THE ACTION OF DIASONE IN THE TREATMENT OF LEPROSY

(PRELIMINARY REPORT)

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The study of leprosy has made definite progress in the last few years, but as regards the treatment progress has been unsatisfactory. In spite of the many drugs which have been tried, the drug which fully satisfies the therapeutic problem presented by the disease has not been found.

It is true that chaulmoogra oil and its derivatives have proved during the course of time to be useful in the fight against leprosy, but it is not less true that this remedy is far from being the *"desideratum"* which is hoped for. This is recognized even by its most enthusiastic defenders.

In considering this problem in another paper (2) we drew attention to the two paths which lie before the investigator who attempts to find a solution:

a) he must either take advantage of the possibilities which are offered by chaulmoogra oil, perfecting its therapeutic action by studying new derivatives and new techniques of administration,

b) or he must try new therapeutic agents which can be used as substitutes.

We have directed our efforts along both paths for some time in the "Professor Enrique P. Fidanza" Clinic for the Treatment of Leprosy in the Carrasco Hospital, by giving on the one hand the esters of chaulmoogra oil by the intravenous drip method (1) or using the duodenal catheter (2) and by studying on the other hand the action of new "sulfa" drugs such as soluthiazamide and diasone.

In the present article we discuss the first results obtained in a group of patients treated with diasone.

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THE USE OF "SULFA" DRUGS IN THE TREATMENT OF LEPROSY

The "sulfa" derivatives have been employed with varying success in the treatment of tuberculosis and as the Koch bacillus is very similar in many ways to the Hansen bacillus, it is logical that these drugs should also be tried in the treatment of leprosy.

Up to the present we have met with only three published articles dealing with the use of "sulfa" derivatives in the treatment of leprosy.

The first is that of FAGET *et al* (3) which appeared in 1943. These workers discussed the results obtained with promin*, the sodium salt of n.n. bidextrose sulfonate of p.p. diaminodiphenylsulfone. They considered this drug to be most active of the sulfanilamides which had been tried in the National Leprosarium of Carville, amongst them being sulfanilamide, sulfathiazole, sulfapyridine, and sulfadiazine. Promin could be given both orally and intravenously. They used it by the intravenous route for these investigations as they considered it was less toxic than if given by mouth. The majority of patients undergoing treatment received 1 to 5 Grams daily for six days of the week, this dosage being continued for months.

These workers found that the most frequent and important sign of intolerance provoked by the use of promin was anemia which was observed in 46 per cent of the patients. It was treated with organic iron, liver, etc. Allergic dermatitis (16 per cent), rhinitis, nausea, and other less important symptoms also occurred as result of treatment with the drug.

The results obtained by FAGET and his collaborators were promising. They showed that cutaneous and mucosal ulcerations were definitely improved as also were ocular lesions.

In a first group of 22 patients undergoing this treatment for a year, 15 were improved, 6 remained the same while 1 grew worse. In a second group of 46 new cases in which the treatment was carried out for an average of 8 months, 26 improved, 17 remained the same while 3 grew worse.

The authors came to the conclusion as a result of these experiments that although they did not consider promin was a specific for leprosy, it did constitute a decided advance in the treatment of the disease.

The second article dealing with this subject is that of SOUZA LIMA and CASTRO CERQUEIRA (4) which is a preliminary report of the results observed in a group of cases treated with soluthiazamide. This drug** is a p.(y-phenyl-propylamine) phenylsulfonamidothiazole-x-y-disulfonate of sodium. It is prepared directly from 2(p.aminophenylsulfonamido) thiazole or thiazamide and a cinnamic derivative. The authors used a solution with a 20 per cent thiazamide base concentration for their experiments. Each 5 cc. ampule thus contained 1 Gram of the drug, the pH of the solution varying between 6 and 7.

One hundred patients were treated, 50 being children with a moderate lepromatous type of the disease and 50 adults with severe lepromatous type. In all, previous chaulmoogra oil therapy had failed.

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* A Parke, Davis & Co. product.

** A product of the Rodhia Laboratories.

The soluthiazamide was given daily intravenously for 6 days per week for series of 3 consecutive weeks with 1 week's rest. The first dose was 1 cc. and it was progressively increased to 5 cc. in the children and 10 cc. in the adults. The patients' blood and urine were periodically examined, remedies being given to counteract the anemia when the blood count fell below 3,500,000. Generally speaking, tolerance was good.

After 8 months trial, satisfactory results could be reported. Infiltration was reduced, with flattening of the leprous nodules and plaques; ulcers healed and ocular lesions improved. Soluthiazamide was definitely proved to have detained the progress of the disease in many of the cases. In view of these results the authors believed further experimental treatment with the drug should be carried out so that definite conclusions might be reached.

The third article we have encountered is a preliminary report published by MUIR (5) in which the results obtained with diasone are discussed. MUIR treated 100 patients of the lepromatous type in the Leprosarium of Chacachacare, Trinidad.

The drug was given both intravenously and orally. The injections were prepared by dissolving 0.30 Grams of powder in 1 cc. of sterilized normal saline. At first the injections were given daily 6 times a week, the initial dose of 2 cc. being gradually raised to 8 cc., but owing to technical difficulties, and also in order to obtain a better tolerance, the injections were reduced to 3 per week, the dose varying always from 2 to 8 cc. When given by mouth capsules containing an equal dose were used.

Intolerance was shown by a lowering of the red blood cell count and hemoglobin. There were, however, no renal disturbances even in those patients already suffering from albuminuria. In some cases there was weakness, loss of appetite, and fever which required suspension of the treatment or a decrease in dosage. When the hemoglobin fell below 71 the dose was reduced to 1.3 Grams or even less, 3 times a week. Iron sulphate was given in those cases where the hemoglobin fell below 78.

The results noted by MUIR were: improvement in the general health; flattening of cutaneous nodules; healing of leprous ulcers; improvement in nasal lesions and inflammatory ocular complications and improvement of the fever and chronic leprous reactions.

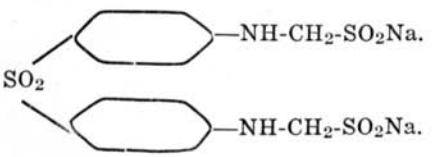
In a first group of 43 patients in which either oral or intravenous treatment was carried out over a period of 3 months, 24 showed frank improvement, 17 slight improvement, and 2 remained the same. In a second group of 41 patients treated only from 2 to 3 months, 36 showed slight improvement and 5 remained the same. None of the patients treated became worse and the longer the treatment was continued the better the results.

MUIR came to the conclusion that the results obtained using diasone were encouraging and if a definite opinion could not yet be given there was reason to believe that a firm step forward in the treatment of leprosy had been taken.

OUR INVESTIGATIONS

The Drug

Diasone is di-sodium formaldehyde sulfoxylate, a derivative of diaminodiphenylsulfone. The structural formula of this preparation is the following:



The compound was independently synthesized by RAIZISS and his collaborators of the Dermatological Research Division of the Abbott Laboratories and by BAUER and ROSENTHAL of the U. S. Public Health Service. It is prepared by the Abbott Laboratories which furnished the supply used in the test at the request of Professor M. H. SOULE.

Diaminodiphenylsulfone and some of its derivatives have proved to be much more effective in the treatment of experimental tuberculosis of guinea pigs than have the derivatives of the sulfonamides. Diasone has been shown to be better tolerated by man than many of the other derivatives of diaminodiphenylsulfone.

The maximum doses of diasone tolerated by laboratory animals when given by mouth are the following: mice, 4 Grams per Kg. of body weight; rats, 7 Grams; and rabbits, 3.5 Grams. Two dogs weighing between 15 and 20 Kgs. were given 1 Gram of the drug per day by mouth for 60 days and appeared to be perfectly well throughout the experiment.

CALLOMON found that guinea pigs tolerate the drug well, using a dose of 0.30 Grams per Kg. body weight daily for periods of over 6 weeks, and FELDMAN and his collaborators, also experimenting with guinea pigs, obtained similar results with doses of 325 to 350 milligrams daily for 182 days.

This drug has proved to be nearly as efficient as sulfanilamide in the treatment of experimental hemolytic streptococcal infection of mice, and also nearly as efficient as sulfadiazine in the treatment of experimental pneumococcal infection in mice. Diasone also has been used by several investigators in the treatment of experimental tuberculosis in guinea pigs with favorable results.

Plan of Treatment

The dosage of diasone is still in the experimental stage. It has been suggested that the average dose for an adult should be 1 Gram daily.

The drug is put up in 5 grain capsules (0.33 Grams) and it is advisable to begin the treatment using one capsule daily, increasing progressively to three. Daily doses of over 2 Grams have been given with no severe toxic reactions.

The drug has been given continuously without rest periods in treatment of tuberculosis; nevertheless it is thought that intermittent administration is best on the same principle as in arsenic or

bismuth therapy of syphilis. Experimental observations show that the diasone concentration in the blood begins to decrease in the majority of cases after 6 to 8 weeks treatment. Keeping this fact in mind we have given diasone in 8 week courses divided by 3 to 4 weeks' rest. We start the course with one capsule the first day, two the second, three the third, repeating this dose for 2 to 3 days. If there is no intolerance, we give four capsules daily for 2 or 3 days, raising the dose to five, six, seven, and eight capsules daily, repeating each increased dose for 2 or 3 days in order to test the tolerance.*

When the maximum daily dose which can be tolerated is reached it is continued until the end of the 8 week course. The average daily dose best tolerated in the majority of our patients has been six capsules which is equivalent to 2 Grams of the drug.

Needless to say this plan of treatment can be modified according to tolerance. Some patients can receive a daily dose of nearly 3 Grams without ill effects while others tolerate only 1 Gram. We agree with MUIR'S opinion that the more intensive and prolonged the treatment the better the results.

Tolerance

As with other drugs of its type, diasone cannot be given unless the patient is kept under constant supervision. It frequently induces reactions which if promptly treated with adequate remedies are not of great importance. With the exception of one case of severe anemia which is discussed presently we have not had any serious complications among our 62 patients undergoing treatment at the present time.

1—Clinical Symptoms

Most of the clinical symptoms of intolerance observed make their appearance during the second week of treatment and are the result of the anemic state provoked by the drug. Almost all diminish or disappear either with temporary suspension of treatment or when anti-anemia measures (liver, iron, vitamin B complex) are taken with continuance of the drug.

Asthenia and *depression* were the most frequent signs of intolerance which have been found in our patients (88.6 per cent). They usually occur during the second week of treatment when the daily dose exceeds 1 Gram.

Cyanotic color of the tissues is also a frequent sign of intolerance and is due to the formation of metahemoglobin.

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* Later experience has shown us that the same dose should be repeated for a longer time (i.e. 4 to 5 days) until the maximum daily dose is reached.

Headache sometimes accompanied by dizziness occurred in 74.2 per cent of the cases. It is nearly always moderate and comes early in the second week. It can be overcome by analgesics or better still by treating the anemia.

Nausea and *loss of appetite* were observed in 55 per cent and 34 per cent of the patients respectively. Only in one case was the intensity of these symptoms sufficient to warrant the suspension of treatment.

Fatigue and *breathlessness on exertion* were seen in 49.8 per cent of the patients. These symptoms are the ones most closely connected with the fall in the blood count.

Leprous reactions of the cutaneous type or localized in the eye were observed in 74.2 per cent of the cases as a result of treatment. The former were much more frequent than the latter and in certain instances were of a violent nature with high temperature and a generalized rash. Simple reactivation of the cutaneous lesions, i.e. their congestion and softening without associated symptoms, was a frequent occurrence in the treatment with diasone and we feel that this focal reaction is the commonest sign of the activity of the drug.

In one of our female patients there was an accentuated inflammatory reaction round the nerves as a result of the treatment with diasone. In a few cases where there was an ocular reaction this was relieved by the intravenous injection of benzylic esters of chaulmoogra oil together with the administration of calcium gluconate.

In some patients there was a well marked *conjunctival* reaction, accompanied by intense vascular congestion and watering. These symptoms disappeared without suspension of treatment.

Finally we may remark that there has been an increase in weight and evident improvement of the general health in many of the patients undergoing treatment.

Red blood cells

All those reporting on the use of the sulfonamide derivatives in the treatment of leprosy have found that they cause anemia.

In a total of 35 cases in which a complete hematological study was made during the course of treatment with diasone we found:

1—In 29 patients (82.8 per cent) the remedy provoked a fall in the red blood count. In 11 cases this was from 500,000 to 1,000,000; in 10 cases, from 1,000,000 to 1,500,000, and in 8 cases from 1,500,000 to 2,000,000.

2—As a general rule the degree of anemia was in direct relation to the dose of diasone administered. It appeared frequently after the second week and when over 20 Grams of the drug had been given.

3—In all cases observed except one in which it was necessary to give blood transfusions, the anemia responded to temporary suspension of the diasone treatment, or to the administration of liver extract or iron.

Hemoglobin

In the majority of our patients under treatment a decrease in the hemoglobin concentration of the blood parallel with the fall in the red blood cells was noted. In 3 cases the hemoglobin fell to 40 per cent and the drug had to be discontinued and anti-anemia measures taken. Fairly often the hemoglobin fell below 70 per cent without the necessity of suspending the treatment.

White blood cells

None of our treated patients had an accentuated leucopenia. In 18.8 per cent the decrease in white blood cells varied between 1,000 and 2,000 and in 18.8 per cent between 2,000 and 4,000. In several cases treatment was begun in spite of the fact that the white blood cell count was below normal without any adverse results. Nevertheless we think the white blood cell count must be taken into special consideration when treating patients with diasone since this is a sulfonamide product and may bring about agranulocytosis.

Treatment of the changes in the blood

We have made use of the current remedies, liver extract, iron salts and vitamin B complex for the treatment of the anemia caused by diasone. In one group of patients we gave as part of the routine after the second week 3 weekly injections of 1 cc. of simple liver extract as well as iron salts by mouth. In another group we gave such treatment only if the blood picture or clinical symptoms advised it. However whether early or late all our patients received anti-anemia treatment and perhaps this was the reason for the fact that diasone was so well tolerated in spite of the high dosage. Treatment was suspended if the blood picture or clinical symptoms warranted it but our experience has not yet enabled us to make precise rules as to when this is necessary. As a general rule we decreased the daily dose when the red blood cells fell to 3,000,000. On occasion we temporarily suspended treatment for 1 or 2 weeks until the blood picture improved and at the same time intensified anti-anemia measures.

In a female patient (L_3) who had received 20 Grams of diasone over a period of 18 days, the anemia became serious (2,300,000 red blood cells and 40 per cent hemoglobin) and 3 transfusions of 200 cc. each were given. This profound anemia, together with asthenia, breathlessness and headache, was associated with a violent leprous reaction with generalized rash and ulceration of lepromata. The leucocyte count rose to 18,000 and this alarming state lasted nearly a week.

Because of these observations we consider that during treatment with diasone it is imperative to keep the patients under strict supervision and above all to make an examination of the blood at least every 10 days.

Results of Treatment

At present we have 62 patients undergoing treatment with diasone. The great majority are of the advanced lepromatous types (L_2 and L_3) only a small number being of types L_1 and Ns. Nearly all these patients had previously been treated with chaulmoogra oil but without success owing to intolerance.

To recapitulate, each course or series of treatment extends over a period of 8 weeks during which the patient receives the drug continuously at the maximum tolerated dose. This dose varies between 3 and 7 capsules (1 to 3 Grams) taken by mouth daily, the total dose given during a series reaching between 180 and 300 capsules (60 to 100 Grams). Between each series of treatments there is a 4 weeks rest.

The following are the results in the 42 patients who have completed at least one series:

No. of series of treatment received	No. of cases treated	Results				
		Condition the same	Improved	Much Improved	Total of cases improved No.	Per Cent
3	5	—	—	5	5	100.0
2	11	4	5	2	7	63.6
1	26	13	10	3	13	50.0
Totals	42	17	15	10	25	59.5

RESULTS

Clinical Results

The most frequent and earliest sign of the activity of diasone is the softening and the ulceration of the nodules, tubercles, and plaques; these lesions lose their hardness, become congested, soften in the middle then ulcerate and become covered with an adherent

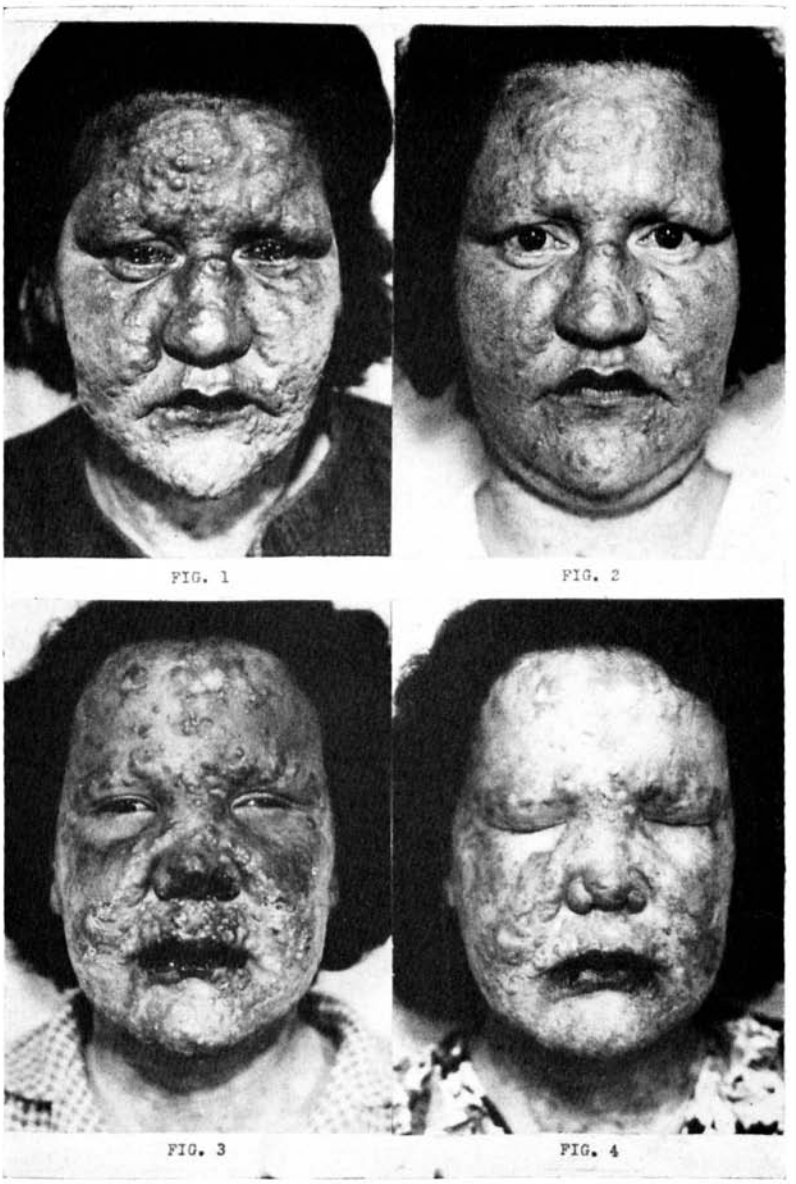

FIG. 1 FIG. 2

FIG. 3 FIG. 4

Figures 1 and 2. Patient L_3 at the beginning of treatment and at 5 months (287 Grams of diasone) after beginning of treatment.

Figures 3 and 4. The result of diasone in an advanced case L_3 after 3½ months treatment (157 Grams). Note the scarring of the nasal ulcers.

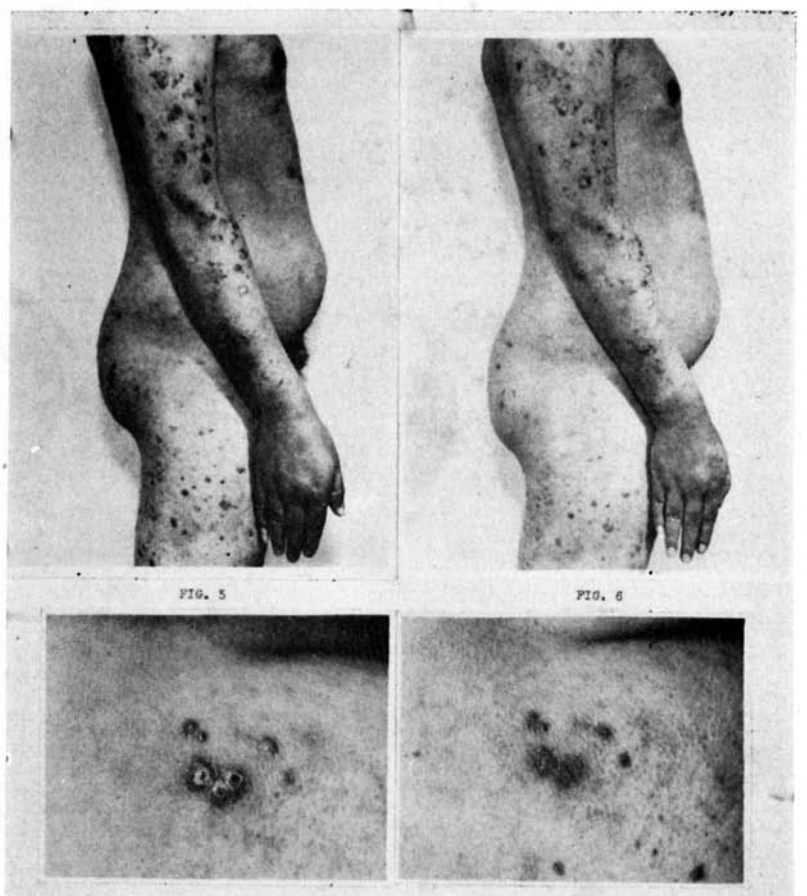

FIG. 5 FIG. 6

Figures 5 and 6. This patient L_2 also shows an evident improvement after a period of treatment in which 61 Grams of diasone were taken. The nodules and leprous plaques are re-absorbing and atrophing in their centers as can be seen in the photograph, leaving an annular plaque.

Figures 7 and 8. Two stages in the retrograde evolution of the lepromatous nodules after 15 days treatment (20 Grams of diasone) and at 3 months (100 Grams of diasone). The ulceration of the nodules and their healing and flattening can be clearly seen.

crust, as can be seen in figure 7. This inflammatory stage is followed by a flattening and reduction in bulk (Fig. 8). Sometimes the re-absorption is complete and the only sign left is a scar or residual stain. In other cases the re-absorption is complete in the center of the lesion but partial at periphery; thus an annular lesion with central atrophy and raised infiltrated edges remains (Fig. 6).

Sometimes these lesions diminish partially or even entirely without any apparent inflammatory reaction. In these cases the lesions progressively flatten and later assume the typical folded or wrinkled appearance which characterizes the involuntary process in this kind of lesion.

The nodules and deep plaques which are made by the confluence of subcutaneous lepromatous infiltrations are also improved by diasone. In these forms also the re-absorption either follows an acute inflammatory stage or may occur quickly and progressively without inflammation. These lesions, only evident on deep palpation, diminish in bulk and sometimes completely disappear.

Ulcerated lesions of the skin and mucosa are appreciably improved by the treatment. The healing which occurs is one of the most impressing results of the drug to the patients. In figure 4 the favorable evolution undergone by ulcerous lesions of the face after 10 weeks treatment can be seen. The healing of the lesions of the nasal mucosa brings about an immediate improvement of the leprous rhinitis and with it that of the respiratory function. The macules (L_1 cases) are the lesions which are least affected by the treatment.

Bacteriological Examination

Bacteriological examination of the patients was made before beginning the treatment and was repeated periodically during the course of the same.

Nevertheless up to now we are unable to give a categorical opinion as to the effect of the drug on the bacillus. In patients who show clinical improvement, the bacteriological picture was characterized by a marked predominance of the granular forms of *M. leprae*. The homogenous bacilli disappear, being replaced by streptococcoid bodies and isolated granules, but always well-staining, which means that they conserve their acid-fastness. In some cases some badly stained and even cyanophile bodies were seen in small numbers. As regards the number of bacilli contained in the lesions we have not been able to show a definite reduction in the treated cases.

To summarize therefore, as a result of our investigations, we

can only draw attention to the morphological changes of *M. leprae* (granulation of the homogenous rods) due to the drug.

DISCUSSION

As our experiments with diasone treatment have covered only a period of 8 months and the number of patients is relatively few we are obliged to be very careful in our estimation of the results obtained. Nevertheless an objective analysis of the facts observed allows us to hold a favorable opinion based on the following reasons:

a) Our investigation has been carried out on patients in an advanced stage of disease all of whom had received prolonged treatment with chaulmoogra oil.

b) In spite of the unfavorable types of cases, none became worse while under treatment; in nearly 60 per cent there was marked improvement, while in the remaining 40 per cent the disease remained stationary.

c) The improvement was the more marked the longer the treatment.

d) The possibility of giving the drug by mouth is a definite advantage in the treatment of an illness over a long period of time.

SUMMARY

The action of the oral administration of diasone has been studied in a group of advanced cases of leprosy of whom almost all had previously been treated with chaulmoogra oil. The drug was given for periods of 8 weeks with a daily dosage varying between 1 and 3 Grams according to individual tolerance; between each period or course of treatment there was a 4 weeks' interval.

Anemia (82 per cent), asthenia and depression (88 per cent), headache (74 per cent) were noted as signs of intolerance. There were no grave consequences and intolerance was readily treated with liver extract, iron, and vitamin B complex.

Activity of the drug was shown by softening, ulceration, and re-absorption of leprous nodules, healing of ulcers, and re-absorption of deep lepromatous infiltrations.

Bacteriologically, granulation of the bacilli was observed but in no case had bacilli completely disappeared from the lesions.

The improvement noted was greater the longer and more concentrated the treatment. The results found after 8 months trial were the following: in 5 cases treated for 3 periods, 100 per cent improved; in 11 cases treated for 2 periods, 63.6 per cent improved; in 26 cases after only 1 period of treatment, 50 per cent improved.

Thus of 42 patients who had completed 1 to 3 periods of treatment, 59.5 per cent showed improvement.

Finally it may be stated that diasone has proved to be effective in the treatment of leprosy in a series of 42 patients observed for 8 months. Further experimental treatment should be carried out so that definite conclusions based on greater experience can be obtained.

ACKNOWLEDGEMENTS

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