EXPERIENCE WITH "AVLOSULFON" SOLUBLE
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"Avlosulfon" Soluble is a preparation recently introduced for administration by injection in the treatment of leprosy. It consists of a 40 per cent W/W sterile aqueous solution of a disubstituted derivative of dianimodiphenyl sulphone known chemically as N,N-diethyl-4,4'-diaminodiphenyl sulphone-a,x'-disulphonate. This substance is freely soluble in water and breaks down rapidly in the body to release half its weight of DDS. Its molecular structure is as follows.

\[
\text{NaOS} - \text{HC} - \text{HN} \rightleftharpoons \text{SO}_2 \rightleftharpoons \text{NH} - \text{CH} - \text{SO}_3\text{Na} \\
\text{CH}_3 \\
\text{CH}_3
\]

Laboratory investigations on the absorption and excretion of this substance were begun by the late Dr. Lowe at the Nigeria Leprosy Service Research Unit shortly before his retirement. The work was taken over while still in its infancy, expanded, and later supplemented by a clinical trial of limited proportions, the impressions gained from which are recorded here, together with the laboratory findings.

Estimations of sulphone in blood and urine were undertaken at intervals during the three days following the administration of "Avlosulfon" Soluble to volunteers in doses of ½ cc., 1 cc., and 2 cc., equivalent to 200 mg., 400 mg., and 800 mg. of the drug. For the purposes of comparison a second series of estimations was undertaken following the oral administration of DDS in doses of 100, 200, and 400 mg. under strictly comparable conditions. In each volunteer as long a series of estimations was undertaken as was practicable. The standard Bratton and Marshall method as modified by Brownlee was used. Estimations were made both of total sulphone and sulphone extractable by benzene. The very large number of estimations involved were undertaken by Miss F. McNulty, Mr. G. Okezie and Mr. S. Drewett. The results are given in Tables 1–4.
**TABLE I**

**Blood concentration of sulphone after the administration of "Avlosulfon" Soluble.**

<table>
<thead>
<tr>
<th>Dose in mg.</th>
<th>No. of estimations</th>
<th>Average blood concentration in mg. per cent estimated as DDS</th>
<th>At hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>200</td>
<td>4 4 3 3 3 6 6 6 6 24 48 72</td>
<td>Total sulphone 0.475 0.45 0.42 0.36 0.15 0.14 0.1</td>
<td>2 3 4 6 24 48 72</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Extracted sulphone 0.25 0.22 0.17 0.13 0.06 0.03</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE II**

**Blood concentration of sulphone after the administration of DDS orally.**

<table>
<thead>
<tr>
<th>Dose in mg.</th>
<th>No. of estimations</th>
<th>Average blood concentration in mg. per cent estimated as DDS</th>
<th>At hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>4 4 4 4 4 4 6 6 6 48 72</td>
<td>Total sulphone 0.64 0.60 0.58 0.54 0.52 0.51 0.5 1</td>
<td>2 3 4 6 48 72</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Extracted sulphone 0.36 0.37 0.37 0.36 0.35 0.34 0.33</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE III**

**Urine concentration of sulphone after the administration of "Avlosulfon" Soluble.**

<table>
<thead>
<tr>
<th>Dose in mg.</th>
<th>No. of estimations</th>
<th>Average urine concentration in mg. per cent estimated as DDS</th>
<th>At hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>200</td>
<td>4 4 4 4 4 4 4 4 6 48 72</td>
<td>Total sulphone 0.43 0.40 0.35 0.32 0.28 0.25 0.23 0.21 0.18 0.16 0.14 0.12 0.10 0.08 0.06 0.04 0.02 0.00 0.00</td>
<td>2 3 4 6 48 72</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Extracted sulphone 0.30 0.31 0.31 0.31 0.31 0.31 0.31 0.31 0.31 0.31 0.31 0.31 0.31 0.31 0.31 0.31 0.31 0.31 0.31</td>
<td></td>
</tr>
</tbody>
</table>
TABLE IV

Urine concentration of sulphone after the administration of DDS orally.

<table>
<thead>
<tr>
<th>Dose in mg.</th>
<th>Average urine concentration in mg. for cent At hours</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2  3  4  6  12  24  48  72</td>
</tr>
<tr>
<td>100</td>
<td>No. of estimations 5 5 4 4 4 5 5 5</td>
</tr>
<tr>
<td></td>
<td>Total sulphone    0.4 0.5 0.6 0.75 1.0 1.1 1.4 1.2</td>
</tr>
<tr>
<td></td>
<td>Extracted sulphone 0.1 0.1 0.14 0.22 0.25 0.3 0.37 0.4</td>
</tr>
<tr>
<td>200</td>
<td>No. of estimations 9 8 7 8 4 9 9 9</td>
</tr>
<tr>
<td></td>
<td>Total sulphone    0.98 1.33 1.76 1.76 1.4 1.6 1.8 1.8</td>
</tr>
<tr>
<td></td>
<td>Extracted sulphone 0.24 0.36 0.46 0.48 0.48 0.45 0.45 0.45</td>
</tr>
<tr>
<td>400</td>
<td>No. of estimations 6 6 6 6 6 6 6 6</td>
</tr>
<tr>
<td></td>
<td>Total sulphone    1.6 2.3 3.3 3.8 4.4 4.4 4.6 4.6</td>
</tr>
<tr>
<td></td>
<td>Extracted sulphone 0.70 0.97 1.3 1.8 1.3 1.2 1.2 0.9</td>
</tr>
</tbody>
</table>

Comments

1. The Concentration of Total Sulphone

The figures for total sulphone following the administration of DDS call for little comment. They are in line with previous records here and are similar to the published findings of other workers. On the whole in our Africans peak levels were rather lower and were attained more quickly than in Indian subjects (Dharmendra 1950b). Apart from this the general characteristics follow the now familiar pattern. The rapid absorption and slow excretion of DDS is evident, with peak blood levels at 4-6 hours after administration, followed by a slow decline, so that after 72 hours the concentration can still be estimated. In urine the peak concentration shows a considerable time lag as compared with blood, and declines even more slowly, so that after 72 hours the concentration is still relatively high. During the first 12 hours, with a dosage over 100 mg., not more than 10% of the dose administered has appeared in the urine.

With "Avlosulfon" Soluble the picture is different. At all doses tested the peak concentration of sulphone in the blood occurred within two hours of administration, but was considerably higher than that attained with the corresponding dose of DDS given orally. This high level is however evanescent, and rapidly declines, so that from about the sixth hour onwards the blood concentration falls below that attained with oral DDS in corresponding dosage. Thereafter it continues lower, and falls more rapidly, until after 72 hours the level is only about 0.1 mg.% regardless whether the dose administered was 200, 400 or 800 mg. The concentration of sulphone in the urine corresponds with these findings. Much
higher levels are attained than following oral DDS, and by 12 hours after administration approximately twice as much has already been excreting in the urine. These findings are in general agreement with those of Touzin and Merland. (Touzin and Merland 1953).

2. The Concentration of Extractable Sulphone

Extraction with benzene is a recognised method of estimating free DDS in mixtures with complex sulphones. It was discussed and applied by Lowe. (Lowe, 1952). During the course of the present work we have not found benzene an entirely satisfactory extractant. Nevertheless it appears to be selective in its action and results follow a consistent pattern both in respect to changes in dosage and to varying times. Where body fluids are concerned it also appears that more is involved than a simple matter of the relative solubility of DDS in water and in benzene. These matters are being considered further elsewhere. We are here concerned primarily not with the absolute concentration of DDS but with comparing the behaviour of ‘Avlosulfor’ Soluble and DDS under corresponding conditions, and from that standpoint the results are interesting and instructive.

Following the administration of DDS, we were able to extract with benzene only 40-50% of the total sulphone present in blood. This proportion remained very constant from the first hour onwards, and did not vary with increase of dose, extractable sulphone thus bearing a constant relationship to the total amount of sulphone present regardless of the actual level of this. In urine, following a dose of 100 mg. DDS, the proportion of extractable sulphone was at first very low, less than 30% of the total, but increased up to a peak level after about 4 hours, following which it declined again. With higher doses the proportion of extractable sulphone tended to approximate more to that found in blood, but the actual levels of both total and extracted sulphone rose much higher than in blood. Taken together, these findings are not capable of explanation simply on the assumption that benzene fails to extract all the DDS present. This may be a fact, but some other factor is also operating. It has been suggested that after absorption DDS in part undergoes a chemical change whereby soluble products are constantly synthesised in small amounts. Our findings would not be inconsistent with this suggestion.
With "Avlosulfon" Soluble the discrepancy between total sulphone and that extractable by benzene is also very noticeable, both in blood and urine. If delay occurred in the body in the breakdown of "Avlosulfon" Soluble to DDS, such a discrepancy would be expected, and would be most marked at first, but tend to disappear with the passage of time. This effect is in fact seen in blood with a dose of 800 mg., but it is not seen with smaller doses, and the findings again suggest that a complex situation is present.

Where actual levels are concerned it is worthy of note that for an hour or so after administration, "Avlosulfon" Soluble yielded a little more extractable sulphone in the blood than did the corresponding dose of DDS. This phase was, however, brief, and from the fourth hour onwards DDS continuously produced a higher figure.

"Avlosulfon" Soluble is thus absorbed into the blood more rapidly than DDS given orally, but it is also excreted much more rapidly than the parent compound. With larger doses there may be some delay in the breakdown of this substance to DDS, but in all the circumstances examined a considerable part of the sulphone present was in a form not capable of extraction by benzene, and suggested a complex situation in which free DDS was not the only breakdown product of "Avlosulfon" Soluble present.

It is of interest to observe whether the differences in behaviour between "Avlosulfon" Soluble and DDS have any bearing on the chemotherapeutic activity of the two substances.

**Clinical Trial of "Avlosulfon" Soluble**

In examining the therapeutic activity of "Avlosulfon" Soluble we were not concerned to establish the fact of its activity against infection with M. Leprae. That could be assumed on the basis of its breakdown to DDS, incomplete though that may be. It was of greater interest to compare the speed of response to it with that expected from the use of oral DDS, in circumstances where its more widely fluctuating blood levels would be operative. It was also of interest to observe the effects of this on the incidence of erythema nodosum.

Two systems of routine oral DDS therapy are in use here, one on a daily, the other on a twice weekly treatment basis. Treatment with "Avlosulfon" Soluble is recommended to be given
on alternate days, but it was felt preferable both on practical grounds and for the purposes of this trial to give the drug twice weekly in a dose of 800 mg. (2 c.c.s), using as a standard of comparison patients receiving oral DDS in the routine but equivalent dose of 400 mg. twice weekly. At this frequency treatment with "Avlosulfon" Soluble would lead to long periods of low blood sulphone concentration punctuated by brief phases of high concentration.

It was not considered necessary to select patients on a basis of long-term observation. Patients with advanced lepromatous leprosy were not chosen, it being considered preferable to choose milder lepromatous and other cases whose normal response to sulphones can be demonstrated unmistakably within less than a year of starting treatment. There was no difficulty in selecting such patients at random from among those being admitted, leaving others of the same types to take routine oral DDS treatment.

Those selected were classified as follows:—

- Lepromatous, moderately advanced ... 4
- Lepromatous, early ... ... ... 9
- Tuberculoid ... ... ... ... 8
- Indeterminate ... ... ... ... 1
- Borderline ... ... ... ... 2

Where necessary, the classification was confirmed by biopsy.

All these patients commenced treatment with a dose of 0.5 c.c. "Avlosulfon" Soluble twice weekly, the dose being increased gradually up to a maintenance dose of 2 c.c.s (800 mg.) twice weekly. After nine months the position of these patients was as follows:—

**Moderately Advanced Lepromatous Cases**

All four patients showed steady clinical improvement. In two of them clinical improvement was pronounced, and accompanied by a decrease in the numbers of acid fast bacilli in routine smears. From the seventh month, in smears from all four patients, significant numbers of bacilli had degenerated to granular forms.

**Early Lepromatous Cases**

All nine patients showed marked clinical improvement within nine months. In two of them smears had become negative for
acid fast bacilli. In all the remainder there was a definite reduction in the number of bacilli in routine smears, and significant numbers had degenerated to granular forms.

Tuberculoid Cases

In six of the eight tuberculoid cases, macules had become flat and inactive by the sixth month. In the other two progress was good, but had not reached this stage in nine months.

In the indeterminate case, erythema had disappeared and macules appeared residual by the fifth month. In one of the two borderline cases there was rapid and dramatic resolution, and smears were negative within six months. The other showed improvement.

These results may be considered very good. Judged by experience five years ago they might even be regarded as outstanding, but in assessing them it is necessary to bear in mind that patients now seek treatment at earlier stages of their infection than formerly, and in consequence the results of treatment with DDS itself are very good, and becoming better. Nevertheless, the progress exhibited by patients receiving "Avlosulfin" Soluble was quite as good as that displayed by corresponding patients receiving oral DDS. This is evident from the records of 33 patients of similar types admitted during the same period and treated with a standard dose of 400 mg. DDS twice weekly. The progress of these was as follows:

Moderately Advanced Lepromatous Cases

Of five cases, all showed definite clinical improvement in nine months, accompanied in all cases with a recognizable decline in the number of bacilli in routine smears.

Early Lepromatous Cases

Eleven cases all showed clinical improvement, within nine months, very marked in five cases. All showed a definite reduction in numbers of bacilli in routine smears, and three had become bacteriologically negative.

Tuberculoid Cases

Out of 17 cases, seven have become inactive in six months, and four more became inactive within nine months. The remaining seven showed marked improvement but were not entirely residual after nine months.
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One indeterminate case became residual within eight months. One borderline case showed great improvement and smears became negative within nine months.

There was thus little to choose between the two groups of patients.

Of the 14 lepromatous cases receiving “Avlosulfon” Soluble, only one suffered from typical erythema nodosum, and that not severely. Two early cases, however, displayed an interesting phenomenon, whereby after showing a rapid decline in bacilli in routine smears they suddenly evolved into the borderline type of the disease, with the eruption of numerous macules of typical succulent appearance, the nature of which was confirmed by biopsy. In one instance this change occurred in the third month, in the other in the fifth month. In both cases resolution thereafter proceeded rapidly. In another similar way one borderline case produced a fresh eruption of macules of a definitely tuberculoid nature in the fifth month, with a change in lepromin reaction from negative to positive. There were no other complications whatever among these patients.

ERYTHEMA NODOSUM

With the exception of the four moderately advanced lepromatous cases these patients were not of a type liable to suffer from erythema nodosum. The activity of “Avlosulfon” Soluble in precipitating erythema nodosum was examined in four other patients carefully chosen for this purpose. These were all fairly advanced leprosy in type, who after much treatment were all in a phase of marked intolerance to oral DDS, any increase above a low critical dose, individual for each patient, precipitating an attack of erythema nodosum. These four patients were transferred to twice weekly treatment with “Avlosulfon” Soluble, commencing with a dose of 0.25 c.c. (equivalent to 50 mg. DDS) and slowly increasing over a period of weeks. In all four cases it was found that whereas for a short time they tolerated a dose of “Avlosulfon” Soluble corresponding to as much as, or a little more than, the critical dose of DDS to which they were accustomed, sooner or later, and in each case within three months, intolerance appeared and the dose had to be reduced, until in three cases even 0.25 c.c.s precipitated erythema nodosum, and the drug was withdrawn.

The subsequent history of these patients is of interest. One of them continued to suffer from repeated and severe attacks of
erythema nodosum even in the absence of chemotherapy, but after ACTH and a period of rest resumed treatment on oral DDS. The others all took DDS in low doses without difficulty. In all cases, however, marked improvement followed during succeeding months.

**DISCUSSION**

Although not the least of the many virtues of oral DDS is its simplicity of administration, the giving of sulphone by injection has been advocated by several workers as the method of choice in special circumstances. Such circumstances are of two types. There is first the situation where for one reason or another frequent treatment is impracticable and it becomes desirable to inject sulphone in the endeavour to provide a depot of the drug in the tissues. In such circumstances administrative expediency may justifiably dictate the method of administration used. It does not imply any special therapeutic virtue in injection treatment. It has, however, been claimed by some workers that when administered by injection sulphones have less tendency to evoke undesirable reactions than when given orally. With preparations which release only small quantities of DDS this is readily explained. The patient simply does not receive sufficient DDS to evoke such reactions. With a preparation such as "Avlosulfon" Soluble this cannot be the case. Nevertheless one of the advantages of "Avlosulfon" Soluble is said to be a tendency for patients receiving it to develop less lepra reaction than when receiving oral treatment. If the term lepra reaction is used in its strict sense, none of our patients exhibited it and no comment can be offered. If it includes erythema nodosum of all degrees, it may be stated that among our patients the tendency for erythema nodosum to appear under "Avlosulfon" Soluble therapy was not less than with oral DDS and in some patients was greater. This is what one would expect from the wide range of blood sulphone concentrations with "Avlosulfon" Soluble therapy. It was of importance only in patients whose tendency to erythema nodosum had already made their treatment a difficult problem.

The high therapeutic activity of "Avlosulfon" Soluble when administered twice weekly is of considerable interest, and various explanations may be offered for it. Bearing in mind that for the greater part of each week the level of total sulphone in the blood was below 0.3 mg.% and that of extractable DDS less than 0.2 mg.%, it may perhaps be suggested in the first place that the
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sulphone level in the blood which suffices for therapeutic activity is in fact lower than is often believed. Lowe suggested some years ago that a blood concentration of free DDS as low as 0.2 mg.% may be therapeutically active, and that the critical level may indeed be lower. (Lowe, 1952.) There is often is virtue, as Muir has pointed out, in doses of DDS considerably lower than those usually employed. Nevertheless, Lowe did notice some slowing down of therapeutic response at a blood level of 0.1 mg.% and it is a matter of clinical experience that in some patients an increase of dose is associated with accelerated resolution of lesions. If an effective low concentration in the blood is the only factor responsible, the rapid response of our patients to "Avlosulfon" treatment is surprising. It is probable that some other factor is involved.

In the second place it may be suggested that virtue exists in the periodic "hammer like" effect of the brief phases of high blood sulphone concentration following each injection of "Avlosulfon" Soluble, which while too brief to lead to toxic signs yet may be sufficient to exert a good chemotherapeutic action. This idea, familiar in some forms of antibiotic and sulphonamide therapy is attractive, but is untenable if it is believed that the active agent is free DDS itself. It was shown earlier in this paper that during the phase of high blood concentration following each dose of "Avlosulfon" Soluble, the concentration of extractable DDS in the blood exceeds that obtained following the corresponding oral dose of DDS only during the first hour, and only by a small amount. The high blood level is due not to free DDS but to soluble derivatives.

This leads to a third possibility. It has yet to be demonstrated how far the chemotherapeutic action of DDS is due to unchanged DDS in the blood and tissues, and how far any water soluble metabolites which may be produced from it in significant amount in the body are implicated. If one of these was active in low concentration, and was also readily synthesised from "Avlosulfon" Soluble, a ready explanation would be forthcoming for the activity of "Avlosulfon" Soluble when administered twice weekly.

Considerable evidence is now accumulating that these products of sulphone metabolism do include active substances. Recently Bushby and Woivod have obtained evidence that in rabbits DDS is metabolised in part to a monosubstituted compound with
glycuronic acid. (Bushby and Woiwod, 1955.) Similar work on "Avlosulfon" Soluble has yielded evidence of two closely related soluble monosubstituted DDS compounds. (Thorpe, 1955.) The antibacterial activity of monosubstituted sulphones is well known, and has indeed been stated to be greater than that of DDS itself. (Smith, M. I., 1949.) If the metabolism of sulphones in the human body proceeds along similar lines to that in the rabbit, the synthesis of active monosubstituted sulphone compounds is likely.

In this connection it is of interest to note the similarity of chemical structure between "Avlosulfon" Soluble and sulphetrone (Solapzone), and also the similarity in the relation of blood levels to therapeutic activity between the two compounds. Sulphetrone has been studied extensively. Dharmendra and his co-workers (Dharmendra, 1950a) found that when given by injection, an aqueous solution of sulphetrone in a dosage of 2.0 gms. twice weekly led to a therapeutic effect comparable with that expected from oral sulphetrone in its standard much higher dosage. Blood concentration of total sulphone followed a pattern similar to that we have found with "Avlosulfon" Soluble. (Dharmendra, 1950b.) Lowe showed that on a injected dose of 3 gms. sulphetrone twice weekly, only a very small proportion appeared in the blood in the form of DDS, yielding a maximal free DDS concentration of 0.12 mg.%. It is thus most unlikely that the very good results reported by Dharmendra on a twice weekly dose of 2 gms. could be accounted for in terms of DDS alone, and Lowe suggested that some other factor, possibly a monosubstituted sulphone may be involved. The work of Bushby and Woiwod gives very strong support to this.

The parallel with "Avlosulfon" Soluble is striking. It lends support to the hypothesis that both these compounds owe part of their activity to water soluble metabolites produced in the body, and which are either themselves monosubstituted sulphone compounds or are a further stage in the metabolism of such compounds. It may very well be asked how far the activity of DDS is due to the production of such soluble products of metabolism, a question of importance in any study of the baffling problem of how sulphones interfere in the physiology of Myco. leprae in the human body.

SUMMARY AND CONCLUSIONS

1. "Avlosulfon" Soluble, a preparation introduced for the treatment of leprosy by injection, is a 40% W/W sterile aqueous
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solution of a simple disubstituted DDS compound, diethyl dianimodiphenyl-sulphone disulphonate. On injection this is said to break down in the body to release half its weight of DDS.

2. Comparison between the levels of sulphone blood and urine attained after the injection of this substance with those attained after the ingestion of DDS in corresponding dosage shows that "Avlosulfon" Soluble is absorbed into the blood more quickly, but is also excreted much more quickly. A short-lived high sulphone concentration in the blood is thus produced, which falls after a few hours to a low level.

3. If "Avlosulfon" Soluble is dissociated in the body to free DDS, this is only one phase in the chemical actions involved. The parent substance itself appears to undergo complex chemical actions in the body so that at any time not more than 50% of the sulphone in the blood of our patients was in the form of free DDS capable of being extracted by benzene. "Avlosulfon" Soluble behaved similarly, indeed with a dose of 800 mg. the proportion of extractable sulphone during the first few hours was even less. As free "Avlosulfon" Soluble if present would almost certainly undergo hydrolysis during the estimation of sulphone by the Bratton and Marshall method and give a colour reaction, it is not possible to eliminate it as a factor responsible for the large amount of non-extractable sulphone present, nevertheless it is certainly not the only factor.

4. Although the makers recommend that "Avlosulfon" Soluble be injected at 48 hourly intervals, a clinical trial in which it was used on a twice weekly basis yielded very satisfactory results, the progress of patients receiving it during the first nine months of treatment being as good as that of a control group receiving oral DDS in corresponding dosage. Complications during treatment were insignificant, but in a small test group it was not found that "Avlosulfon" Soluble had less tendency to evoke erythema nodosum than the parent compound. "Avlosulfon" Soluble thus appears to have no advantages over the parent compound, but where treatment by injection is desired it is a convenient and satisfactory preparation.

5. The high therapeutic activity of "Avlosulfon" Soluble on twice weekly treatment is interesting in view of the blood sulphone levels with which it is associated. For the greater part of the time the level of extractable DDS in the blood of our patients was less than 0.2 mg.%. While a DDS level as low as
this may very well have virtue, it appears likely that some other chemotherapeutic agent is also operating. The brief phases of high blood sulphone concentration which follow each injection of "Avlosul­fon" Soluble are produced mainly not by extractable DDS but by derivatives which are more freely soluble. In view of its being a disubstituted compound, it is not likely that "Avlosul­fon" Soluble is chemotherapeutically active, but soluble monoal­ substituted compounds could be produced during its hydro­lysis, and evidence exists not only that such compounds are pro­duced, but that they are therapeutically active. A parallel appears to exist between "Avlosul­fon" Soluble and Sulphetrone in this respect, and it appears at least possible that the activity of DDS itself may be due in part to the synthesis of such substances from it in the body.

Acknowledgements
My grateful thanks are due to Miss F. McNulty, Mr. G. Okezie, and especially to Mr. S. E. Drewett, for the numerous laboratory estimations entailed by this work, and to patients and members of staff of the Usukoki Settlement for their co-operation; also to Imperial Chemical (Pharmaceuticals) Ltd. for generous supplies of "Avlosul­fon" Soluble and much co-operation; and also to the Director of Medical Services, Eastern Region, Nigeria, for permission to publish.

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