone).

Findings

TABLE I *Bacillary Index, Mean Values; Maximum Possible*, 12.

Drug	*Control Oral Dapsone*	*Oily Dapsone Suspension*	*Avlosulfon Aqueous Suspension*	*Avlosulfon Soluble*
At commencement	7.8	9.4	9.4	8.5
After one year	6.7	7.6	8.4	7.5
Improvement	1.1	1.8	1.0	1.0
	(14.1%)	(19.2%)	(10.6%)	(11.8%)

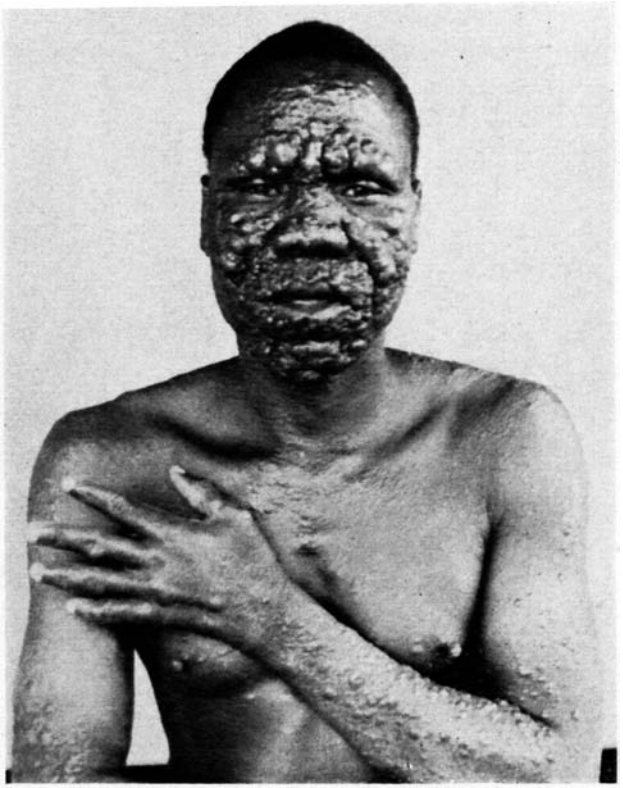

PLATE NO. 1. (*February*, 1958)

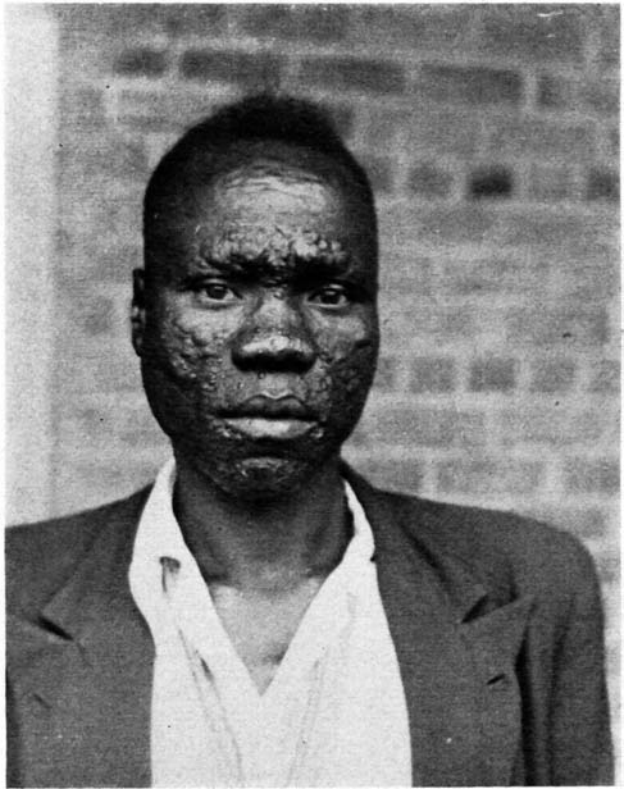

PLATE NO. 2. (*February*, 1959).

Clinical improvement as a result of one year's treatment with fortnightly injections of 'Avlosulfon' Soluble. Case No. 708 *(K.H.) A gross nodular leproma of eleven years duration. Oral dapsone therapy was instituted in October,* 1957 *and clinical improvement was detectable in January,* 1958. *After four months of oral therapy, injections of 'Avlosulfon' Soluble were substituted and a photograph (Plate No.* 1.) *was taken. A second photograph (Plate No.* 2.) *taken a year later in February,* 1959 *shows the striking improvement which has occurred.*

The improvement in bacillary index can be seen from Table I. This index cannot be regarded as an accurate yard-stick for measuring progress as too many variable factors are involved in taking, making, and reporting smears. All that can be said is that improvement has occurred in all four groups with a bias of doubtful statistical significance in favour of the oily suspension.

TABLE II *Evidence of Degenerative Change in the Bacilli*

Assessment of Bacterial Degeneration	*Control Oral Dapsone*	*Oily Dapsone Suspension*	*'Avlosulfon' Aqueous Suspension*	*'Avlosulfon' Soluble*
Nil (—)	—	—	—	—
Slight (+)	3	1	2	2
Marked (++)	7	9	10	9
Gross (+++)	3	3	1	2

Definite evidence of degenerative change in the bacilli occurred in all patients in the series as can be seen from Table II. There was no significant bias in favour of any one group and the tendency is in agreement with that shown by the change in the bacillary index.

TABLE III *Objective Clinical Improvement—Examiner's Assessment*

Assessment of Improvement	*Control Oral Dapsone*	*Oily Dapsone Suspension*	*'Avlosulfon' Aqueous Suspension*	*'Avlosulfon' Soluble*
Nil	—	—	—	—
Slight	5	8	4	8
Marked	8	5	9	5

TABLE IV *Subjective Clinical Improvement—Patient's Assessment*

Assessment of Improvement	*Control Oral Dapsone*	*Oily Dapsone Suspension*	*'Avlosulfon' Aqueous Suspension*	*'Avlosulfon' Soluble*
Nil	—	—	—	—
Slight	3	3	3	4
Marked	10	10	10	9

It is necessary to state what is meant by 'clinical improvement' when assessing progress. In this paper it is taken to mean evidence that the body defences are gaining ascendancy over the bacillary invasion. It is seen mainly as subsidence of lepromatous infiltration a process which can generally be discerned even during episodes of erythema nodosum leprosum (ENL) or other reactions which might tempt the assessor to record that the leprosy is 'worse'. The majority of our patients undergoing such reactions of moderate severity could distinguish the two processes. By this conception increases of

paralysis and anaesthesia and the occurrence of reactional lesions may not indicate that the patient's leprosy is worse but may rather be scars of an otherwise successful battle. Tables III and IV indicate that no patient has become worse under treatment and that clinical progress has been well maintained in all groups. There is little to pick and choose between them on this score.

Erythema Nodosum Leprosum (ENL)

DAVISON[17] (1957) regards ENL as a normal reaction in lepromatous leprosy receiving sulphones. It is universal experience that in susceptible subjects this reaction is provoked by high dosage or too rapid increase in dosage and lessened by reduction of dosage. This would suggest that the incidence of ENL in a given group of lepromatous patients might serve as an index of the therapeutic activity of the sulphone in use. The reaction is not confined to sulphone drugs, witness its occurrence perhaps in less degree with isoniazid and the thiosemicarbazones, nor is it merely an accompaniment of drug induced bacillary degeneration, witness the freedom from ENL of patients receiving the new potent drugs diphenylthiourea and diethyldithiol-isophthalate which produce a rapidity of destruction of the bacilli not previously experienced in the history of leprosy treatment. It can only be said that the significance of ENL is still obscure and that the question as to whether it is beneficial or harmful is still under debate. It does certainly interfere with therapy and lead to irreparable physical lesions. The incidence of ENL in the present series is set out in Tables V and VI.

TABLE V *Incidence of Erythema Nodosum Leprosum (ENL)*

Incidence of ENL Reaction	*Control Oral Dapsone*	*Oily Suspension of Dapsone*	*'Avlosulfon' Aqueous Suspension*	*'Avlosulfon' Soluble*
Nil	4	2	4	6
Mild	3	5	4	3
Severe	3	3	5	2
Very Severe	3	3	Nil	2
Total ENL	9 (69%)	11 (84%)	9 (69%)	7 (54%)

TABLE VI *Reduction in dosage necessitated by ENL over a period of one year expressed as a percentage of the scheduled total dosage for the year.*

	Control Oral Dapsone	*Oily Dapsone Suspension*	*'Avlosulfon' Aqueous Suspension*	*'Avlosulfon' Soluble*
Reduction in dosage	11.0%	14.5%	6.0%	11.0%

A distinct difference is seen in the incidence and pattern of ENL

reactions in the four groups. The total incidence is high. However, about 15% of the reactions were so mild that the patients did not consider them worth reporting and they were discovered only as a result of close routine surveillance and questioning. The hydnocarpus oil vehicle produced beyond doubt the highest incidence and the greatest severity of ENL reactions. In addition two cases of erythema multiforme (papulate variety) occurred in this group which have not been included under ENL in Table V, and the two cases which were eliminated from the series as a result of gross reaction were in the oily suspension group.

The 'Avlosulfon' Aqueous Suspension (ICI Compound 20, 177) provoked the same number of reactions as occurred in the oral dapsone group but the duration of reactions and their severity as reflected in dosage reduction which they caused was only half (54.5%) of that encountered in the oral dapsone group.

The 'Avlosulfon' Soluble (ICI Compound M 2196) gave rise to the least number of ENL reactions but these tended to be moderately brisk and the dosage reduction called for was equivalent to that in the control group where more reactions occurred. Dosage reduction was probably exaggerated by our greater caution, which seemed indicated by the extreme fluctuation of blood levels produced by this sulphone. Thus, although the 'Avlosulfon' Soluble group received a dosage in terms of dapsone identical to that of the control group, the incidence of ENL was less.

Side Effects

Before the trial began the 52 selected patients were questioned as to what side effects they experienced on standard oral dosage of 300 mg. of dapsone twice a week. There were 37 who admitted to various side effects occurring from 5 to 24 hours after swallowing the tablets and passing off generally by the 48th hour. The side effects, which were quite independent of episodes of ENL, were as follows:

No. of Patients	*Nature of Side Effect*
7	General tiredness and physical depression interfering with performance of the task allotted for the day.
22	Various paraesthesiae including formication, biting, prickling and burning sensations in the skin and superficial tissues.
11	Deeper aches and neuralgic pains often described as being felt 'in the bones'.
17	Headaches, mostly frontal.
7	Abdominal colic.

Sleep was commonly disturbed by such symptoms on the night following treatment but none of the patients admitted to troubled or excessive dreams. One patient obtained temporary relief from his burning sensation by taking a cold bath in the night.

TABLE VII *Incidence of side effects*

Drug	*Control Oral Dapsone*	*Oily Dapsone Suspension*	*'Avlosulfon' Aqueous Suspension*	*'Avlosulfon' Soluble*
No. of Patients	9	1	—	5

It will be seen from Table VII that side effects are virtually absent from parenteral sulphones with the exception of 'Avlosulfon' Soluble, and that despite the high blood concentration produced by this drug side effects were markedly fewer and milder than with oral dapsone. As might be expected, no clear relationship was found between the incidence of ENL and the above side effects. Of the 36 patients who had no ENL, 11 (68%) had no side effects. It can therefore be assumed that the phenomena are separate. An attack of ENL may of course mask the occurrence of side effects.

TABLE VIII *Incidence of Pain on Intramuscular Injection*

Drug	*Oily Dapsone Suspension*	*'Avlosulfon' Aqueous Suspension*	*'Avlosulfon' Soluble*
No. complaining of mild pain	6	11	9
No. complaining of severe pain	7	2	4
Average duration of pain (days)	2.5 days	1.3 days	2.1 days

The incidence of pain following the administration of the parenteral sulphone preparations can be seen from Table VIII. The oily suspension proved to be the most painful. Several patients were unable to perform manual labour for one or two days following injection into the deltoid muscle and swelling was a feature in most patients of this group. Two sterile abscesses occurred which had to be opened. The 'abscesses' were found to be virtually depots of oil and resulted from inadequate massage and failing to change the site of the injection sufficiently in subsequent injections.

Pain and swelling with 'Avlosulfon' Aqueous Suspension were negligible.

'Avlosulfon' Soluble caused moderate pain on intramuscular injection but the local reaction was not incapacitating and was not associated with abscesses or significant local swelling.

All patients were asked at the conclusion of one year of injections whether they wished to continue with injections or to resume oral dapsone. Only three patients, all in the oily suspension group and all timid souls, expressed a preference for tablets on account of the discomfort of the injections. The reasons given for preferring

injections were the absence of side effects and of general physical depression which the patients associated with oral dapsone treatment.

Anaemia

The causes of anaemia in sulphone treated leprosy are complex. It is common in untreated lepromatous leprosy as a result of depression of the haemopoietic system or actual involvement of the bone marrow. It also complicates sulphone treatment of dermatitis herpetiformis and other skin conditions occurring in patients who have no leprosy. Furthermore it is common experience that a fall in haemoglobin accompanies severe ENL reactions in treated leprosy.

Gross anaemia was seen only in the hydnocarpus oil group and occurred in three out of the original 15 patients in the group, associated with ENL, and severe enough to give rise to some anxiety. It is of interest that the anaemia was haemolytic in type and accompanied by pre-hepatic jaundice with no evidence of hepatitis. Improvement followed reduced sulphone dosage coupled with the administration of iron and liver extract in two patients, but the third patient was eliminated from the series because of the severity of the anaemia and slow response to treatment.

Haemolysis accompanying ENL reactions would appear to be an allergic phenomenon. HART[18] (1955) draws attention to the fact that red blood cells, like the tubercle and leprosy bacilli, have a predominantly lipid outer layer the composition of which influences their sensitivity to haemolysis during thermal shock, and BOYDEN[19] (1955) points out that if red blood cells are treated with polysaccharides (from a variety of different bacteria) these cells can be rendered susceptible to specific anti-polysaccharide sera. The association of ENL with haemolytic anaemia would suggest a common basis. Presumably a polysaccharide derived from the *M. leprae* antigen complex is involved in both phenomena forming in the latter a lipo-polysaccharide complex on the surface membrane of the red blood cells and rendering them susceptible to circulating antibodies. If further experiment confirms that there is an increased incidence of both ENL and haemolytic anaemia when hydnocarpus oil is used as the vehicle it might be regarded as circumstantial evidence of adjuvant action by the oil. To quote HANKS[20] (1958), "injection of oils and esters into leprosy lesions probably constitutes the first clinical application of the adjuvant principle to an immunological problem". In this case the esters were not injected into the skin lesion and a meeting of esters and antigen in the regional lymph glands must be postulated, which is not improbable. Granulomatous reactions in regional lymph glands have been demonstrated by UNGAR[21] (1948) following subcutaneous injections of synthetic fatty acids into sensitized guinea-pigs. The fact that leprosy bacilli also reach the regional lymph glands is neatly illustrated by the

lymphadenitis which so often heralds an ENL reaction. It is of interest to note that the glands most prone to such inflammation are those situated in cold parts of the body such as the sub-mental, pre-auricular and epitrochlear glands whereas those lymph nodes which are maintained at body temperature appear to escape. The dosage of ethyl esters of hydnocarpus oil used in the present series is insufficient for therapeutic advantage (unless given by the intra-cutaneous route) and leprologists are now unwilling to claim that the vehicle can exert any appreciable synergistic therapeutic action in this dosage. It may well however predispose to the occurrence of ENL reactions.

Other Reactions

The classical lepra reaction did not occur. No cases of dapsone psychosis, incipient psychosis, sensitization dermatitis, or hepatitis were seen and no other major reactions complicated therapy.

Discussion

Therapeutic Action

There is little to choose in therapeutic effectiveness between the many sulphones which have been used in leprosy and it was not expected that one drug in this trial would prove more potent than another. It was anticipated that 'Avlosulfon' Soluble in such widely spaced dosage might show some falling off of bacteriostatic action and it is of considerable interest that no such inferiority of therapeutic action was demonstrated. TOUZIN[15] (1953) has doubted the necessity of maintaining a constant blood level and DAVEY[16] (1956) has suggested that brief phases of high blood sulphone too transient to produce toxic signs may exert a good chemotherapeutic effect by periodic 'hammer like' action. Both authors were referring to their experience with 'Avlosulfon' Soluble injected twice a week. Their opinions are strongly supported by our experience with fortnightly spacing of the injections. A second year will be required to confirm initial impressions, but, to borrow a phrase from the cardiologists, 'regular irregularity' of blood level with a 'hammer blow' lasting a few hours and an 'effective concentration' maintained for only three out of fourteen days has produced clinical improvement comparable to that achieved by sustained blood concentrations.

Reactions

The incidence of reactions in the four groups is interesting and indicates the need for accurate definition of the term. The 'lepra' reactions which occurred were all of the erythema nodosum or erythema multiforme type. The use of the term lepra reaction by workers in other continents, especially India, suggests that reactions among other races may approximate more closely to the picture of

classical lepra reaction as encountered in untreated or hydnocarpus treated leprosy. It has been claimed that lepra reactions and ENL are less frequent when sulphones are administered parenterally. This has not been our experience. Indeed the incidence and severity were markedly greater in the hydnocarpus oil suspension group.

It has also been claimed that a fluctuating blood sulphone level predisposes to reactions. In the 'Avlosulfon' Soluble group exhibiting gross blood fluctuation the incidence of ENL was actually less than in the other groups nor was it related to the time of peak sulphonaemia. Reactions beginning in the second week after injection were as frequent as those occurring during the first week when blood concentrations were high.

Lepra reactions and ENL must be distinguished from drug side effects. This may appear a statement of the obvious but may not be easy for leprosy workers contending with uneducated and primitive people and a language barrier. Although no significant reduction of the incidence of ENL occurred when dapsone was given parenterally, unpleasant and depressive side effects common with oral dapsone were greatly diminished. It must be admitted that such side effects are less common when dapsone is given orally in *daily* dosage of 100 mg., as is our practice with outpatients at this leprosarium, than with twice weekly dosage of 300 mg. In the case of 'Avlosulfon' Aqueous Suspension side effects appeared to be virtually eliminated. The relative well-being which results from freedom from such side effects may lead the patient to state that 'reactions' are less with injection therapy than with oral dosage.

The significance of the increased incidence of ENL in the oily suspension group must remain obscure in the present state of our knowledge. Our findings agree with those of COCHRANE[22] (1959) that the oily vehicle has a greater liability to precipitate reactions. ENL may be regarded as an allergic flare-up which is a concomitant of successful sulphone therapy but not necessarily part of the essential immune mechanism of the host. It only occurs and is therefore only a nuisance in lepromatous leprosy. Injection therapy however lends itself best to the outpatient treatment of tuberculoid leprosy in which ENL reactions do not occur. In such patients skin sensitization (tuberculin type) is an essential factor in the immune reaction and adjuvant action of the oil, if proven, may be of advantage.

Psychological Factors

The psychological appeal of injections varies from community to community. In Nyasaland the Bantu people have great faith in the healing power of the needle and (with the exception of timid individuals) a painful injection is deemed more potent than a painless one and may be more appreciated if not repeated too often. The immense popularity of neoarsphenamine as used in yaws campaigns

in the continent can be partly attributed to the bitter taste experienced during injections which impressed primitive patients. Injection therapy is therefore a useful device for popularising leprosy treatment in Africa. Therapeutic benefit and faith in the drug are established before injections begin to pall. Ideally the injection should be as painless as possible and in this respect 'Avlosulfon' Aqueous Suspension was the most satisfactory preparation.

Ease of Injection

The viscosity of the suspension in ethyl esters of hydnocarpus oil calls for considerable muscular effort on the part of the injector particularly when a 20 ml. syringe is used. This difficulty was not encountered with 'Avlosulfon' Aqueous Suspension and the small volume of the injection (3 ml.) apart from reducing pain at the injection site is an advantage in mass treatment, saving time spent in charging syringes. Neither the oily nor the aqueous suspension showed any tendency to cake on standing for periods up to two years and needle blocking was not a nuisance with either preparation. The needle used in all injections was a gauge 20 serum needle with an internal diameter of 0.9 mm.

Summary and Conclusions

A trial is described of one short acting sulphone ('Avlosulfon' Soluble) and two long acting sulphones (dapsone suspended in ethyl esters of hydnocarpus oil and 'Avlosulfon' Aqueous Suspension) given in roughly equivalent dosage by intramuscular injection at fortnightly intervals. The control group received dapsone 300 mg. twice a week by the oral route. Thirteen lepromatous patients in each group completed the first year of the proposed trial and preliminary results are presented and discussed.

No significant difference in therapeutic activity has been detected between the four preparations. The effectiveness of 'Avlosulfon' Soluble administered at fortnightly intervals in dosage equivalent to 1.2 g. of dapsone supports the view that a sustained blood sulphone level is not essential and that briefly sustained high peak levels at fortnightly intervals are therapeutically active.

The claim that dapsone administered parenterally gives rise to fewer 'lepra' reactions and ENL than by the oral route was not confirmed, but side effects of the drug were markedly less when it was administered by injection. The grossly fluctuating blood sulphone levels produced by 'Avlosulfon' Soluble did not provoke an excess of ENL reactions.

On the grounds of freedom from pain, absence of side effects, convenience of injection and economy in the total quantity of sulphone used the 'Avlosulfon' Aqueous Suspension was considered to be the preparation of choice.

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