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THE CHEMOTHERAPY OF LEPROSY IN NIGERIA

WITH AN APPENDIX ON
GLANDULAR FEVER AND EXFOLIATIVE DERMATITIS
PRECIPITATED BY SULFONES ¹

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INTRODUCTION

The Belra Research Unit of Nigeria was formed late in 1947, and started work in January 1948, with its headquarters at the Uzuakoli Leprosy Settlement where Dr. T. F. Davey, the superintendent, had been doing research and had initiated work with sulfones in 1946.² The Unit is a small one, the staff being as follows: John Lowe, M. D., director, Michael Smith, B. Sc., biochemist, Edna Smith, secretary, Gabriel Okezie, technician, and three African assistants. The work of the Unit is planned, for the present, as a short-term project with limited objectives.

SULFONE TREATMENT

EVALUATION OF THE TREATMENT

This work of the Unit involves the careful selection of patients, including as many severe lepromatous cases as possible; the accurate assessment of their clinical and bacteriological status before treatment; careful clinical and laboratory studies

¹ Adopted from the annual report for 1948 of the Nigeria Research Unit, British Empire Leprosy Relief Association, with changes approved by the author.—EDITOR.

² The Unit is greatly indebted to Dr. Davey for many facilities provided, including laboratory accommodation, the loan of staff, the valuable records of the work already done by him, and also for his help and cooperation throughout the year.

during the treatment; a study of toxic effects; careful assessment of the results, early and late; and the repeated examination of patients after the cessation of treatment.

Besides ordinary clinical examination, the following laboratory procedures have frequently been used: repeated bacteriological examinations of skin and mucous membranes; lepromin testing with bacillary antigen standardized by weight; hematological studies, including hemoglobin estimations, red cell counts, white cell counts, differential counts and erythrocyte sedimentation rates, and icterus index estimations, van den Bergh test, Schlesinger's test, Ehrlich's test and others. Laboratory examinations for other diseases complicating leprosy have been numerous, the commonest being the Paul-Bunnell test for glandular fever, the Ide test for yaws, various liver function tests, blood examinations for microfilaria (*loa loa* and *perstans*) and for malaria parasites, stool examinations for helminth infection, etc. During treatment, blood sulfone estimations have been a routine procedure. Thus the studies have been as thorough as possible, considering the limited staff available.

In assessing results of treatment, careful clinical and bacteriological examinations are made. Clinical observations are of course of great value, and they have given undoubted evidence of improvement which in many cases has been marked, but they always have to be interpreted and the personal factor influences this interpretation. Bacteriological examination, with the grading of positive findings from 4+ (lepra bacilli in enormous numbers) to 1+ (bacilli scanty and not easy to find), have been made as routine. Because the findings are little influenced by the personal factor, we plan to make the diminution of bacilli in or their disappearance from the skin and mucous membranes our main criterion in judging the efficacy of sulfone treatment.

All material for bacteriological examination is taken by our own skilled technician, all slides are stained under close supervision, and all are examined by the European staff of the Unit. Multiple examinations are made, and any change from positive to negative is verified at once by repeated multiple examinations, and, of course, periodical re-examination.

The total number of patients who have received sulfone treatment is 295, made up as follows:

Routine sulfone treatment, lepromatous cases	234
Routine sulfone treatment, nonlepromatous cases	17
Experimental treatment with diaminodiphenyl sulfone	54

These groups include all patients who have had sulfone treatment in the past or are having it at present. The 54 of the experimental treatment group are discussed in a later section of this report.

RESULTS OF THE ROUTINE TREATMENT

In lepromatous cases.—Of the total of 234 cases in this group, 7 are omitted from the analysis; three died and four ceased treatment before any significant results were obtained. The remaining 227 are divided into four groups for this analysis.

Group A: This group comprises 34 cases treated for more than two years (mostly 32 months, first with diasone 21 months and then sulphetrone 11 months). These cases were selected for sulfone treatment for either of two main reasons, (a) the severity of the leprosy and its complications, or (b) persistent failure to respond adequately to hydnocarpus oil treatment. All were bacteriologically positive, 15 showing many bacilli (3+ or 4+), and 19 showing moderate or small numbers (2+ or 1+).

Judged clinically, the results of treatment have been as follows: almost complete disappearance of signs of activity of the disease; healing of lepromatous lesions of skin and mucous membranes, with the disappearance of signs of inflammation of skin, nerves, and eyes; shrinking and atrophy of nodules and infiltrations of the skin. In other words, the treatment has caused apparent clinical arrest of the disease, the persisting lesions being mainly if not entirely "residual," consisting of shrunken skin lesions, fibrotic nerves, and trophic lesions.

Judged bacteriologically, there has been a consistent and all-round bacteriological improvement in practically every case, as is shown in Table 1. No less than 23 of the 34 (68%) are now bacteriologically negative. Even the cases originally 4+ have shown a marked reduction in the number of bacilli, as well as the morphological changes in the bacilli which are discussed later; and most of them show no bacilli in the mucous membranes, so their infectivity is presumably much reduced. One of them is now negative; so are all of the eleven 1+ patients, all but one of the eight 2+ patients, and four of the ten 3+ patients. Of the eleven patients who are still positive many, if not most, appear likely to become negative during the next year.*

TABLE 1.—*Bacteriological improvement in 34 cases treated with sulfones for more than two years.*

Status at beginning of treatment		Present status				
Positivity	Cases	4 +	3 +	2 +	1 +	Neg.
4 +	5	-----	1	2	1	1
3 +	10	-----	3	1	2	4
2 +	8	-----	-----	-----	1	7
1 +	11	-----	-----	-----	-----	11
Total	34	-----	4	3	4	23

Group B: This group of 35 cases has been treated for between one year and two years with sulphetrone. It includes a particularly large proportion of florid and highly positive cases. Judged clinically, it has shown a steady diminution of clinical activity, as described for Group A.

* In a personal communication written in March, 1949, the author stated that the percentage of negatives had already increased from 68 to nearly 80. As a sort of index of bacteriological improvement of this group, it can be calculated that the average degree of positivity, which was 2.26 before treatment, had dropped to 0.65.—EDITOR.

While in some of the cases the disease now appears clinically inactive, in others there are still periods of activity, usually short but sometimes frequently recurring, during which inflammatory signs may be seen in skin, nerves and occasionally in the eyes. This activity is possibly, or probably, caused by an allergic reaction of the tissues to the products of the action of the sulfone on the leprosy lesions and bacilli. These periods of "activity" seem to be accompanied by, or followed by, clinical and bacteriological improvement. Judged bacteriologically, this group shows a steady diminution in the number of bacilli in the lesions, and a change in morphology of the bacilli, but so far only six (17%) of the 35 cases have become negative. These six were all classified 1+ when treatment started.

Group C: This one consists of 91 cases treated between 6 and 12 months with sulphetrone. Judged clinically, they show various degrees of improvement, marked improvement being seen in the more florid kind of case with numerous and prominent lesions. Signs of "reaction" are not uncommon in these cases treated for a short period, but these signs are usually of short duration and lead to no permanent change. In a few patients these periods of reaction have been severe, frequently repeated, and troublesome, the most troublesome feature being neuritis, most commonly in the ulnar nerve. With care, however, the treatment can be continued, and gradually reactions become less common and less severe. Judged bacteriologically, this group shows considerable improvement, marked in a few cases. So far 11 cases (12%), nearly all 1+ when treatment started, have become negative.

Group D: This group consists of 68 patients treated for less than six months. Clinical improvement is already evident in some of them, but in most it is slight. Bacteriological improvement is not yet marked in most of them, although two have become negative, both of them having originally been 2+.

These results indicate a uniformly good response, clinical and bacteriological, in lepromatous leprosy, but they also show the slowness of bacteriological improvement to the point of negative findings. During the first year of treatment a small number of slightly positive cases become negative; during the second year the number is still small; it is only in the third year that the negatives increase markedly. However, the data recorded for Group A are most impressive and encouraging, although it should be recalled that this group of 34 cases treated for nearly three years contained a low proportion (only 15%) of 4+ cases, and a high proportion (23%) of 1+ cases.

Our observations, consequently, indicate strongly that the results of sulfone treatment, although excellent, are not likely to be fully demonstrated in severe lepromatous cases until the third or fourth year of treatment, only the milder and the weakly positive cases becoming negative early. The only 4+ and 3+ cases that have become negative are in the group treated for nearly three years.

In common with other workers we have observed marked

changes in the morphology of the stained bacillus. The body appears thin and feebly staining, but large intensely staining granules are often seen. These changes frequently appear after a few months of treatment. Later the bacilli show a fragmented appearance and finally are hardly recognizable as bacilli. The significance of these changes is not certain but they may indicate degeneration, if not death, of the bacilli.

Several workers have suggested, and one has reported (3), that in lepromatous cases subsiding under sulfone treatment the results of the lepromin test may change from negative to positive. So far we have been unable to confirm this.

In tuberculoid cases.—While most workers have reported little or no benefit from sulfone treatment of nonlepromatous forms of leprosy, one worker (5) has reported good results in tuberculoid cases. We have treated experimentally ten patients showing active tuberculoid lesions, the activity being shown by thickening, erythema and signs of inflammation in the lesions and of the nerves supplying the lesions. Most of these cases were of "major" or intermediate degree, none being "minor;" two were bacteriologically positive when treatment started. All showed good response. In some of the major tuberculoid lesions, within a few days, there was a focal reaction with the scaling and desquamation and, in two cases, slight superficial ulceration. These changes were followed by steady subsidence of activity. The two bacteriologically positive cases rapidly became negative. The nerves supplying the lesions become less tender, though in most of the cases thickening has remained.

Of four tuberculoid cases treated for eight or ten months, all now show only residual lesions. Of six treated for less than six months, all show incomplete healing of the lesions. None has developed any new patches or shown involvement of nerves previously unaffected.

It is well known that tuberculoid lesions often show spontaneous subsidence. In Nigeria this occurrence seems to be rare, and the chronicity of tuberculoid lesions is striking. One of these ten cases was kept under observation for three months with no treatment and showed no changes, but treatment was followed by rapid subsidence. It is believed that the results here reported are almost certainly significant, although a longer study of a greater number of cases is needed.

Permanence of results.—On this subject our data so far are limited. Ten lepromatous patients have become negative and have ceased treatment for periods varying between 5 and 14

months, and so far none has shown clinical or bacteriological evidence of reactivation of the disease.

GENERAL CONCLUSIONS

The main clinical findings in this study of sulfone treatment, and conclusions to be drawn from it, are as follows:

1. The treatment is very well tolerated. In only two cases has it been impossible to establish and maintain the treatment, because of allergic manifestations (exfoliative dermatitis) discussed later; attempts are being made to desensitize these patients. In one other case the occurrence of a retrobulbar neuritis caused us to stop treatment, but whether it was caused by the treatment is not clear.

2. Under reasonably good medical supervision, laboratory control can be minimal. The main considerations are the detection of anemia by hemoglobin estimations, if necessary, and the detection of an occasional high blood sulfone level.

3. The treatment of anemia before beginning sulfone therapy, and the prevention of anemia during the treatment by routine daily administration of iron (ferrous sulphate), are essential.

4. In some of our patients the presence of varying degrees of cirrhosis of the liver, probably nutritional in origin, evidenced by disordered liver function and anemia, has made sulfone treatment difficult. In such cases special measures to combat the anemia and malnutrition have had to be used.

5. Complications of sulfone therapy are usually not serious and occur mostly during the first year of treatment; later they become less frequent and much milder. These mild complications mainly take the form of brief "reactions," resembling in some respects lepromatous reaction, the so-called erythema nodosum. Temporary exacerbations of neuritis and of iridocyclitis have been seen. These complications may necessitate temporary reduction of dosage or interruption of treatment. The duration of these complications is usually not more than a week or two.

6. Severe complications have been seen in the form of glandular fever precipitated by sulfone treatment, sometimes severe and complicated by hepatitis, and of an exfoliative dermatitis. This matter is discussed in an appendix.

7. Clinical improvement is most marked in the more severe lepromatous cases with florid lesions and complications. In less marked cases improvement is less obvious, but it is seen in practically all cases treated for a year or more.

8. The effect of the treatment on the complications of

leprosy, such as eye involvement or the involvement of the respiratory passages, has been marked. The effect on trophic lesions is slight.

9. Bacteriological improvement is slow but sure. A few slightly positive cases become negative quite early. The first year of treatment sees a few cases becoming and staying negative. During the second year some negatives are seen, but not in cases highly positive before treatment. In the third year the number of negatives increases markedly and steadily. Our findings indicate that the majority of lepromatous cases can be rendered bacteriologically negative, but in very florid cases treatment for four years or even more may be necessary.

10. The uniformity of response is striking, although reactions and temporary setbacks may be seen during the first year or eighteen months. We cannot record a single case with more than one year of treatment in which the progress of the disease has not been checked. Of the deaths in our patients, none has been due to leprosy and only one due to the treatment (exfoliative dermatitis).

11. Ten cases have ceased treatment on becoming negative and have been observed for periods up to fourteen months. None has relapsed as yet.

12. While only a few tuberculoid cases have been treated there are strong indications of the value of sulfones in this form of leprosy. In some cases a few months' treatment has caused disappearance of all signs of activity.

13. In patients with no signs of activity but with only residual and trophic lesions, sulfones are of no value.

14. In lepromatous cases sulfone treatment is believed to be far more effective than any other. Moreover, the good results in tuberculoid cases suggest that it may be of great value in all active cases of leprosy.

EXPERIMENTAL COMPARISON OF DIFFERENT SULFONES

CLINICAL FEATURES

Our plan to have two groups of cases treated in parallel with diasone and sulphetrone could not be carried out because of dollar difficulties in procuring diasone. Some comparison, however, is possible from our records of different patients treated at different times with the two drugs. The following general conclusions are drawn.

The effects of diasone and sulphetrone are similar. Diasone appears to be the more toxic of the two, and a lower dosage is

indicated. This difficulty is partly, if not entirely, neutralized by the fact that therapeutic effects can be produced with relatively small doses. Sulphetrone is very well tolerated, but a higher dosage appears necessary. There is no clear indication that it is better than diasone; judged on bacteriological findings it is possible that diasone is better. The results of pharmacological studies which have been made may have a bearing on the above findings.

PHARMACOLOGICAL FEATURES (BY M. S.)

Studies have been carried out with sulphetrone, diasone and 4,4'-diaminodiphenyl sulfone (more accurately named bis-(4-aminophenyl) sulfone). They have been administered entirely by the oral route. The findings here quoted were made on patients who had already received sulfones for several weeks.

Absorption and excretion.—Only 10 to 20 per cent of the daily oral intake of sulphetrone appears in the urine; 30 to 50 per cent of the intake of diasone appears in the urine; 80 to 100 per cent of the amount of diaminodiphenyl sulfone ingested appears in the urine, the drug being almost completely absorbed.

As much as 70 to 90 per cent of the daily oral dose of sulphetrone is excreted in the feces. Whether this is due to concentration by the liver and excretion through the bile duct, or simply to nonabsorption, or both it is not yet possible to say. Of the intake of diasone, 50 to 60 per cent is excreted in the feces. The amount of diaminodiphenyl sulfone so excreted is negligible.

Degradation.—By selective extraction methods applied to urine we have found that both of the proprietary sulfones studied are degraded in some measure to diaminodiphenyl sulfone. The degradation of sulphetrone is of a low order, less than 6 per cent; figures for diasone are higher but the work is not yet complete.

Acetylation.—Acetylated derivatives are not present to any great degree in the urine of patients on sulfone treatment. Less than 5 per cent acetylation of the parent substance and diasone occurs, while sulphetrone is not acetylated at all.

Conjugation.—Preliminary studies indicate that combination with glycuronic acid is not a major factor in the detoxication mechanisms of the body towards the sulfones.

Persistence.—The blood-level/time curves for the sulfones show that that of diaminodiphenyl sulfone encloses a greater area than that of either diasone or sulphetrone. Blood levels of diaminodiphenyl sulfone are still measurable 14 days after the

cessation of a treatment, as much as 2 to 3 mgm. per 100 cc. Urine levels are also appreciable after this period. The proprietary sulfones are eliminated from the blood and urine more rapidly than this. Caution must be exercised in the interpretation of the tests for residual concentrations of sulfones in urine, as we have found that some of our cases excrete diazotizable substances of metabolic origin not allied to the sulfones.

Toxicity.—We have not been able to detect the spectrum of methemoglobin in the blood of any of our sulfone-treated patients. Within the first two weeks of treatment a slight hemolytic anemia occurs, but after that there is no evidence of hemolysis. Diaminodiphenyl sulfone therapy is associated with a continuous slight hemolysis.

The study of liver damage in African patients treated with sulfones is complicated by the fact that evidence of liver dysfunction is common among the normal population here. The methods of studying liver function have included estimations of urobilin and urobilinogen in urine, plasma bilirubin, the hippuric acid synthesizing power of the liver, and two tests of the proportion of circulating gamma globulin—the Takata-Ara and the alcohol turbidity tests. Abnormal excretion rates of urobilin and urobilinogen are frequently encountered. This matter is being investigated further. No evidence has been seen of appreciable liver damage occurring during treatment.

OTHER OBSERVATIONS ON SULPHETRONE

Blood and tissue levels.—A study has been made of the relationship between residual blood levels and skin levels and dosage of sulphetrone, with doses varying from 2 to 8 gm. a day. Up to 4 gm. in a 10-stone (63.6 kgm.; 140 lb.) adult, the blood level in milligrams per 100 cubic centimeters of blood is slightly less than the daily dose in grams. Further increases in dosage produces only slight corresponding increases in the blood level; 4 mgm. per 100 cc. is easily obtainable, 6 mgm. per 100 cc. is obtainable with difficulty, while 8 mgm. per 100 cc. cannot be maintained on any dosage practicable in ambulant patients.

Skin levels have been found to parallel the blood levels, with no evidence of concentration in the skin. Similar levels of sulphetrone were found in leprous and normal skin. The only occasion when high skin levels were reported, was when novocaine had been used by mistake as the local anesthetic for the skin excision; novocaine itself has the power of producing the color reaction used in sulfone estimations, and in such work, such local anesthetics give erroneous results. Estimations upon sweat, tears,

saliva and lymph have afforded evidence that sulphetrone is distributed evenly throughout the body fluids. The reported concentration of sulphetrone in liver and bile (1) has not been verified owing to lack of postmortem material.

Methods of oral administration.—Studies of the blood, urine and feces levels of sulphetrone were made when there were variations in (a) the frequency and (b) the methods of oral administration. There were no appreciable differences of absorption or blood levels whether the daily dose was given in hourly portions or in our usual twice-daily portions; or whether the tablets were administered whole or crushed; or whether iron mixture was taken simultaneously with the dose, or at widely differing times, or not at all. Twice-daily administration was found to maintain a reasonably steady blood level for the 24 hours.

PRELIMINARY STUDIES OF DIAMINODIPHENYL SULFONE

This substance is presumably the active principle of all the sulfones; the more complicated ones are believed to act by liberating it slowly in the body. It is toxic, and a study of the action of small doses was a part of the original plan of work of the Unit. The Havana Congress recommended a study of the value of this sulfone injected in small doses, that recommendation probably being based on the idea that absorption after oral administration is poor. It was decided here to study pharmacologically the results of oral administration in small doses in a small number of carefully selected and carefully observed cases, with most stringent laboratory control for evidence of toxic effects. The results have been striking.

Nine cases were chosen for the experiment. A daily dose of 0.1 gm. was well tolerated, and was found to produce appreciable blood and urine levels. After two weeks the dose was increased to 0.2 gm. per day, after two weeks more to 0.3 gm., and so on. Administration was continuous, with no breaks whatever. It was not till the dose exceeded 0.5 gm. a day that laboratory tests revealed evidence of toxicity (increased hemolysis); and, although the patients were quite fit, the experiment was ended without any ill effects. Long before this a good level of 1 to 2 mgm. per 100 cc. had been established and maintained. Balance experiments after oral administration showed almost 100 per cent absorption from the gut; negligible amounts were detected in the stools, while most of the daily dose was detected in the 24-hour urine specimen. Detectable blood levels and excretion

of the drug continued for two weeks after cessation of administration.

This experiment provided the basis of a therapeutic trial now in progress with 54 patients on a standard daily oral dose of 0.3 gm., attained slowly as detailed above. Six weeks of treatment, continuous in most cases, has produced no toxic effects of consequence. Oral administration is preferred to injection because it is much easier to carry out, and it appears to be safer since toxic effects and liver damage have been recorded on a similar total dose given by injection twice a week (2). "It is not at present advisable to use it."³ Our method of treatment, if effective, should prove most economical in drug, staff, labor and equipment. The full therapeutic assessment of this form of treatment will take much time.

CLINICAL STUDY OF LEPROSY IN NIGERIA

With our main efforts devoted to sulfone therapy, no systematic study of the clinical features of leprosy in Nigeria has been made during the year. Nevertheless, we have examined many hundreds of cases and have gained certain general impressions. To study the early lesions is extraordinarily difficult here because in almost every case they have been obscured by the so-called "native treatment," which produces marked scarring. Furthermore, in this part of Nigeria, clinics for hydnocarpus-oil treatment are so numerous and widespread that almost all cases have had their lesions modified by intradermal injections. Thus, fresh untreated cases are difficult to find in any number; but the following general statements may be made about leprosy in this part of Nigeria.

Much the commonest lesion in the general population is the minor tuberculoid one. Major tuberculoid cases are seen, but in no great number in great severity. Lepromatous cases do not form a high proportion of the total, but of such cases the diffuse kind is much the most common. The most striking feature in lepromatous cases is the marked and widespread nerve involvement frequently seen, although with few tropic lesions.

A feature of most cases of leprosy of both tuberculoid and lepromatous types appears to be extreme chronicity, often without very marked severity. Tuberculoid cases apparently remain active for years and rarely show spontaneous subsidence. Mild or moderately severe lepromatous cases of very long standing are also very common. Severe complications or sequelae of lepro-

³ Verbal quotation from Cochrane.

matous leprosy, such as blindness and laryngeal obstruction, are relatively rare.

An attempt has been made to find and study cases of leprosy with macular lesions showing no anesthesia and no bacilli, since such cases have been reported by others (4). So far we have found only one such case. In definitely leprous lesions careful examination has almost invariably shown either some blunting of sensation or the presence of acid-fast bacilli. Some cases have been seen with indefinite macules rather like the kind described, but in other parts of the body there have been definite manifestations of the disease such as thickened nerves and loss of sensation. Moreover, even in these cases careful examination of the patches will usually show one of the cardinal signs of leprosy.

EPIDEMIOLOGICAL STUDIES IN NIGERIA

During the year little work has been done under this head. The Unit shared in one small local survey of 3,000 persons. The striking findings were a high incidence in the population (9%), a low proportion of lepromatous cases (below 10%), most unusual findings with respect to sex and age distribution. The proportion of cases in children was very low, and there was a higher incidence among females than among males. Previous surveys done in this part of Nigeria have apparently shown similar findings.

ACKNOWLEDGMENTS

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APPENDIX

GLANDULAR FEVER AND EXFOLIATIVE DERMATITIS PRECIPITATED BY SULFONES

Here are summarized the main facts about glandular fever infection observed here, and the peculiar action of sulfones in precipitating attacks of glandular fever in persons harboring the infection. These facts result from studies carried on throughout the year, including several hundred differential white cell counts and Paul-Bunnell tests, and some Barrett adsorption tests in persons showing fever and lymphadenitis or lym-

phadenitis without fever, in persons with leprosy on sulfone treatment, in persons with leprosy not on sulfone treatment, and in persons with neither leprosy nor sulfone treatment.

Glandular fever infection, usually subclinical, appears to be widespread in the general population of this part of Nigeria, the tests giving positive results in over 50 per cent of persons studied. Clinical glandular fever is not uncommon in children, but in adults it is relatively rare. The infection commonly shows itself not in definite bouts of fever, but in a chronic generalized lymphadenopathy, a positive Paul-Bunnell test (titers of 112, 224 or more), and a mononucleosis in the peripheral blood with presence of some immature cells.

When persons with such afebrile glandular fever are given sulfones for the treatment of leprosy, there are not infrequently precipitated severe attacks of classical glandular fever with high irregular pyrexia, generalized lymphadenitis and frequently splenomegaly, and evidence of disordered liver function with in some cases marked jaundice. The blood shows marked mononucleosis with many immature lymphoblast-like cells, and a marked rise in the Paul-Bunnell titer to 224, 448 or 896, although this rise often appears late in the fever and sometimes—particularly in cases with jaundice—only when the fever has subsided. The fever usually lasts 10 to 14 days, but the high-titer Paul-Bunnell tests, the mononucleosis, and the enlargement of lymph nodes persist for many months. Relapses of the fever may be seen with or without the resumption of sulfone therapy.

These clear-cut attacks of glandular fever precipitated by sulfone therapy have been practically confined to adult males, in whom their incidence has been about 12 per cent. In addition, there has been a similar number of less definite cases. They have nearly all occurred between two and five weeks after the initiation of the treatment. In women and children the manifestations of the glandular fever infection during sulfone therapy have been much less clear-cut and of minor importance, although odd bouts of fever with lymphadenopathy, positive Paul-Bunnell test and mononucleosis are quite commonly seen.

The attack of glandular fever itself, while often severe, has never been dangerous to life; but danger to life has occurred from the simultaneous occurrence of a severe generalized exfoliative dermatitis caused by the sulfone treatment. This dermatitis has occurred only in persons during an induced attack of glandular fever, although it is caused by sulfones as is shown by the persistent sensitivity to minimal doses of the drug, which will produce a severe recurrence of the dermatitis long after the glandular fever has subsided.

Thus two factors appear necessary to produce the exfoliative dermatitis, one being sulfones and the other glandular fever. One of the two patients in whom sulfone sensitivity has persisted has been tested and found equally allergic to sulfonamides, the giving of a single tablet being followed by general dermatitis. A knowledge of these phenomena is of importance in the prevention of serious illness and possibly an occasional death during sulfone therapy in Nigeria.

Addendum:

The report presented above is practically as it was written one year ago. Work during 1949 has given strong evidence to support and amplify the views expressed.

Twenty-eight active tuberculoid cases have now been treated, some with sulphetrone and some with diaminodiphenyl sulfone, all with striking results, signs of resolution usually appearing within one month, sometimes within two weeks. The resolutions were complete in the skin in six months, that of nerve-trunk lesions being slower.

The daily oral administration of diaminodiphenyl sulfone has now been continuous for one year, the number of cases growing from nine to about one hundred. In tuberculoid cases the response appears to be even quicker than with proprietary sulfones; in lepromatous cases the response is at least as good as, and probably better than with the proprietary sulfone. Toxic effects have been negligible as long as two rules have been observed. The standard daily dose, 300 milligrams (here given in one dose), is never given without at least one month on lower doses, 100 milligrams for two weeks, 200 milligrams for two weeks; this is most important. The standard dose is not exceeded except in special circumstances, although we are now experimenting with slightly higher doses.

It is now proposed to extend this form of treatment widely, and gradually to drop the use of proprietary sulfones. This will reduce the cost of sulfone treatment to a mere one twentieth of its previous cost (15 shillings a year instead of 12 to 15 pounds), and in addition by this method there is much saving in syringes, needles, sterilization, staff and equipment.

Mr. Smith has carried out detailed pharmacological studies of three sulfones, sulphetrone, diasone and diaminodiphenyl sulfone, and the very valuable results have been summarized in a paper now awaiting publication. The results confirm and amplify the findings reported above, and greatly favor the oral administration of diaminodiphenyl sulfone. He has been able to demonstrate the spectrum of methemoglobin (or methemalbumen) in sulfone-treated cases.

Exfoliative dermatitis has been seen in about 2 per cent of our sulfone-treated cases, and has now been seen in the absence of glandular fever. Patients sensitive to sulfones can be desensitized by the daily injection of small but increasing amounts from 10 milligrams upwards.

The glandular fever of sulphone-treated cases is apparently an example of a phenomenon not unknown in human medicine and in veterinary medicine, the precipitation of an attack of a virus disease by chemotherapy. Other instances are the precipi-

tation of herpes zoster with arsenic and in dogs, of encephalitis and hard-pad disease with sulfonamides. —John Lowe.

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