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CONTENTS

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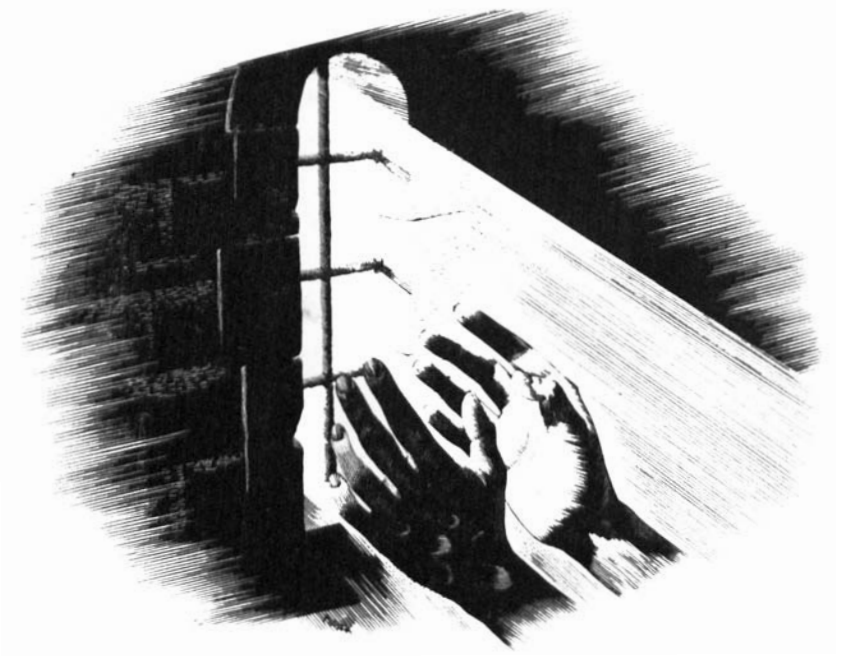

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EDITORIAL

Because of the rapid development of cheaper and more economical methods of sulphone therapy, it has been decided to issue another sulphone number. It is hoped that with the articles in the July-October issue of the Review, and those of this issue, workers will feel that they now have available authoritative opinion on the dosages, indications and dangers of sulphone therapy. We particularly welcome Dr. Lowe's contribution. Dr. Lowe was one of the first workers to use the parent substance by mouth, and this article is based on very great experience and demands the closest attention.

We publish the findings of a conference of leprosy workers held in the offices of BELRA on September 17th, 1951. These findings summarise the position of therapy to date. While the treatment of leprosy is now most satisfactory, the very fact that other remedies, such as the thiosemicarbazones, are being seriously discussed and compared, indicates that there is still scope for therapeutic research. To discover a drug which will destroy *M.leprae* quickly and in large numbers may not be the chief aim of therapy, for a remedy of this nature might produce serious effects, due to the rapid liberation of the toxins of M.leprae. Nevertheless the search for more active, quicker acting, and less toxic drugs must continue, for in a disease as widespread as leprosy, while treatment must be largely through the aid of untrained personnel, any drug the administration of which may give rise to toxic effects, must be looked upon with great caution and used until such time as a safer remedy is discovered.

Sulphone therapy has now passed the realm of controversy, and there is available enough information to assist individuals to select a sulphone preparation which is most suitable for use. The selection of this will depend on the experience of the workers, and the conditions pertaining in the country in which they work.

In passing, a plea might be made for agreeing on one abbreviation for the parent sulphone, diaminodiphenylsulphone. M. I. Smith, Feldman and others use the abbreviation DDS, while Muir, Lowe and the West African workers refer to DADPS or Dapsone. The Editor of the *International Journal of Leprosy* adopts the former abbreviation, and invariably refers to the parent sulphone as DDS. It would therefore be well if workers would adopt this, and in future this journal will refer
DDS.

The Medical Secretary of BELRA has just returned from the Pan-American Leprosy Conference. It was a great privilege to meet the workers in the Argentine and Brazil, and have the good fortune to visit the Armed Forces Institute of Pathology in Washington, and discuss matters of mutual interest. The opportunity thus afforded of studying histopathological material was of very great value, and has helped greatly to clear up points of doubt, particularly in relation to classification. A full report of the Medical Secretary's visit will appear in a forthcoming number of the Review.

STUDIES IN SULPHONE THERAPY

JOHN LOWE

PART 1. THE MODE OF ACTION OF SULPHONES

In papers already published (1 to 6), experience in the treatment of leprosy has been described, and the theoretical and practical considerations which led to the adoption, in mass treatment of leprosy in Nigeria, of the use of the parent sulphone, diamino-diphenylsulphone, (DADPS in Europe and DDS in America) in preference to its derivatives such as promin, diasone and sulphetrone.

DADPS, previously considered too toxic to use in human beings, was found relatively non-toxic and therapeutically active when given in small doses; it appeared that the soluble derivatives were probably inactive in themselves, but were rendered active only by being broken down to DADPS.; when given orally this breaking down was probably brought about mainly by the action of the stomach acid, some of the ingested sulphone however being unabsorbed and being passed in the stools, while some of the absorbed sulphone remained in its original, probably inactive, form, and was passed in the urine.

The giving of complex sulphones was therefore considered an irrational, expensive and troublesome method of securing the action of sulphone in the body, a purpose which could be achieved more rationally and much more simply and cheaply by the giving of small doses of DADPS. itself.

The attempt to make the use of complex sulphones more economical, or less toxic, or both, by giving them in the form of injections appeared even less rational than their oral use, for breaking down by the stomach acid was thereby prevented, and the amount of DADPS liberated reduced still further.

Previous papers described the treatment of leprosy by the oral administration of DADPS, at first experimentally, and later on a large scale as the routine treatment in the Nigeria Leprosy Service; this service

is now treating about twenty thousand patients by this method, with a bare minimum of medical supervision, and in most cases with no laboratory control of treatment. This mass treatment has been going on for over one year, and the success of this great experiment now seems assured. The cost of the treatment is a few shillings a year for each patient instead of 20-40 times this figure if the complex sulphones are given orally.

Since this work was instituted here and the earlier papers were published, it has become clear that groups of workers in other countries had been thinking and working on similar lines, and a number of papers with similar conclusions have appeared. More knowledge on the mode of action of sulphones is now available, and I have recently studied the matter more thoroughly.

The object of the present paper is to summarise the available published information, and to present the results of our further investigations. The matter is not merely of theoretical interest, but is of great practical importance in the treatment of leprosy and possibly of other diseases including tuberculosis.

Before going on to recent developments, it appears desirable to summarise the main facts about the development of sulphone therapy.

DADPS was shown to have marked anti-bacterial action on gram-positive organisms *in vitro* and in animals (7 and 8). Later it was shown to have a considerable action on *M. tuberculosis* in animals (9). Attempts to use it in man in doses of 1-2g. a day gave rise to serious toxic effects (10 and 11) and less toxic derivatives were sought. The first was promin (promanide); this was found toxic to man in oral doses of 1-2g. a day (12 and 13) but was well tolerated by intravenous injection, and this procedure became a routine procedure in the treatment of leprosy, and of tuberculosis until other agents replaced it. Nevertheless there were indications (12, 14) that the active as well as the toxic principle of promin was DADPS, that oral administration liberated more DADPS than parenteral administration, and that the reduced toxicity of injections might sacrifice therapeutic efficacy.

In tuberculosis, the results of sulphone therapy were disappointing, and were soon overshadowed by the results obtained with streptomycin. Promin given by injection has remained a standard treatment for leprosy, particularly in the U.S.A.

Other disubstituted sulphones followed promin, the best known ones being diasone and sulphetrone. These were tolerated on oral administration, in daily doses up to 1.8g and 6.0g respectively, and they have now been used for several years with good results in leprosy. While no such claim was made for other disubstituted sulphones, it was claimed for sulphetrone that it was active without being degraded. There is now considerable evidence that this is not so. Nevertheless injections of sulphetrone have been used and recommended for the treatment of leprosy in spite of the fact that injections prevent the degradation by acid hydrolysis in the stomach.

Later still, mono-substituted sulphones were introduced, and there was evidence that these were active per se without degradation to DADPS.

All these complex sulphones are expensive to use on a large scale; for wide-spread leprosy treatment in the poor countries where leprosy is common, a cheaper sulphone, (preferably given orally because of the lack of staff to give injections, particularly intravenous injections) was urgently needed.

At least three groups of workers, one British, one French, and one

Brazilian, saw reason for the belief that DADPS itself might, if used in small doses, be found to be a cheap, powerful and safe therapeutic agent in leprosy and possibly in other diseases.

The British group, encouraged by Francis who had used DADPS in veterinary medicine, and by Muir (who had been the first British worker to use sulphone therapy and had reported very favourably on the results obtained), included Cochrane in India, Lowe and Smith in Nigeria, and Molesworth in Malaya. Cochrane (15) was the first in the field to use DADPS, giving it by injection, unfortunately in doses too big to avoid serious toxic effects, although the results were promising. Molesworth and Narayanaswami (16) followed Cochrane in giving it by injection, but in smaller doses, and has reported good results. Lowe and Smith (5) gave it orally in low and very gradually increasing doses, and, without serious toxic effects, obtained results at least as good as with the complex sulphones they had previously used, and at a small fraction of the cost. Smith (17, 18) made studies here of the pharmacology of the different sulphones, with the results already outlined. The new work here recorded is really a continuation and amplification of the work done here by Smith.

The French group included Rist, Boyer and others in Paris, and Floch and Destombes in French Guiana. Boyer and others (19, 20) studied the pharmacology of sulphones and their use in experimental infections in animals and in human tuberculosis. Floch and Destombes (21) treated leprosy with small doses of DADPS, using both injections and oral administration. They reported good results.

Rist (9) had been the first to show the action of sulphones on experimental tuberculosis in animals; he has recently (22, 23) abandoned his previous view that DADPS was too toxic for use in man; he now views DADPS as the most active, perhaps the safest and certainly the simplest and cheapest of the sulphones, and thinks no complex sulphone is likely to be more effective.

In Brazil, de Souza Lima (24) has experimented with DADPS given orally, with results similar to those obtained by British and French workers.

In view of the recent developments in the use of DADPS in leprosy, tuberculosis workers are now re-examining the action of sulphones in tuberculosis, and some, particularly in France, consider that DADPS may have a part in the therapy of tuberculosis, for in addition to having some, possibly only slight, action itself, it has the action of delaying or preventing the development of streptomycin-resistance in the bacilli of patients under combined streptomycin-DADPS treatment. There is also some evidence that it prevents the development of PAS. resistance.

This then is the present position. It has been found that small doses of DADPS are safe and well tolerated, and give the full therapeutic effect in treatment. It is the belief of most who have studied the subject that complex disubstituted sulphones probably act by liberation of DADPS in the body, that they have not been shown to have any advantages over DADPS; they are much more expensive, especially when given orally. The present tendency in several countries is to abandon the use of complex sulphones and to use only DADPS.

It must be admitted that the truth of these ideas has not been fully demonstrated. Some strong evidence to support these views has recently been published, and further evidence is given in the present paper.

It should however be clearly understood that these views are

in accord with general chemical and pharmacological experience. As Wade (35) states " a widely accepted doctrine of sulphone activity demands, besides the *para* relationship of the essential constituent groups, that one or both amino groups be free or potentially free. Theoretically, because in promin, diasone and sulphetrone both the amino groups are occupied by substituents, they should be " blocked " and hence inactive." Wade goes on to say that *because of their instability* this is not so in practice. This is the crux of the matter; disubstituted sulphones, it is believed, owe their activity to their instability.

Methods of studying the metabolism of sulphones.

When complex sulphones are administered, it has long been believed that some of the sulphone in the body remains in its original complex form, while some is degraded to DADPS and possibly other derivatives, but until recently it was impossible to say how much of the sulphone present, in a specimen of blood, for example, was in its original complex form, and how much had been broken down. In the literature of sulphone treatment, blood levels are quoted as though all the sulphone in the blood was in the form in which it was originally given, although this has long been known or suspected to be untrue.

DADPS is readily soluble in organic solvents such as benzene and ethyl acetate, but is practically insoluble in water; the disubstituted sulphones promin, diasone and sulphetrone, are readily soluble in water, but are insoluble in the organic solvents mentioned. These facts have recently been used as the basis of several methods of separating and estimating DADPS from the blood of animals receiving complex sulphones. In the present paper the results of such studies in human beings are reported.

Before we go on to consider this work, there is one earlier piece of work to be mentioned. Disubstituted sulphones, before diazotisation and coupling as in the Bratton and Marshall process used in their estimation, have to be hydrolysed with acid to free the amino-groups; with DADPS, with its amino groups already free, this is not so.

M. I. Smith and co-workers (25) studied promin and sulphetrone in solutions and in the blood of animals (a) by direct diazotisation at room temperature and (b) by diazotization after acid hydrolysis, and obtained evidence that both were unstable *in vitro* and in the body fluids, producing DADPS.

Michael Smith (18) extracted, with ethyl acetate, the urine and blood of patients receiving sulphetrone or diasone, and

demonstrated the presence of DADPS; estimations of blood DADPS levels in such patients proved difficult.

The first successful attempt to study the matter thoroughly, in animals, was that of Titus and Bernstein (26) who extracted blood and urine with methyl-isobutyl-ketone, and then extracted this with acid. They were able to demonstrate the presence of DADPS in the body fluids of animals receiving disubstituted sulphones, and also were able to estimate its concentration. Their findings are discussed later.

Boyer and co-workers (20) used another method of studying the same subject in animals. Their method consisted essentially of the extraction with a solvent, and paper chromatography to identify the substance extracted, as DADPS.

Later still Francis and Spinks (27) used another method for extracting DADPS, the solvent used being benzene; the benzene extract is then extracted with acid, and the sulphone present estimated after diazotization and coupling. Their results also are discussed later.

The main method used in our present work is a modification of that of Francis and Spinks; we have found that, in our work, ethyl acetate appears a more efficient extractive than benzene; other modifications have been rendered necessary by the conditions of our work, in human subjects on low doses instead of in animals on high doses, and in rather primitive conditions in Africa, with no electricity to make the use of the electric absorptiometer possible. The method is described in the appendix.

The instability of disubstituted sulphone in vitro.

It has been presumed, or definitely stated, that disubstituted sulphones are stable in neutral solution *in vitro*. For example Brownlee (28) in his original report on sulphetrone stated " 40% solutions are stable when neutral or slightly alkaline, and a 60% solution may be autoclaved." The omission to state whether weak solutions are stable and can be autoclaved is, perhaps, significant. (In a more recent statement, the instability of weak solutions is reported by the makers of sulphetrone). Brownlee et al (29) also stated that sulphetrone was not a pure substance and that 6% of it was not sulphetrone in the chemical sense: what it was they did not state. They did state however that boiling with normal acid produced a complex of high molecular weight, and only by more drastic hydrolysis was it possible to recover a small proportion of the whole as DADPS. Smith et al (25) however pointed out the instability of sulphetrone, as well as promin, and

Boyer et al (19) found that in neutral solution in water both promin and sulphetrone are unstable in concentrations below 5%, that they precipitate, and that the precipitate consists of DADPS. Francis and Spinks (27) record the rapid hydrolysis of promin and sulphetrone to DADPS by N/10 HCl at room temperature.

Using the method of separating DADPS described above, I have studied the composition of sulphetrone and its stability *in vitro*, with the following findings.

(i) Ten different examinations on different occasions of sulphetrone in tablet and in powder form showed that between 0.24% and 0.32% of the diazotizable material present in freshly prepared solutions was extracted with benzene, and was presumably DADPS.

(ii) In weak solutions (5mg per cent), the effect of boiling for one hour, or of autoclaving for one hour was to increase the benzene extractable portion between twenty and twenty-six times. These results were obtained in all of seven different experiments.

(iii) These results were obtained with solutions made in distilled water, which was, as usual, very slightly acid; making the water neutral or even very slightly alkaline did not prevent the increase in benzene extractable material, but only reduced the increase somewhat.

(iv) Stronger (20%) solutions were considerably more stable on boiling or autoclaving, the increase in benzene extractable material being reduced to 6 or 7 times instead of 15 to 25 times. In 50% solutions on autoclaving, the increase was only 2-3 times.

(v) Weak solutions in distilled water were unstable even at refrigerator temperature, and precipitated benzene-extractable material in a few days. At room temperature in the tropics, this change occurred more quickly and, on boiling, almost immediately. Strong solutions were much more stable.

The conclusions from these experiments are (a) that freshly prepared solutions of sulphetrone contain a considerable trace of DADPS. (b) sulphetrone in solution is unstable and is easily degraded to DADPS: that the conditions which favour this degradation are high dilution, high temperatures and acidity (though neutralization does not entirely prevent it); (c) that the mechanism of this degradation is probably one of hydrolysis and that the greater stability of concentrated solutions is probably the lack of enough free H irons to hydrolyse much of the large amount of sulphetrone present.

Similar experiments, with similar results were carried out with diasone. Here the amount of benzene extractable material found in freshly prepared dilutions is lower, about 0.2% and the increase produced by boiling or autoclaving is lower. The nature of the process and the factors influencing it appear to be the same as with sulphetrone.

A similar study of promin has shown that in solutions, particularly in weak solutions, it is very readily hydrolysed to

DADPS; it appears to be the least stable of the disubstituted sulphones examined by me. On storage and on heating it shows steadily increasing quantities of DADPS.

The influence of this instability on chemotherapeutic activity in vitro.

This matter has been studied by Francis and Spinks (27) and by Boyer, Rist and Saviard (19). Francis and Spinks compared the activity *in vitro* of five different sulphones against Str. agalactiae, the 0.2% solutions used being sterilised (a) by infiltration and (b) by autoclaving. In the conditions of experiment (a), diasone was 27 times less active than DADPS, and promin and sulphetrone were 250 times less active. In experiment (b) in which the solutions were sterilized by autoclaving, the activity of promin was increased 26 times, and that of sulphetrone 9 times; of course they both remained much less active than DADPS.

Boyer and his co-workers (19) studied the activity of several sulphones against Proteus X19 before and after autoclaving both strong and weak solutions. They found that, in 50% solution, the activity of sulphetrone was increased only five times by autoclaving, but in 5% solution the increase was twenty fold. Promin gave similar findings but on a lower level. They also investigated the effect of incubation on the activity of complex sulphones, and found that activity steadily increased. They attributed the increase of activity of sulphones, on autoclaving and on incubation, to the liberation of DADPS by hydrolysis. They concluded that there was no reason whatever to suppose that disubstituted sulphones act by virtue of their full molecule, either *in vitro* or *in vivo*, without giving off DADPS.

The practical importance of this work is obvious. It indicates that much of the past experimental work on the action of different complex sulphones *in vitro* is invalidated. It now appears that the action often attributed to the molecule of the complex sulphone is really attributable to the molecule of DADPS, present as an impurity from the beginning, or produced during the course of the experiment by hydrolysis of the complex sulphone to DADPS.

The instability of disubstituted sulphones in vivo on oral administration.

As early as 1940 Johnson (14) made findings that indicated that orally administered promin underwent a change in the body, this change being much more marked than after parenteral administration, and in 1941 Hinshaw and Feldman (13) found that

oral promin was more toxic than injected promin, and therefore adopted injection as the routine form of treatment.

Studies in Animals.

Titus and Bernstein (26) studied DADPS and four disubstituted sulphones given orally and parenterally to mice and dogs, using their method already cited for estimating the blood concentration of both DADPS and the complex sulphone in the same specimen. They found that after the administration of the complex sulphones by either method, DADPS was found in the blood, but that oral administration produced considerably higher levels than injection. This they attributed to acid hydrolysis in the stomach. In the Squib mouse test of therapeutic activity in animals, all the complex sulphones tested were considerably less active than DADPS. They did not mention the occurrence of DADPS as an impurity in the complex sulphones.

Francis and Spinks (27) gave sulphetrone, promin and diasone orally and by injection to rabbits, mice and rats. They found DADPS present. After injection, the blood and urine DADPS concentrations were much lower than after oral administration; the chief breakdown of the complex sulphones probably occurred in the stomach. In therapeutic tests, the effect produced by the soluble derivatives of DADPS was closely related to the blood concentrations of free DADPS produced. In streptococal infections in mice, DADPS was much more active than promin and diasone, and sulphetrone was the least active; all were given orally. They concluded that complex sulphones have no advantage over DADPS except solubility, a very conservative statement on the evidence they give. Boyer et al (20) have reported similar studies with similar results.

Studies in man.

The early but not entirely successful attempt by Smith (18) to study the degradation of disubstituted sulphones in the human body has already been mentioned. The present report is really a report of the continuation and development of the work started here by Smith, and it has been made possible by the kindness of J. Francis and A. Spinks in making available to me the manuscript of an article (27) then awaiting publication which gave the details of their method of estimating DADPS and complex sulphone in the same specimen of blood.

No report on such studies in man has yet been seen by me, and this may be the first report of this kind.

Oral administration in man. The questions to be investigated were (a) Does the oral administration of disubstituted sulphones produce an appreciable blood concentration of DADPS? (b) Is the blood DADPS level so obtained sufficient to explain fully the therapeutic effect of orally administered disubstituted sulphones in leprosy, or is it necessary to postulate an additional effect of the undegraded complex sulphone? (c) Is it possible to estimate the degree to which complex sulphones are hydrolysed to DADPS, in the gastro-intestinal tract before absorption, or in the body after absorption?

Before attempting to answer these questions, we give in tabular form the results of the blood sulphone estimations carried out during the present study. We have carried out several thousands of blood sulphone estimations not included here; but the findings are all in accord with those here recorded.

DISUBSTITUTED SULPHONE GIVEN ORALLY

(1) *Sulphetrone.*

Daily dose	No. of obs.	Total sulphone as sulphetrone mg%		DADPS mg%	
		Range	Mean	Range	Mean
1g.	21	0.25 — 1.0	0.7	0.06 — 0.12	0.08
2g.	19	0.50 — 2.0	1.4	0.08 — 0.25	0.14
3g.	21	1.50 — 3.0	2.1	0.10 — 0.37	0.21
4g.	23	2.0 — 3.0	3.1	0.14 — 0.40	0.25
5g.	27	2.5 — 5.0	3.5	0.20 — 0.55	0.31

(2) *Diasone.*

0.6g.	15	0.4 — 1.0	0.6	0.1 — 0.2	0.15
0.9g.	9	0.75 — 2.2	1.2	0.10 — 0.28	0.21
1.2g.	10	1.50 — 2.2	1.75	0.25 — 0.50	0.37
1.5g.	8	1.60 — 2.2	1.90	0.35 — 0.70	0.50
1.8g.	21	1.70 — 3.2	2.2	0.45 — 0.75	0.63

(3) *Promin.*

0.2g.	6	Trace	Trace	Trace	Trace
0.4g.	9	0.8 — 1.2	1.1	0.12 — 0.20	0.18
0.6g.	9	2.2 — 3.8	2.9	0.50 — 0.70	0.55
0.8g.	19	4.0 — 5.0	4.5	0.60 — 0.90	0.78

The three questions raised above can now be discussed.

It will be seen that all the three disubstituted sulphones studied, when given orally in their usual doses, produce a considerable amount of free DADPS in the blood. Sulphetrone usually given by mouth in doses of 3-6g a day, gives at these dosage levels a free DADPS blood level of 0.2 to 0.5mg%. Diasone in its usual dose of 0.9 to 1.8g a day gives a DADPS blood level from 0.2 to 0.6mg%. Promin has rarely been given by mouth as it is considered too toxic; we have found the tolerated dose is not more than 0.8g a day, and this we find gives a DADPS blood level of about 0.8mg%.

It will also be noted that the usual dose of these sulphones, which has been based on the tolerated dose, varies inversely with the degree to which the particular sulphone produces DADPS in the body. Sulphetrone for example produces less DADPS and is usually given in high doses. Diasone produces more DADPS and the usual dose is less. Promin has been considered too toxic for oral administration; the reason now appears to be that it is so very rapidly degraded to DADPS; we find if the dose is reduced to give a DADPS blood level comparable to that produced by other sulphones, it is well tolerated and is effective. These facts are all in keeping with the view that the therapeutic as well as the toxic principle of those sulphones is DADPS.

The second question, whether the blood DADPS level is high enough to explain the therapeutic action of these sulphones, can also, it is believed, be answered in the affirmative. Evidence, to be discussed later, is strong that the therapeutic blood level of DADPS in leprosy is certainly as low as 0.2mg% and possibly even lower than this. This DADPS blood level is attained and often much exceeded when the complex sulphones are given in their usual doses. It therefore appears unnecessary to postulate any additional action of the undegraded complex sulphone.

The third question, whether it is possible on the evidence here given to say to what extent the complex sulphones are hydrolysed to DADPS either before or after absorption from the gastro-intestinal tract, is one which cannot be easily answered. Numerous facts have to be considered.

The proportion of the ingested complex sulphone that is absorbed varies with different sulphones and in different patients, and is possibly influenced by the amount of the gastric acidity. The DADPS produced in the stomach is absorbed much more readily than the undegraded sulphone; further it appears probable that most of the DADPS is produced in the stomach, and that little hydrolysis of the complex sulphone occurs after absorption.

As is described later, DADPS itself in the body tends to undergo a change to a water-soluble derivative, and is mainly excreted in this form. For these reasons the question under discussion is a complicated one. It is impossible to say how much DADPS has been produced from a given amount of complex sulphone given orally; all that one can say is that at the time of the examination, a certain proportion of the sulphone in the blood is in the form of free DADPS and that the rest is in a water-soluble derivative.

Moreover the figures given in the table, as they stand, are misleading unless it is realised that the figure for total sulphone has been calculated on the assumption, known to be untrue, that the sulphone present is all in its original form. The true position is made clear if all the estimations are recorded as sulphone radicle, namely DADPS. The amount that is free can then be estimated and compared with the total.

When this is done, the figures for the three complex sulphones given orally, at the highest dose used, are as follows. (The calculations are based upon the means recorded in the table.)

		Total blood level as DADPS mg%	Free DADPS mg%	Free DADPS as % of total
Sulphetrone	5g. a day	0.7	0.31	45%
Diasone	1.8g. a day	0.88	0.63	72%
Promin	0.8g. a day	1.10	0.78	71%

It will thus be seen that with orally administered sulphetrone, nearly half the sulphone radicle present in the blood is in the form of free DADPS, while with promin and diasone the proportion is nearly three quarters. It will also be seen that as a medium for the production of DADPS in the blood, sulphetrone is poor, diasone is better, and promin is the best, producing the highest level with the smallest dose.

The evidence produced above indicates strongly that disubstituted sulphones given orally in man produces DADPS in the blood in considerable amount, this amount being adequate to explain their therapeutic action without postulating a separate action of the undegraded disubstituted sulphone. It is found moreover that about half or more of the sulphone radicle present in the blood is in the form of free DADPS.

Injection

Here again the same questions arise. When the disubstituted sulphones are injected in the usual doses recommended, is DADPS liberated in the body in appreciable amount, and, if so, is this amount sufficient to explain the therapeutic action of such injections?

The data obtained in our studies of this matter are here presented in tabular form.

(1) *Blood sulphone levels in patients given Sulphetrone by injection.*

Dose—3 g twice weekly.

Time after injection.	No. of Obs.	Total sulphone as Sulphetrone mg% Range	Mean	DADPS mg% Range	Mean
2 hours	22	7.5 — 20.0	11.5	0.025 — 0.25	0.06
4 hours	6	7.5 — 15	9.8	0.05 — 0.2	0.1
24 hours	12	1.5 — 6.0	3.3	0.025 — 0.2	0.08
48 hours	4	1.5 — 2.5	1.8	0.05 — 0.2	0.095
72 hours	45	0.5 — 3.0	1.3	0.025 — 0.2	0.12
		Dose—1 g daily.			
4 hours	8	3.5 — 5.0	4.5	0.01 — 0.08	0.06
24 hours	2	2.0 — 25	2.25	.06 — 0.08	0.07

(2) *Blood sulphone levels in patients receiving Promin injections.*

Time after injection.	No. of Obs.	Total sulphone as Promin mg% Range	Mean	DADPS mg% Range	Mean
2 hours	1	5.4	(5.4)	(0.2)	(0.2)
24 hours	10	1.0 — 3.7	2.0	0.05 — 0.25	0.1
48 hours	3	0.8 — 1.25	1.1	0.05 — 0.2	0.1
		Dose—4 g daily 6 days a week.			
2 hours	1	10.0	10.0	0.275	0.275
24 hours	12	1.0 — 2.5	1.9	0.075 — 0.3	0.15
48 hours	5	0.8 — 1.5	1.3	0.075 — 0.15	0.11

This table makes the following points stand out clearly.

(1) The total blood sulphone as sulphetrone is high soon after the injection but rapidly falls.

(2) The blood DADPS level is low soon after the injection but falls slowly.

(3) The blood DADPS level produced by injections of sulphetrone remain fairly constant at a little above or below 0.1mg%. With promin injections the blood DADPS levels are rather higher, between 0.275 and 0.1mg%.

A consideration of these findings and of other findings recorded in the present paper leads to the following tentative conclusions.

(1) The blood DADPS levels produced by injections of disubstituted sulphones are very low; actually they are not much higher

than would be explainable by the presence of traces of DADPS as an impurity in the sulphone injected. These facts indicate that after injection there is very little production of DADPS in the body.

(2) If the therapeutic action of such injections is due to the DADPS blood level produced, then the therapeutic dose of DADPS must be exceedingly small. Elsewhere in this paper is produced evidence that blood DADPS levels of the order of 0.2mg% are therapeutically active, and promin injections produce levels of this order. It is however doubtful whether levels of about 0.1mg%, such as are produced by sulphetrone injections, are enough to explain the therapeutic action of these injections. It is possible that some other factor contributes to this action.

In this connection, a personal letter of Dr. E. H. Payne of Park Davis and Company (the makers of promin) may be quoted. "When the disubstituted sulphones such as promin go into solution, there is a constant interchange of radicals due to hydrolysis which produces a wide variety of potential compounds. One of these is a mono-substituted derivative, and we know that these compounds are very active." Here lies a possible explanation of the activity of injections of disubstituted sulphones.

Even if these ideas are true, the injection of disubstituted sulphones remains an illogical method of treating leprosy. Why use a substance believed to be inactive in the expectation that it will produce, in the solution to be injected or in the body after injection, an unknown and probably varying amount of active sulphone (DADPS and monosubstituted sulphone)? Surely it is better to administer a known amount of a sulphone known to be active. The treatment of leprosy with DADPS is rational and now widely practised. The monosubstituted sulphones are also rational and are being widely used, although high cost and currency difficulties limit their use, particularly since they have not been shown to be superior to DADPS.

Once again to sum up. The injection of disubstituted sulphones produces a very low blood DADPS blood level, actually at about the lowest limit for therapeutic activity. There is evidence that very little DADPS is produced in the body after such injections. If the therapeutic activity of such injections is due entirely to DADPS, the therapeutic blood level of DADPS is very low. Other evidence pointing to this conclusion is quoted later. On the other hand it is possible that injections of disubstituted sulphones are therapeutically active, partly because in the solutions before injection, or in the body after injection, mono-substituted sulphones are

produced, and these are active. I have been unable to investigate this matter.*

PART 2. THE USE OF DADPS.

The first worker to attempt to use DADPS in human beings was apparently Buttle (8) who gave doses of 1 to 2g a day to patients with respiratory injections; toxic effects were early and serious, and the attempt was abandoned. It was apparently this (unpublished) experiment and perhaps other experiments of a similar nature that created the idea that DADPS was too toxic for use. A similar attempt with similar results was made by Long (11). The next trial was made nearly ten years later by Cochrane (15). He gave twice weekly injections of 1.25g in leprosy, and reported good results, but found that toxic effects were too frequent and too serious to make this form of treatment widely applicable. This dosage and method of administration were apparently chosen arbitrarily. Molesworth and Narayanaswami (16) gave twice weekly injections rising from 0.2 to 0.5g and reported good results without the toxic effects reported by Cochrane. Lowe and Smith (5) in Nigeria, arguing from experience with complex sulphones that a therapeutic blood level of DADPS should be 1mg% or less, found that this blood level could be maintained on an oral dosage of 200-300mg a day, and that this dosage was well tolerated if attained slowly over 4-6 weeks. Moreover they found that DADPS was so completely absorbed from the gut after oral administration that it was unnecessary to give injections. Later Lowe (1 and 2) found that twice weekly oral doses rising to 400-500mg maintained a good blood level, were well tolerated, and gave good results. Other workers experimenting with DADPS at the same time in other countries obtained almost identical results. These workers included Floch and Destombes (21) in French Guiana, de Souza Lima (24) in Brazil, and Rist and Cottet (23) in France. The use of DADPS in the treatment of leprosy is now being widely practiced, particularly in Malaya where Molesworth is treating many hundreds of patients, and in Nigeria where over twenty thousand patients are now being treated. It is also widely used in French territories and in India.

The question of dosage of DADPS is still being studied and no final conclusions have yet been reached. In this section of this paper, an attempt is made to summarise the published evidence on this matter, and the results of our own recent studies.

The maximum tolerated dose.

Lowe and Smith (5) found that daily doses of 300mg slowly

* See note at end of article.

attained over several weeks were well tolerated, but that higher doses produced evidence of increased haemolysis making them inadvisable. Later Lowe (2 and 4) experimented with daily doses up to 500mg but found that this high dosage not infrequently caused serious psychosis; moreover the higher doses did not produce more rapid improvement. Later still Lowe and Davey (6) found it advisable to make the maximum daily dose 200mg, because psychosis occurred on 300mg in some cases.

Floch and Destombes (21) found that the maximum well tolerated dose was 250mg a day. Rist and Cottet (23) reported that doses over 200mg. a day produced slight side effects. De Souza Lima (24) used a maximum dose of 200-300mg a day. It appears that all these workers were working at the same time, without knowledge of the results of the others; the similarity of the findings is very striking. Later some workers in India, (Cochrane, Smith, and Dharmendra, personal communications) found 300mg. a day too much for many Indians, although Dharmendra (30) finds that 200mg a day is a safe and effective dose. As already stated, Molesworth has used twice weekly injections up to 500mg without toxic effects, and Lowe has used the same twice weekly dose given orally. Cochrane's original 1.25g given twice weekly was definitely toxic.

It may be concluded that the maximum well tolerated dose is 200mg a day, though here many patients have had 300mg a day for two years without toxic effects. For twice weekly treatment a dose of 500mg is well tolerated; for various reasons discussed later, twice weekly treatment now appears preferable to daily treatment.

Minimum therapeutic dose

Lowe (2) reported a good therapeutic response in leprosy to 100mg a day. Chatterji (31) found that a dose of 50mg a day was therapeutically active, and Dharmendra (30) has reported similarly. Muir (32, 33) has made similar findings. There has been so far little more evidence on this point.

The studies of the complex sulphones reported in the earlier part of this give support to the idea that the minimum therapeutic dose of DADPS may be very low.

In order to get a clear indication of the minimum therapeutic dose in leprosy, the following experiment was carried out.

Six patients previously untreated were chosen; they were all active tuberculoid cases which are expected to show a definite response to treatment within a few weeks. For two months, the

dose given was 15mg a day; for the next two months 30mg a day, for the third two months 50mg a day, and then for a further two months 100mg a day.

The following observations were made.

Dosage 15mg a day for two months.
Out of 6 cases, 4 showed a rather slow but definite response to treatment; the other two showed no definite response. During this period 22 observations on blood levels were made. The range was 0.06 to 0.12 and the mean 0.09mg%.

Dosage 30mg a day for two months.
During this period all six cases showed slow but definite improvement. Observations on blood levels showed a range of 0.15 to 0.25mg% with a mean of 0.18.

Dosage 50mg a day for two months.
During this period the speed of response in all six cases was more rapid, and was not appreciably slower than in similar cases on our ordinary standard dose. The blood levels showed a range of 0.15 to 0.32mg% and a mean of 0.24.

Dosage 100mg. a day for two months.
During this period improvement was maintained but showed little acceleration if any. The blood levels showed a range of 0.15—0.50mg% and a mean of 0.34.

The experiment was interpreted as indicating that doses as low as 30mg a day, and blood levels as low as 0.2mg% are capable of producing a clinical response in such cases, but probably not the maximum response.

Optimum therapeutic dose

On this subject it is not possible to make definite pronouncements. Certain things are clear however. As has been stated previously, improvement under treatment is not proportional to the dose given. Doses above 300mg a day do not appear to accelerate progress. Experience here does not even justify the statement that 300mg a day is definitely better than 200mg a day, or even than 100mg a day. At present our standard doses are 200mg a day or 400mg twice a week. These doses are so well tolerated in most cases that we hesitate to reduce this standard dose. There are however patients who for various reasons (sulphone sensitivity, intercurrent disease) have received doses much smaller than this, and have nevertheless made good progress.

More recent experience has shown that twice weekly treatment with doses rising slowly to 400mg, is better tolerated than daily treatment with 200mg a day, the complications being fewer and less severe and interruptions in treatment being fewer. Possibly for this reason, the response to treatment appears to be at least as good as, if not better than, that seen with 200mg a day.

Further, experiments now in progress indicate that treatment given once weekly, with doses rising slowly to 500 or 600mg is

equally well tolerated and produces a good response. Treatment twice weekly or once weekly instead of daily usually appears to prevent that serious complication, sulphone psychosis. Twice-weekly oral treatment with doses of 400mg produces a maximum blood DADPS of about 0.8mg% which falls to about 0.3mg% before the next dose. On once weekly 500mg doses, the maximum is a little higher and the minimum a little lower. If intramuscular injections are used, the maxima are lower and the minima are higher, the muscle acting as a reservoir from which the sulphone is slowly liberated. Our experience here indicates that the optimum dosage for good tolerance and good therapeutic response is a dosage rising slowly to 400mg twice a week, though it appears possible, if not probable, that 200-300mg given twice weekly, or the 400-500mg given once a week would give equally good results.

Absorption, metabolism, storage, excretion and toxicity of DADPS in man

This matter has been carefully studied here. A previous report by Smith (15, 16) is amplified and modified in some respects by the work done since and here reported for the first time.

Absorption of orally administered DADPS is almost complete, about 85% of the sulphone given appears later in the urine. Moreover the absorption is very rapid; as Dharmendra (30) has reported and I have confirmed, after the administration of a single dose of 10mg, sulphone appears in the blood within ten minutes. The absorption is obviously from the upper part of the intestinal tract.

When the sulphone content of the blood of a patient receiving DADPS is examined by the method outlined in the earlier part of this paper, it is found that about 80% of the circulating sulphone is in the form of free DADPS, and about 20% is in the form of a water-soluble derivative. Thus some of the DADPS undergoes a chemical change in the body. It is not known what this water-soluble derivative is; one worker with a good knowledge of the subject has suggested to me that it is a mono-substituted sulphone that is produced; such sulphones are known to be therapeutically active.

Excretion is mainly by the kidneys, though sulphone can be detected in considerable amount in all the fluid excretions of the body, including the sweat, saliva, sputum, tears, etc. Excretion by the kidneys is a slow process. When treatment is stopped in a patient receiving ordinary doses of DADPS, sulphone is found in the blood in appreciable amount for periods up to several weeks, and sulphone can be detected in the urine for even longer periods.

When the urine of a patient receiving DADPS is examined by the methods described earlier in this paper, it is found that about 80% of the sulphone excreted is no longer in the form of free DADPS, but is in a water-soluble form, presumably the same form which is found in much smaller amount in the circulating blood, and which is briefly discussed above. These findings differ from the findings of M.I. Smith (34) who in a letter quoted by Wade (35) reported that in rabbits DADPS is excreted unchanged, but they agree with the findings made in dogs by Titus and Bernstein (26) and in rabbits by Francis and Spinks (27) of a water-soluble derivative in the urine.

Regarding *concentration and storage in the body tissues,* we have failed to confirm the earlier report of Cochrane that sulphones including DADPS are concentrated and retained in the skin, and Cochrane himself has since withdrawn this claim. The only tissues which concentrate sulphone appreciably are the kidneys and the liver which excrete sulphone. In the case of the liver, the sulphone excreted is reabsorbed from the gut, so is not lost to the body.

It is the complete absorption and slow elimination of DADPS that makes it such an economical therapeutic agent. Therapeutic blood levels are built up and maintained on a very small dose. The same factors render high doses dangerous, particularly if frequently repeated, for a toxic blood level is easily built up.

In our experience, *acute toxicity* is seen with blood levels of 2.0mg%. To produce this level, 2000mg a week or more is needed. The important toxic effects are acute haemolysis and liver damage. Levels between 1.0mg% and 2.0mg% usually produce no acute toxic effects, but if they are long maintained *chronic toxicity* appears; the serious effects include haemolytic anaemia, liver damage and, later, psychosis. A safe blood level lies between 0.2 and 1.0mg% and averaging about 0.5mg%. There is thus a considerable margin between the toxic and the therapeutic blood levels. Expressed in dose per week (it is sounder to consider this rather than the daily dose) therapeutic doses should range between 300mg and 1200mg a week and are almost always non-toxic, while doses totalling over 2000mg a week will usually be found toxic in varying degree. Here again the margin is considerable.

As with the sulphonamides, the danger of long continued administration is allergy, as shown by drug fever, dermatitis, and hepatitis occurring between the 3rd and 9th weeks of treatment; this danger can be greatly reduced by a slow induction of treatment, the standard dose not being attained for several weeks. If

allergy ocurs, treatment for allergy followed by careful desensitization is needed.

The whole question of dosage of DADPS, toxic effects and allergic effects is more fully discussed elsewhere (2) though since that report was written the much greater safety of twice weekly treatment has become still more clear.

Sundry observations

In Nigeria, as elsewhere, women with leprosy are sometimes found pregnant, or with very young children being breast fed; the question therefore arises of the advisability of starting or continuing sulphone treatment in such cases. Because of trypanosomiasis in cattle, milk is not available here and artificial feeding presents great difficulties. *The use of DADPS in pregnant women and nursing mothers* has therefore been closely studied. Twice weekly treatment with doses not exceeding 400mg is well tolerated by pregnant women; it can be continued till a few days before confinement. There is no obvious harmful effect on the child in utero or at birth. After the confinement, DADPS treatment can be resumed at once, but a dose lower than usual may be advisable for the first few weeks, if the mother is suckling the baby. The breast milk contains appreciable amounts of sulphone, and the baby may tend to develop a blue colour, visible in the eyes, the lips, the palms of the hands, and elsewhere. This blue colour is not of grave import, disappears if the treatment is stopped for a short time, and subsides slowly even if the treatment is continued. After a few weeks, the ordinary standard dose can be maintained.

This treatment of pregnant women before and after childbirth appears to benefit the mother, for the exacerbations of leprosy so common during the puerperium have not been seen, and the harmful effects of pregnancy, confinement, the puerperium, and lactation on the disease appear to be prevented; some patients show continued steady improvement during the whole period. The child suffers no harm, and the treatment may be of some value in preventing leprous infection by the mother or by other patients in contact with the child.

These findings should not be interpreted as indicating that every possible step should not be taken to separate the child from sources of infection as soon as possible after birth. In Nigeria this separation is frequently impossible however.

Observations of the other infections present or absent in our large numbers of patients under continuous sulphone therapy for several years may give information of interest regarding *the range*

of activity of DADPS. Infections with gram-positive cocci, such as the pneumococcus, the streptococcus, and the meningococcus have not been seen. Such infections are possibly suppressed by DADPS. Gram-negative coccal infections are quite common, including staphylococcal and gonococcal infections. Boils due to staphylococcal infection, and tropical myositis apparently due to the same cause, are quite common.

We have failed to confirm the findings of others that DADPS has an action in filarial infections and in fungal infections of the skin; any benefit seen in such infections must, we feel, be due to the control of secondary infections, probably streptococcal, which are not uncommon in these two conditions.

One case of tetanus, a gram-positive organism, has been seen. Virus infections are common, including influenza, dengue, and glandular fever, and there is evidence that sulphone may precipitate an attack of glandular fever in a person harbouring the infection.

We have seen no clear indication that sulphone has any definite action in suppressing tuberculous infection, but analysis of our records shows that it appears rare for tuberculosis to be diagnosed for the first time in a patient who has long been on sulphone treatment. A few cases have arisen in patients who have recently started sulphone treatment, but these may be cases of late detection. This matter will be studied further. A common cause of death in leprosy institutions is tuberculosis of the lungs, which is not infrequently contracted in such institutions.

In a few cases, we have used DADPS alone and in combination with streptomycin in the treatment of established tuberculosis of the lungs. The effect of DADPS alone is not marked, but used in combination with streptomycin it appears to have a definite action in preventing or delaying the appearance of streptomycin resistance. These findings are in agreement with those of certain French workers who use DADPS in this way in tuberculosis instead of para-amino-salicylate. It is certainly much simpler and cheaper to use, and the dose is very much smaller.

One important practical point arises from this study of secondary or complicating infections in leprosy in patients receiving sulphone. These infections very rarely respond to sulphonamides; the infecting organism is usually not one which is susceptible to the action of sulphonamides, or it is a sulphonamide-resistant strain. It is advisable to resort at once to other forms of treatment for these secondary or complicating infections. Penicillin is of outstanding value in many of these cases.

SUMMARY

1. The history of sulphone treatment is briefly described.

2. The theoretical considerations suggesting that disubstituted sulphones such as promin, diasone and sulphetrone need to undergo chemical change to be made active are outlined, and also the reasons for the belief that the active agent is DADPS.

3. The published evidence based on studies *in vitro* and in animals, indicating that disubstituted sulphones, in solution and in the body, contain appreciable quantities of DADPS, and that the therapeutic activity parallels the DADPS content, is reviewed. The lack of similar evidence in man is noted.

4. The results of similar studies made here in patients with leprosy receiving disubstituted sulphones, by mouth or by injection, are presented and discussed.

5. It is found that disubstituted sulphones given by mouth in their usual doses produce DADPS blood levels well above the minimum for therapeutic activity. Promin, previously considered too toxic for oral administration, is found to produce high DADPS blood levels with small oral doses. The tolerated dose of disubstituted sulphones is proportioned to the amount of DADPS produced.

6. This evidence is interpreted as indicating that with disubstituted sulphones given orally, the active and the toxic principle is the same, DADPS.

7. With disubstituted sulphones given by injection, in their usual dose, the DADPS blood level is found to be low, at about the lowest limit for therapeutic activity, and it is suggested that their therapeutic effect is partly attributable to monosubstituted sulphones produced in the solution injected or in the body after injection. No experiment to prove this hypothesis has been possible here.

8. The marked differences between the DADPS blood levels observed in (a) patients receiving disubstituted sulphones orally, and (b) patients receiving them by injection are attributed to the acid hydrolysis to DADPS in the stomach in the former group, and the absence of such hydrolysis in the latter group.

9. The literature of the use of DADPS in medicine is briefly reviewed.

10. The results of studies of the minimum therapeutic dose, the maximum well-tolerated dose, and the optimum dose in treatment are presented. The minimum active dose is found to be 30mg a day. The maximum well-tolerated dose is 200mg a day. The optimum dose in treatment is considered to be 800-1200mg weekly, given either in 6 daily doses of 200mg (with one day a week break) or preferably 400mg given twice weekly. Treatment given once weekly, with doses rising to 500-600mg, is practicable and effective. The importance of the very gradual induction of treatment, the standard dose not being attained for several weeks, is again stressed.

11. The absorption, storage, and excretion of DADPS are discussed. The completeness of the absorption, and the slowness of excretion, mainly by the kidneys, are striking. No evidence of storage or retention in particular tissues has been obtained. The finding is recorded that DADPS is partly converted in the body to a water-soluble form, and is excreted by the kidneys mainly in this form.

12. Acute toxicity is seen only in very high doses; chronic toxicity (as shown by anaemia, liver damage, psychosis) is rare on the doses here recommended. The fever, dermatitis, hepatitis etc. sometimes recorded in the first few weeks of treatment are due to allergy, and are not true toxic effects; treatment for allergy, followed by careful desensitization, is needed before treatment can be resumed in ordinary doses.

13. The use of DADPS in pregnant women and nursing mothers is found possible, and beneficial to the mother, and harmless to the child.

14. The range of activity of DADPS is discussed. Patients receiving sulphones very rarely develop secondary infections caused by gram-positive organisms. Secondary infections rarely respond to sulphonamides, and other agents must be used in their treatment. Penicillin is the most valuable.

15. The value of DADPS in tuberculosis of the lungs is briefly discussed.

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When the work was nearly completed, a valuable symposium on the subject was published in the International Journal of Leprosy, and ably commented on by the Editor, Dr. H. W. Wade (35). This symposium and discussion has been found very useful in the writing of this paper.

APPENDIX

Method of estimating DADPS in the blood of a patient receiving complex disubstituted sulphone.

The method used has been as follows:—An amount of blood, 5 c.c., 2.5 c.c., or 1.25 c.c., is placed in a small stoppered bottle, and ethyl acetate (10 or 20 c.c.) is added, and the bottle is shaken vigorously for five minutes. The contents are then poured out into a suitable test-tube, and the two layers are allowed to separate. As much as possible of the upper layer is then removed, first by pouring and then by pipetting, and filtered through a filter paper into a small measuring cylinder until the amount of filtrate recovered is 4/5th of the amount of ethyl acetate originally added. This filtrate is then poured into a small stoppered bottle, and N/1 HC1 (7.5 or 15 c.c.) is added, and the whole is vigorously shaken for five minutes. The contents are then poured out into a suitable test-tube, allowed to separate and as much as possible of the lower (acid) layer is carefully pipetted off, into a small test-tube. The amount actually recovered does not matter. Diazotization and coupling is then carried out by the method of Bratton and Marshal as described by Brownlee (36) and the intensity of the colour produced is read by means of a Lovibond comparator and a sulphone disc. From the reading, the concentration of DADPS in the blood or other fluid examined is calculated.

The amount of blood, of ethyl acetate, and of N/1 HC1 used will depend on the expected DADPS level. For levels of 1 mg% or a little more, 1.25 c.c. of blood, 10 c.c. of ethyl acetate, and 15 c.c. of HC1 are used. For levels higher than this the original fluid has to be diluted suitably. For levels between 0.5 and 1.0mg%, 2.5 c.c. of blood may be used, *or* the acid used may be reduced to 7.5 c.c.; for levels between 0.5 and 0.25mg%, 2.5 c.c. of blood is used *and* the acid is reduced to 7.5 c.c.; for levels lower than this, the amount of blood used may be increased to 5 c.c. and of ethyl acetate to 20 c.c., while the amount of acid used is the lower one, 7.5 c.c. All these variations are necessary to bring the final colour produced well within the range readable

on the sulphone disc. Readings too low in the scale are inaccurate. If the colour produced is more than can be read on the scale, a dilution of the final fluid to twice its volume with distilled water may be enough to make it readable, and such readings are reasonably accurate; dilutions greater than this give very inaccurate results and should not be used; the whole test must be repeated so as to produce a greater final dilution, and a readable result.

The calculations are based on the following facts. The sulphone disc is designed to read sulphetrone in a final dilution of one in 15, and the figures then represent milligrams per cent. For DADPS in a dilution of 1 in 15, the figure has to be divided by 5 to give a mg% value. Further if the DADPS from 2 or 4 c.c. is being estimated, the factor 5 has to be multiplied by 2 or by 4. Further still if the amount of acid used is 7.5 instead of 15 c.c., a further factor of 2 is introduced. Thus the reading on the sulphone disc in the Lovibond comparator has to be divided by a factor which may be 5, 10, 20, or 40 according to the amount of blood used and the amount of acid used in the final dilution.

The loss of one-fifth of the ethyl acetate used in the extraction process is allowed for in the above outlined calculation by regarding the amount of blood used as one-fifth less than it actually was, 4 c.c. instead of 5 c.c., 2 c.c. instead of 2.5 c.c. etc.

Example. A patient is receiving sulphetrone by mouth in doses of 5g. a day. The blood is taken and the sulphetrone is estimated as sulphetrone by the method of Brownlee (36) at 4.0mg%. 2.5 c.c. of blood is then taken, extracted with ethyl acetate, and the ethyl acetate is extracted with 7.5 c.c. of N/1 HCl, diazotized, and coupled, and read on the sulphone disc. The reading is 6. To get the DADPS content of the blood, this value 6 has to be divided by 5 (for DADPS instead of sulphetrone), and further by 2 (because the sulphone from 2 c.c. of blood instead of from 1 c.c. is being estimated) and further still by 2 (because the final dilution with acid was to 7.5 instead of 15 c.c.). Thus the DADPS value in mg% is 6 divided by 20 = 0.3mg%.

(The significance of these figures may not at once be apparent. DADPS 0.3mg% if read as sulphetrone would be five times greater —1.5mg%. The total blood sulphetrone has been estimated as sulphetrone at 4mg%. Thus nearly 40% of the sulphone radicle present in the blood is in the form of DADPS).

Tests of the accuracy of the method were carried out in known standard solutions or suspensions of DADPS in water, and in normal blood. Also to water and to normal blood known amounts

of complex sulphone and DADPS were added, and the total sulphone, the DADPS by extraction, and the residual sulphone after extraction were estimated. The recovery of DADPS from such mixtures varied between 75% and 105% and averaged 83%. The estimation of residual sulphone after extraction of mixtures in blood was difficult and sometimes impossible, and for this purpose benzene extraction as used by Francis and Spinks gave better results. But DADPS values given by ethyl-acetate extraction were slightly higher and more consistent than with benzene extraction, although we have used both methods extensively, in collecting the data given in the present paper.

It is considered that the method here described, while not absolutely accurate, is accurate enough for the purpose for which it has been used in the present study. DADPS blood levels as low as 0.1mg% can be estimated with fair accuracy; below 0.1mg% DADPS can be detected but not estimated with great accuracy.

LATER NOTE

The work reported above was done with finely levigated sulphetrone powder supplied by Dr. G. Brownlee, then of Burroughs Wellcome. The solutions were made in plain distilled water, were autoclaved, and then used for injection.

Recently we have repeated part of this work, using sulphetrone " granules " supplied as marketed for injection purposes by Burroughs Wellcome; the solutions for injection have been made in distilled water with 0.5% carbolic acid as recommended in the *Leprosy Review* (Vol. 22, p.85).

Our findings in this recent study are here outlined:

(a) Sulphetrone " granules " appear to contain considerably more DADPS than the finely levigated sulphetrone previously used.

(b) Solutions prepared for injection by the method recommended appear to contain more DADPS than the solutions made from finely levigated sulphetrone previously used.

(c) The blood DADPS levels after injection prepared from sulphetrone " granules " are rather variable, but the maxima are considerably higher than those seen with the sulphetrone injections previously used.

These facts are probably of importance. Injections of sulphetrone are now normally prepared from " granules " by method used in this recent work, which makes it still more probable that injected sulphetrone acts by means of DADPS.

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FINDINGS OF A MEETING OF LEPROSY WORKERS

CONVENED AT THE OFFICE OF THE BRITISH EMPIRE LEPROSY RELIEF ASSOCIATION, 167, VICTORIA STREET, LONDON, S.W.1., ON MONDAY, SEPTEMBER 17TH, 1951, AT 10.30 A.M.

AGENDA

1. To review the present position with reference to chemotherapy in leprosy, and issue an agreed statement for the guidance of workers in the field.
2. To review the present position with regard to the use of B.C.G. in the leprosy campaign.

Present: Dr. E. Muir, Medical Adviser, B.E.L.R.A. (Chairman), Dr. R. G. Cochrane, Medical Secretary, B.E.L.R.A., Dr. John Lowe, Medical research worker to the Government of Nigeria, Dr. T. F. Davey, Area Superintendent, Nigeria Leprosy Service, Uzuakoli, Nigeria, Dr. and Mrs. Barnes, Ogoja Leprosy Settlement, Nigeria, Dr. J. Ross Innes, Inter-territorial Leprologist, E. African High Commission, Dr. J. A. K. Brown, recently appointed Adviser on Leprosy to the Government of Uganda.

SULPHONE TREATMENT OF LEPROSY

1. GENERAL.

(1) The development of sulphone therapy has now reached the stage when it can be strongly recommended as the basic routine treatment of all active cases of leprosy. Some of us consider that Hydnocarpus Oil treatment by intradermal injections is a useful supplementary treatment.

(2) The mode of action of sulphones is not completely understood. It is probable that the more complex (disubstituted) sulphones are rendered active by being broken down to simple compounds (DDS and probably mono-substituted and other sulphones). The therapeutic action of sulphones can be obtained by administering any of these.

(3) The giving of disubstituted sulphones in the usually recommended doses by mouth is an effective, but uneconomic, method of treatment, and need not be further considered here.

(4) Our experience of disubstituted sulphones by injections is practically confined to sulphetrone. Such injections are considered to provide a cheap and effective form of treatment.

(5) Monosubstituted sulphones are reported to be active *per se*, and when given orally, to provide a safe and effective

treatment of leprosy. Our experience of them is very limited. Their cost at present excludes their use on a large scale.

(6) DDS (parent sulphone, diaminodiphenylsulphone) is highly active and is so well absorbed and so slowly excreted, that its effective dose is very low. Its oral administration is simple and effective, but its insolubility renders injections troublesome.

2. COMPLICATIONS OF TREATMENT, TOXIC AND OTHERWISE.

The complications of treatment here mentioned have been seen in all forms of sulphone therapy. They are much less common and less severe with the drugs and doses now recommended than in the past, but they still may occur. Sulphone treatment needs workers capable of detecting and dealing with these complications as they arise.

(a) *Reaction, neuritis,* etc., though seen in cases without treatment, is more common in cases under sulphone therapy, particularly in the early phases. If it is mild, the treatment has to be stopped until it has subsided. Injections of antimony are commonly used in the treatment of this complication, but results are not constant, and some favour other remedies. In time the condition subsides, but frequently recurs. For severe neuritis, procaine injections into the affected nerve have been found useful.

(b) *Drug fever, with general dermatitis, hepatitis, lymphadenitis, etc.* This complication has been recorded as frequent in West Africa, where it seems probable that a local factor contributes to its causation. The fever in lymphadenitis and hepatitis is indistinguishable clinically and serologically from glandular fever (infectious mononucleosis). The dermatitis, which may be severe and exfoliate, is similar to other severe drug dermatitis (arsenical and sulphonamide). The whole condition is caused by an intense allergy to sulphones and sulphonamides.

Early diagnosis, immediate cessation of sulphones, the avoidance of sulphonamides, and anti-histamine treatment are of great importance. A failure in this matter may lead to death.

When the condition has subsided, sulphone treatment can be resumed only after very careful desensitization, starting at minute doses. In desensitization oral administration twice weekly of a soluble sulphone (e.g. sulphetrone) rising slowly from 5 mgm. is very useful.

The syndrome makes its first appearance always during the first few weeks of treatment, though it may recur later. The first three months of treatment need careful watching. The very

gradual induction of treatment is advisable to minimise the danger.

(c) *Anaemia.* In well nourished patients treated with the doses recommended below, serious anaemia is rare. When it occurs, factors other than sulphone treatment usually contribute (e.g. malnutrition, hook worm, etc.). In severe lepromatous cases, leprosy itself frequently causes aneamia. Routine haemoglobin estimations are unnecessary. Proper clinical examination will detect any cases of anaemia. Iron administration is not necessitated by sulphone treatment, as here outlined, though in ill-nourished patients with parasitic infections it is advisable.

(d) *Hepatitis* is usually a part of the drug fever syndrome described above. It has however been seen separately. Treatment must be stopped until the patient has fully recovered.

(e) *Cyanosis.* This is rarely visible in dark skinned people, but in others it is not uncommon. It is reliably reported to be more common in patients living at high altitudes (above 5,000 ft.), when it may cause serious distress. Apart from this, it is usually of little or no significance.

(f) *Psychosis.* On the higher doses previously used (particularly with DDS) this complication was not uncommon. Now on the lower doses it is rare. It commonly occurs only after prolonged continuous treatment. It is characterised by excitement, by depression, or by alternating phases of excitement and depression. There may be a tendency to suicide. The psychosis slowly subsides when sulphones are withdrawn. Sulphone treatment can later be resumed at a lower dosage, or an alternative treatment, such as thiosemicarbazone, may be substituted.

3. RECOMMENDED FORMS OF TREATMENT.

The two forms of treatment which are simple, cheap and widely applicable are here outlined. Other forms of treatment, though probably not less effective, are much more costly and less widely practicable.

(a) *Sulphetrone* (pure crystals). 50% solution in distilled water sterilised in an autoclave at 15 lbs. for 30 mins. or boiled for 30 mins.

Intramuscular or subcutaneous injections are given:—

First two weeks	.5 c.c. (0.25 g.)	twice	a week
Second two weeks	1.0 c.c. (0.5 g.)	,,	,,
Third two weeks	1.5 c.c. (0.75 g.)	,,	,,
Fourth two weeks	2.0 c.c. (1.0 g.)	,,	,,
Fifth two weeks	2.5 c.c. (1.25 g.)	,,	,,
Thereafter	3.0 c.c. (1.5 g.)	,,	,,

(b) *DDS.* Supplied in 100 mg. and 50 mg. tablets. Tablets given orally twice weekly.

Weeks 1—4 ...	...	100 mg.	twice a week
,, 5—8 ...	...	200 mg.	,, ,,
,, 9—12	...	300 mg.	,, ,,
Thereafter ...	...	400 mg.	,, ,,

For children the dose is reduced, but not necessarily according to body weight.

The above is a *standard* dosage regime and should be followed where possible. A good clinical response can be obtained with smaller doses and with less frequent administration; weekly treatment is practicable and appears effective. Some workers suggest parenteral sulphone (DDS) in cocoanut oil suspension once in 14 days, and report a clinical response. These facts make outpatient treatment widely practicable.

4. CHOICE OF TREATMENT.

The opinion of this group divided. Some advocate injections of sulphetrone because they considered it less toxic, and because they consider administration of the proper dose is easier to control, and abuse of the treatment easier to prevent.

Others think that DDS is no more toxic, is cheaper and much easier to administer. In the administration of the oral dose twice weekly, the patient should not be given tablets to take away with him unless the physician can trust him to use them according to his instructions, thus preventing serious abuse of the drug. In any case, the importation and distribution of any sulphone drug should be carefully controlled, and its administration supervised by trained medical personnel.

5. DURATION OF TREATMENT.

Progress under treatment, though usually sure, is often very slow, and clinical improvement is usually much quicker than bacteriological improvement. Tuberculoid cases with widespread disease should be treated for at least a year to 18 months. The treatment of bacteriologically positive cases must be continued until the patient becomes and remains bacteriologically negative, and loses all clinical signs of activity. Until now the continuation of negative results for one year has commonly been the criterion for discharge. In one country a considerable relapse rate has been recorded on this regime, and it has been recommended that patients should continue treatment for a much longer period. The length of treatment should vary with the severity of the case and the time

required to become negative. Where it is practicable the advisability of necessary periodic after-treatment with sulphones might be seriously considered.

6. SUNDRY POINTS.

(1) *Sulphones in prophylaxis.*

It has been suggested that sulphones should be used in persons seriously exposed to infection, as a prophylactic. Such sulphone administration would be unlikely to have any harmful effect. No evidence is yet available of the value of such prophylactic treatment. This is a matter needing careful investigation.

(2) *Sulphone resistance.*

So far no clear indication of any kind has been seen to show that prolonged or intermittent sulphone treatment produces sulphone resistant bacilli in the person treated.

(3) *The influence of sulphone treatment on anti-leprosy work in general.*

Sulphone treatment itself is not the answer to the wide problems of leprosy. Early diagnosis, the early institution of treatment, segregation of infective cases, other remedial measures (including surgery) and rehabilitation of patients, all these activities are vital. Many of these activities have, however, already been facilitated and encouraged by improved results of treatment, and the opportunity now afforded for these increased activities should be seized and used fully.

7. OTHER DRUGS IN TREATMENT.

Streptomycin, though having some action in leprosy, appears unlikely to play any major part in treatment.

The thiosemicarbazones are giving promising results, but there is no indication that they are in any way superior to sulphones. They are more expensive and less widely applicable. They appear unlikely to rival or replace sulphone treatment, but they provide a useful alternative treatment in patients in whom sulphone administration presents difficulties (particularly allergy) or produce inadequate response.

B.C.G. has been found useful, particularly by workers in Brazil, in turning negative lepromin tests into positive. In the experiment referred to, 30 children of leprous parents were given .1gm. of B.C.G. orally once a week for three weeks, the lepromin test being done on the same day as the first dose of B.C.G. was given, and all but four gradually developed positive results. After a year all the 30 children showed positive lepromin tests. At the

same time, as a control, 15 children were lepromin tested, but were not given B.C.G., and all gave negative results. If these findings are confirmed, and if B.C.G. is found to increase the resistance of children to leprosy, we may have another important tool in combatting the disease.

OBITUARY

We regret to announce the death of Dr. James Maxwell, who was for some years a member of the Executive Committee of BELRA. In 1900 he went out to Formosa, where he succeeded his father at the Mission Hospital at Tainan. He was one of the foremost in promoting medical education in China, in helping and co-ordinating teaching and research in the various medical colleges throughout that country, most of which were the result of medical missionary effort.

He was secretary of the China Medical Missionary Association and Editor of the *China Medical Journal.* In 1929 Maxwell became head of the department of field research at the Lester Institute in Shanghai, where he had an opportunity of giving help and advice to research workers and others, a form of work for which his wide experience of China made him particularly suitable. In 1937 he became Director of the Institute of Hospital Technology.

Of all medical subjects the one which interested Maxwell most was leprosy. From 1927 to 1940 he was adviser for Eastern Asia to The Mission to Lepers. He took part in the formation of the Leonard Wood Memorial at Manila in 1931. He published a Handbook on Leprosy, and at the age of 74 he returned again to China to work for The Mission to Lepers, and was instrumental in forming a new agricultural colony at Zangpeh, in association with the leprosy hospital at Hangchow.

All who knew James Maxwell remember him as a man of great energy and joyful enthusiasm. During the Japanese war with China he remained on in the occupied territory, and organised the work of the International Red Cross until it was necessary for him to return home in 1940.

Dr. Maxwell was planning to return home last August, as he felt that under the present regime he could do no more in the meanwhile. But a cable was received on August 11th telling us that he had died suddenly of cerebral malaria.

Mrs. Maxwell accompanied and assisted him through all his journeys, and we extend to her, and to their three daughters, our deep sympathy.

E. MUIR.

REVIEWS.

" La Lepra," by R. Chaussinand.

In writing this conveniently sized monograph of some two hundred pages, Dr. Chaussinand has done the same service to the French speaking world as Cochrane and Muir have done for the English speaking peoples. The voluminous classics of Hansen and Jeanselme are seldom read in these busy days, and even the moderately sized textbook of Rogers and Muir is not as widely read as it might be. Any author therefore who produces a concise, but adequate, account of leprosy, suited to the general practitioner in the tropics, is to be heartily congratulated. Dr. Chaussinand has done this work well, his writing is compellingly lucid in the best tradition of Laenner and Transzean. He shows due respect for authority, but his work is no mere copy; it bears the strong imprint of original observation and research.

Those having experience of leprosy in the African negro will readily realise that Chaussinand's descriptions apply more closely to the disease in Indo-China, as we seldom see the severe lepromatous form depicted, or the neural abscesses described.

The author's own exhaustive researches on the cultivation of the *M.leprae,* as also a review of the literature, justifies his conclusion that the organism has not been grown serially with success. It occurs to us that as the only milieu in which the bacillus does thrive is the human tissue, it seems worth while experimenting with artificial tissue cultures, and as the natural incubation period is two to three years, so the culture should be continued for an adequate length of time, as suggested to us by Turner.

Chaussinand does well to stress that rat leprosy is a different disease to human leprosy, as the rat is refractory to inoculation with the human bacillus, and the geographic distribution of the two maladies do not correspond. The differentiation of the two diseases is further emphasised by the fact that the animal infection is resistant to sulphones, as has recently been demonstrated by Francis.

The clinical description of the disease is both concise and precise, and should be read by those bemused by the various classifications of international conferences. It is unfortunate, however, that the term macule, originally meaning a flat stain of the skin, is used to describe also elevated lesions, originally called plaques. The author is of course appreciative of the distinction, but uses the one term to cover both lesions, because of the common

usage. It is this confusion, or perhaps only a printing error, which led in figure 21, to raised split pea lesions being captioned as macules. The clinician is being severely criticised these days by laboratory workers, independent observers who analyse his results and statisticians, so he should strive after the most exacting precision. The points made in differentiating a tuberculoid case in reaction from the true lepromatous form are well made, but it might have been mentioned that the most reliable criteria are the previous history, and the subsequent course of the malady. This differential diagnosis is most important, as to confuse the two would lead in a clinical trial of a new drug to a false result, as of course the tuberculoid case in reaction tends to a spontaneous subsidence of the lesions.

A most interesting theory on the cross immunisation of leprosy and tuberculosis is described, and supported by arguments so closely made that any fair summary of them is impossible. I venture therefore only a few comments. Chaussinand is of the opinion that the statement of Rogers and Muir that tuberculosis is a common fatal termination of leprosy is too categoric. He holds that it is not true for allergic tuberculoid leprosy which is, on the contrary, resistant to tuberculosis, and records that in 500 tuberculoid cases he found only three with *M.tuberculosis* in the sputum. This argument would be more convincing if post-mortem examinations had been made, a formidable task, and also if the corresponding incidence in lepromatous cases of the same country had been given for comparison. Gehr is quoted as saying that tuberculosis is less prevalent in countries where leprosy is endemic. This does not totally accord with the increase of phthisis in Nigeria. Contrariwise, leprosy is quoted as being rare in countries where tuberculosis is endemic, but the possible causes of the decline of leprosy in Europe are so numerous that it is scarcely justifiable to ascribe it to the rise of tuberculosis. Most authorities will agree with the practical conclusion that B.C.G. vaccination should be more widely applied in countries where both diseases are endemic.

Dr. Chaussinand is to be congratulated for his defence of chaulmoogra therapy, particularly in combination with sulphones, as the present day tendency is to abandon this time honoured remedy. The arguments for the employment of diamino-diphenylsulphone in preference to the more complex preparations are made with clarity. They are (a) that the more complex substances are broken down to the parent sulphone in the body, and thereby exert their action; (b) DADPS can be administered orally; (c) it is cheap and therefore suited to mass therapy. We originaly shared

the enthusiasm of Dr. Chaussinand for an apparently ideal drug, but in our practice using the dosage scheme he describes, it proved too toxic.

Due no doubt to the publication of the monograph last year, no mention is made of the thiosemicarbazones in leprosy, nor to, the relapse rate after apparent cure with sulphones, published by the Carville workers.

We would urge especially physicians in this country to peruse this most readable text, if only because of its style, which never leaves one in doubt as to the author's meaning.

J. BARNES.

Addendum to " Leprosy " (3rd Edition) by Rogers and Muir.

It is a remarkable fact that amongst British Commonwealth workers on leprosy the most outstanding have had long connections with the three Presidency Capitals of India—Calcutta, Madras and Bombay.

In Calcutta Sir Leonard Rogers, the revered and still active doyen of tropical workers, successfully strove in the early part of this century to rescue leprosy from the Slough of Despond, to rationalize its pathology, and to inspire new methods of therapy. His disciples, colleagues and successors, Muir and Lowe, not only carried on the good work in Calcutta, but have since had wide experience in the West Indies and in tropical Africa. Muir, who recently returned to the U.K., enriched with new experience in the Purulia Leprosarium, in Bihar, has now collaborated with Sir Leonard in the production of a much needed therapeutic " addendum " to their standard work on leprosy.

The advent of the sulphones has apparently improved our powers of affording relief to sufferers from leprosy. It is, however, particularly necessary to remind ourselves that leprosy is a disease to be prevented or treated; a scientific problem to be approached in a cool, detached and critical spirit; not a cause to be won!

The somewhat over-optimistic reports on the curative powers of chaulmoogra derivatives in certain forms of leprosy led to premature " Leprosy can be cured " propaganda twenty years ago, with subsequent disillusionment. We must be most careful not to let history repeat itself and to " play down " the sulphones and newer remedies till they are thoroughly tried and understood. This is especially necessary as invasion of the body by *M.leprae*, is apparently resisted by a high proportion of human beings, whilst many others cope successfully with the bacilli after invasion, without developing clinical signs of the disease. A number of those who

develop clinically demonstrable lesions do so temporarily and cure themselves spontaneously; the remainder fight long battles with the bacilli and eventually win through at a terrible price of suffering and mutilation.

Safe and successful therapy must encourage the gradual destruction of the bacilli and their products without killing too many too quickly, with resulting severe reactions, nerve strangulation and agonizing pain.

It cannot be said that any safe, reliable standard sulphone therapy has yet been worked out.

Even with the small number of active cases at the Jordan Hospital, the leprosy unit at Redhill, four forms of sulphone therapy are at present on trial. With one major lepra reaction from DDS, one moderately severe reaction from thiosemicarbazone, and a case of retrobulbar neuritis from the same drug, it is obvious that we have much to learn.

On general principles it is better to be safe than sorry. Earlier workers tended to give sulphones in too high dosage. Some workers would not agree with Rogers and Muir that " there is a considerable space between the minimum effective dose and the maximum subtoxic dose." The suggested daily dose of 4 mg. per kilo of body weight would by some be regarded as high.

The inexperienced worker will " ca' canny " with the sulphones, starting with small doses and gradually working up towards the higher recommended dosage as his experience increases.

The ' Calcutta School ' are to be congratulated on the prompt production of this inexpensive but comprehensive and thought-provoking " addendum." Lowe's fine work in Africa is, naturally, commended. It would have been a gracious act if some reference had been made to one described by Lowe as " the father of DDS therapy "—R. G. Cochrane, whose introduction of an injectable DDS and of sulphetrone as a watery solution for parenteral use has had a powerful influence on sulphone therapy, and whose fine researches on skin and nerve pathology inspired Khanolkar's most important recent researches in Bombay.

GEORGE R. MCROBERT.

International Journal of Leprosy, Vol. 18, 2, (April-June, 1950).

Organization of the Anti-Leprosy Campaign in Madagascar, by Grimes, C. A full account of the development and present status of leprosy activities in Madagascar, by the medical officer in charge of the Leprosy Service.

Laws and Regulations relating to Leprosy in the United States of

America, by Doull, J. A. The title of this article is an indication of its scope and contents, and should be consulted in the original by those interested.

Lipoids in the Reactional Tuberculoid Leprosy Granuloma, by Campos, R. de C. J. The author has studied the question of the presence of lipoids in leprous granulomas by means of staining frozen sections of skin with Sudan IV. He found that cells of the granulomatous lesions of almost all lepromatous and reactional tuberculoid cases contained lipoid material, whereas the granuloma of the ordinary tuberculoid was wholly lacking in lipoid. The value of this observation in the differential diagnosis of lepromatous and tuberculoid leprosy is discussed.

An Acid-fast Microorganism cultivated from Leprous Material. Bacteriological and Serological Observations by Terni, M. and Signorini,, F. L. Attempts were made to cultivate the leprosy bacillus on Dubos' medium, and the larvæ of the wax method of *Galleria mellonella* (an insect very susceptible to tuberculosis infection.) All attempts failed except one, and this one was a skin leproma inoculated into a larvæ and then into Petrognani's medium. Three months later a colony of acid-fast gram-positive bacteria, aerobic, nonencapsulated, nonspore-forming and non-motile were observed. Optimum growth was obtained at 37° C. Complement-fixation tests and attempts to lyse the organism by macrophages led the authors to conclude that the bacteria were more like those of *M.leprae*, than *M.tuberculosis.*

Evaluation of the Cardioliphin Antigen in the Tests for Syphilis in Leprosy. By Shively, J. A. and Kuhns, D. M. The cardiolipin antigen was shown to reduce significantly the number of false positives obtained in the serological test for syphilis in patients suffering from leprosy. False positives with the cardiolipin complement-fixation test were obtained in 31 out of 120 known syphilitic patients, compared with 63 Kahn positives and 59 Kolmer positives.

Allergie et Para-Allergie dans la Lepre. By Floch, H. and Destombes, P. The authors suggest that results obtained by lepromin testing indigenous and non-indigenous inhabitants of French Guiana, confirm the theory of relative immunity developed by indigenous inhabitants of French Guiana (as opposed to the relative non-immunity of Europeans resident there). They consider the results of lepromin tests in endemic and non-endemic areas, and disagree with the conclusion of Dubois that a positive reaction in

a person in a non-endemic country is caused by a local irritant action of the body towards the bacilli. They consider that a positive test in a non-contact is due to a para-allergy developed by the use of other acid-fast organisms. Results of tuberculin tests in infants and children are given, and comparison is made with the results of lepromin tests carried out at the same time. From their studies the authors conclude that the tubercle bacillus is capable of producing a state of para-allergy to the leprosy bacillus. They have now commenced a study of the effect of B.C.G. vaccination on negative reactors to lepromin, in an attempt to produce a state of positive para-allergy.

The Tissue Sites most favourable for the Development of Murine Leprosy in Rats and Mice. By Hanks, J. H. and Backerman, T. The authors attempted to discover the tissues and organs in which the most rapid development of *M. leprae murium* occurs. Known numbers of bacilli obtained from clarified supernatants of bacillary emulsions were used for inoculation. Inoculations were made in the anterior chamber of the eye, the brain, the peritoneum, the dermis and epidermis and the testes. The results presented are of a highly technical nature and those interested in this aspect of leprosy should consult them in the original. Using the Hawaiian strain of *M. leprae murium*, it was discovered that the Wistar strain of rats are relatively resistant to infection. Intraperitoneal inoculation of these rats did not produce a progressive infection of the omentum, mesenteries, lymph nodes, spleen, etc., and thus this leprosy conforms more closely to the human than usual. The testes proved to be the organ from which the greatest number of bacilli could be recovered, and in which the greatest lesions were produced.

The Mitsuda Reaction in a Non-Leprous Area. By Rotberg, A. Bechelli, L. M. and Keil, H. The authors examine the question of lepromin positive non-contacts. They study the lepromin and tuberculin reaction in non-contacts in non-endemic areas, and in non-contacts in endemic areas. Using lepromin and tuberculin they cross tested each of the above groups. 18 per cent of non-contacts in non-endemic areas were lepromin positive—this figure was approximately the same for both healthy cases and active tuberculoid cases. In an endemic area the percentage of positives in non-contacts was 54 per cent. 13 per cent of non-contacts in a non-endemic area were both lepromin and tuberculin negative, whilst 18 per cent were strongly tuberculin positive and lepromin negative. These figures would seem to disprove the para-allergy theory of

Floch and Destombes, mentioned elsewhere in this Journal. The authors suggest that the explanation of the phenomenon of tuberculin positive, lepromin negative, cases, is that cross sensitization is not obligatory. The matter is left very much in doubt by the authors, who conclude that if the cross sensitization theory is not satisfactory or possible in any other way, it will be necessary to search for other factors to explain the positive lepromin reactions in non-endemic countries. This careful article is well worth a detailed study.

Promacetin in Treatment of Leprosy. Progress Report. by Johansen, F.A. et al. Promacetin, the latest of the sulphones, is basically DDS, orthosubstituted with a single sulphonamide grouping. It possesses two free amino groups. It is active in streptococal infections in mice, and in pneumococcus pneumonia in man. It is not active against tuberculosis in guinea pigs. 27 patients were treated with this drug; 23 were lepromatous, one tuberculoid. 17 patients had received no previous treatment. Two had had chaulmoogra oil and 8 sulphones. No serious toxic effects were observed, and the cases responded kindly to treatment. A significant fact was that patients (treated with other sulphones previously) having stationary residual lesions, showed renewed clearing up on promacetin therapy. The authors suggest that wider application should be made of alternating sulphones in the treatment of leprosy. The article also raises the interesting point that promacetin, which fails to protect the guinea pig against tuberculosis, is apparently effective in another acid-fast infection, i.e. leprosy. This raises the pertinent question as to whether drugs of possible value in the treatment of leprosy, should be found by experimental screening methods used, as at present, in experimental tuberculosis in animals.

M. SMITH.

Four Years Experience of Sulphone Treatment of Leprosy. By Lowe, J. and Davey, T. F. (Trans. Roy Soc. Trop. Med. Vol, 44, No. 6. June, 1951.)

The authors present the results as a whole of 4 years sulphone treatment of leprosy. Experience has been confined to diasone, sulphetrone (orally) and DDS (called DADPS in the article).

Diasone was used in 40 cases for 18 months, and in 20 for a further few months, but treatment with this drug finally ceased because of currency difficulties.

Sulphetrone was used in 260 cases for periods varying up to

3½ years. DDS has been used in 400 cases for periods up to 21 months, and has now been adopted for routine treatment. The dosage of DDS used has been standardised at 200 mg. a day, given after a preliminary course of 6 weeks on 100 mg. With all sulphone therapy freshly prepared ferrous sulphate has been given routinely to combat anaemia.

The authors go on to discuss the pharmacology of the sulphones and suggest that DDS is the active principle of the proprietary sulphones, and can produce the same effect in small doses as the larger doses of the complex sulphones.

Toxic effects are given as follows:—(a) *Anaemia*, for which iron only is necessary. (b) *Dermatitis* occurred in 2% of patients: if sulphone treatment is not stopped this dermatitis may proceed to exfoliation or death. Dermatitis was recorded as rare in female patients. Dermatitis always occurs during the first six weeks of treatment, or not at all, and if a relatively low dose is maintained during the initial 6 weeks of treatment, the occurrence of dermatitis may be prevented and its incidence considerably reduced. Instructions are given regarding the desensitization of patients who have become allergic to sulphones. *Sulphone psychosis* was observed in 6 of 350 cases being treated with DDS, but no cases were observed in 200 other cases being treated elsewhere. *Reaction*—erythema nodosum—is not considered to be a toxic effect of the sulphones, but an effect of the sulphones upon the bacillus. It is not considered that this condition is of bad prognostic import. Anti-histamine drugs were found of little value in this condition, but in the neuritis that accompanies reaction they are sometimes of value. Antimony compound is of value in controlling the reaction. *Glandular fever.* The administration of sulphones can precipitate an attack of glandular fever, presumably in a person with a latent infection.

Clinically the response to treatment is the same as that now generally accepted. Bacteriologically, six tables are presented to show the results of treatment. The group started in 1946, having had diasone, then sulphetrone, and then DDS treatment for a period of 40-48 months, records a negative rate of 80%. Another group treated only with sulphetrone for 30-38 months records a 40% negative rate. A third group treated mainly with sulphetrone for 24-30 months shows a 40% negative rate. A fourth group, having had 12-24 months with sulphetrone and then 5 months with DDS, shows a negative rate of 28%. Group E, after 12-18 months treatment with DDS, shows a 24% negative rate.

In the discussion of results the authors bring out two main points: (1) the constancy of response, and (2) the slowness of

response. With regard to (1) it is stated that improvement occurred in every case treated, and that in no case was it found impossible to use the sulphones; and with regard to (2) it is stated that the time necessary to render cases inactive and negative is directly proportional to the severity of the infection. 1+ cases usually take 1 year, 2+ cases 2—3 years, 3+ cases 3-4 years, and 4+ cases 4—5 years. The suggestion is made that the long time necessary for dead *M. leprae* to disintegrate in the tissues is one factor which has to be considered when the bacteriological slowness of response is in question. In tuberculoid cases response is much faster, clinical changes being occasionally demonstrable within 1 week. Skin lesions subside rapidly, nerve lesions more slowly. It is considered that the sulphone treatment of tuberculoid leprosy is highly satisfactory

DDS is considered to be the sulphone of choice, and has now been adopted as the standard treatment in Nigeria and elsewhere.

The authors report their results on blood and skin levels of DDS, and go on to discuss the value of DDS treatment in various types of cases.

A later note to the article gives the authors' views a year later. Twice weekly treatment is better tolerated and no less effective than daily treatment. 400 mg. twice weekly is suggested as the dose, and with this regimen the incidence and severity of toxic effects are considerably reduced. Iron treatment may be omitted in well nourished patients since the anaemia is unusual. The authors have shown that the administration of complex sulphones by mouth produces a therapeutic blood level of DDS. 20,000 cases are now under treatment in many widely scattered centres.

Of 139 lepromatous cases discharged, no clinical relapses have been seen; two showed scanty bacilli on bacteriological examination, and both cases became negative again within a few months of re-starting treatment.

Attempts have been made to speed up treatment by combining DDS with other chemotherapeutic agents. *Streptomycin* has a rapid therapeutic effect in tuberculoid cases, when given in short courses either alone or in combination with DDS. *Thiacetazone* is giving promising results, but it cannot be used with DDS. *P.A.S.* is much less active than DDS, thiacetazone or streptomycin.

M. SMITH.