LEPROSY RESEARCH UNIT

UZUAKOLI

1960 REPORT

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LEPROSY RESEARCH UNIT, UZUAKOLI
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INTRODUCTION

The Leprosy Research Unit at Uzuakoli is under the administrative control of the Ministry of Health, Eastern Region, Nigeria. It is an integral part of the Regional Leprosy Service, being intimately associated with this Service in the Owerri Province and related to that in other Provinces through Settlements that co-operate in drug trials.

The financial support, which used to come from the Colonial Welfare and Development Fund, through the Federal Government, is now assured directly by the Federal Government.

The research projects of the Unit are made possible and greatly facilitated in all ways by the Settlement at which it is located. The advantages of the complete fusion of administrative, medical and laboratory activities, are everywhere apparent.

The patients admitted to the Settlement for various reasons—medical, social, orthopaedic—form a typical cross-section of the clinical forms of leprosy occurring in the Eastern Region, and as such prove suitable for study and research. A diminishing proportion of these patients, however, is composed of untreated and highly positive lepromatous cases, suitable for drug trials. If adequate funds were available to ensure the support of such of these patients as are necessitous and who are now treated at Clinics near their homes, they could be admitted to the Settlement and thus not only profit from the more adequate medical attention, but also participate in the work of the Unit.

An interesting, and epidemiologically important, aspect of recent admissions, is that nowadays the average villager does not recognise lepromatous leprosy, its rarity being an indication of the success of the leprosy campaign in the area. To temper an understandable optimism, we must expect to see leprosy developing in people already infected by such "open" cases, and now in the variably long incubation period of the disease.

As long as there is a hard core of patients still suffering from clinical leprosy and still highly positive bacteriologically after many years of adequate and controlled treatment, and, furthermore, as long as the more seriously infected patients must ordinarily face at least four years of treatment, with no guarantee of freedom from neurological complications, there is no room for complacency. The sulphones cannot be the final answer to the problem of leprosy. More research is needed.

A feature of the work of the Unit during the year has been the increase in the number of people coming for consultation who have diverse non-leprous skin conditions. They have been suspected of having leprosy. There is a need for a Dermatological Clinic in association with the Research Unit.

A.—CHEMOTHERAPY

Therapeutic trials have continued on the following drugs:—

(*a*) Thiambutosine; Diphenyl thiourea; DPT or compound SU 1906;
(*b*) Diamino-diphenyl-sulphoxide;
(*c*) Ditophal; Diethyl-dithiol-*iso*phthalate;
(*d*) Sulphaphenazole; (p-amino-benzene-sulphamido)-2-phenyl-pyrazole; "Orisul";
(*e*) Repository Sulphone; compound 59K 401;

Trials have been undertaken on the following drugs:

(*f*) An azulene derivative; AZ–8;
(*g*) Nialamide; a Mono-amine oxidase inhibitor: "Niamid";
(*h*) A long-acting Prednisolone;
(*i*) A dicoumarin: methoxypsoralen; "Oxsoralen";
(*j*) A substituted Anilino-*apo*safranin (Rimino-compound): B. 663;
(*k*) Mono-benzyl ether of hydroquinone: a depigmenting ointment.

Investigations of these preparations will be briefly referred to.

(*a*) *Thiambutosine* (*Diphenyl thiourea, DPT, Ciba compound SU* 1906). (*Ciba S.A.*).—The studies that have continued with this compound have been especially directed towards assessing its final place in the treatment of leprosy. It would appear that the drug is of definite value in cases of neuritis, of incipient psychosis, and of intolerance to sulphones. Its therapeutic value is on a par with that of Dapsone, but its higher cost will never make it a serious competitor of Dapsone in mass treatment.

A definite drawback to prolonged use of the drug is the development of resistance during the second year of treatment in a proportion of patients, as shown by the more or less sudden reappearance in the routine monthly smears of morphologically normal bacilli, often coupled with an absolute increase in the density of bacilli at the sites habitually smeared. It is suggested therefore that the drug should be supplemented during the second year by another standard drug. The incidence of lepra reactions in patients under treatment with the drug is no higher than occurs with Dapsone; in fact, some patients troubled by prolonged or recurrent reaction under Dapsone therapy, may be comparatively free from reaction when placed on DPT therapy.

(*b*) *Diamino-diphenyl-sulphoxide* ("*Medapsol*", *I.C.I.*).—The suspicion of the toxic properties of this drug or of certain of its complex metabolites, has been confirmed during the year. Full urinary studies have shown that a regrettably high proportion of patients suffer from kidney toxaemia, when the drug is administered in adequate dosage for prolonged periods. The commonest finding is a slight transient or recurrent haematuria and albuminuria; rarely the haematuria is severe and prolonged. Blood urea estimations have been within normal limits.

In view of these findings, the trial has been abandoned, and it is recommended that the drug be not used in future for the treatment of leprosy. It is recalled that its therapeutic value approximates to that of Dapsone, while it is more expensive to manufacture.

(*c*) *Ditophal* (*Diethyl-dithiol-isophthalate*; "*Etisul*" *I.C.I.*).—Trials have continued during the year with several objectives:—

(*i*) To ascertain if the early promise would be fulfilled that the drug would materially shorten the period of treatment and cause rapid and permanent

bacteriological negativity. The conclusions are unfortunately equivocal, and no definite pronouncement can yet be made.

(*ii*) To ascertain if certain new liquid formulations of the drug were acceptable to patients.

Good results, from this standpoint, were obtained with the first formulation, which encouraged the makers to pursue their efforts in this direction.

A further trial was undertaken with a new liquid preparation (Formulation 565). There were three groups of patients: those who had used the earlier liquid preparation; those who had used this earlier preparation and the original ointment; those who had used neither. The consensus of opinion was that Formulation 565 was acceptable; it rubbed easily, disappeared more rapidly from the skin, and the odour was not only more effectively masked, but disappeared quicker. The preparation is probably more effective therapeutically, also, since the active ingredient is not adsorbed on to the solid particles of the excipient, which remain on the skin surface.

(*iii*) To resolve the continuing problem of the efficacy of Etisul. In view of the conflicting reports on the matter, a double-blind trial was instituted at Uzuakoli and Oji River Settlements, using Dapsone in both groups, and Etisul in one group and a similarly "scented" but therapeutically inert mixture in the other group. Thus, the effect of Dapsone, and the possible effect of cutaneous friction, were identical in the two groups of paired patients. The trial awaits statistical analysis, but the initial impression is that there is no substantial difference in clinical and bacteriological improvement between the two groups.

(*iv*) Since biochemical findings with tagged Etisul suggest that the product disappears rapidly from the tissues, it is possible that daily inunction would give definite and unequivocal results. A new series of patients, therefore, will apply a liquid formulation of Etisul daily for six days a week, for a period of ninety days; no other drug will be given during this period.

(*d*) *Sulphaphenazole*; 3-(*p-aminobenzenesulphonamido*)-2-*phenyl-pyrazole*; "*Orisul*" (*Ciba*).—A small pilot trial of this long-acting, non-toxic sulphonamide was completed. There were four patients with lepromatous leprosy (two of whom had proved resistant to treatment); six with the borderline form (four of whom were positive bacteriologically); and four with the tuberculoid form.

It was found that after six months treatment, Orisul had a slow but definite effect on the morphology of *M. leprae*, but none on the bacteriological index; there was some resorption of the bacteriologically negative infiltration of borderline and tuberculoid leprosy, and some repigmentation of tuberculoid lesions, but no change was observed in the degree of lepromatous infiltration.

There was thus no clear indication that a further trial of a larger group of patients should be undertaken.

(*e*) *Repository Sulphone;* 59*K* 401 (*Bristol Laboratories, Inc.*).—This trial was undertaken at the request of the World Health Organisation, which is very desirous of finding a sulphone preparation that can be injected at infrequent intervals, for use in countries where communications are poor and leprosy control still difficult.

The preparation tested is a suspension of Dapsone in ethyl chaulmoograte, gelled with an aluminium stearate.

During the trial, a method was elaborated for determining a concentration of sulphone in the serum of less than one part per million. (Bratton and Marshall technique).

Four tuberculoid cases, four lepromatous, and two borderline, participated in the trial. It was not found possible to maintain a therapeutically active sulphonaemia by injections less frequent than fortnightly. The optimum dose of the preparation was 6 ml.; the duration of satisfactory sulphonaemia could not be lengthened by increasing the dose to 9 ml. Thirty-one days after an injection of this size, the blood sulphone level was still of the order of 0.08 mgm. per cent. Two of the patients developed large abscesses which discharged the unaltered product.

(*f*) 1.4 *dimethyl-7-isopropyl-azulene; AZ-8* (*Beris Laboratories*).—In view of very satisfactory reports on the value of this substance in various inflammatory and allergic conditions (including one on leprosy), the World Health Organisation requested the Unit to investigate its value in Lepra reaction.

This azulene derivative has been credited with stimulating the phagocytic activity of the leucocytes, including the monocytes, and of the entire reticulo-endothelial system.

Twenty-three patients, who in the course of their treatment with diverse anti-leprosy drugs had developed lepra reactions of varying severity, were treated with the drug by the oral and intramuscular routes.

An unsustained initial improvement in some patients was followed by recurrence of symptoms, and even by exacerbations. The reactions were so severe that treatment had to be discontinued in five cases.

The claims made for this preparation in the treatment of Lepra reaction were not confirmed.

(*g*) *Nialamide; a mono-amine oxidase inhibitor; "Niamide"* (*Pfizer*).—In view of the glowing reports concerning this product in the treatment of chronic depressive and painful states, a pilot trial was undertaken in a group of patients having chronic nerve pain, or mental depression, or incipient drug-induced psychosis. No marked psychological or mental improvement was noted, and nerve pain was not controlled on standard doses.

It is concluded that this product will have no place in the treatment of the various clinical manifestations of depression in sufferers from long-standing leprosy.

(*h*) *A long-acting Prednisolone* (*Pfizer*).—The proved value of the corticosteroids in reactional states in leprosy suggested that a prednisolone that maintained a therapeutic efficacy when given by injection once weekly, might have definite advantages.

Interim results indicate that there is a class of patients, mainly with long-standing or recurrent reactive states of mild or moderate degree, of stable intensity, who are able to take anti-leprosy treatment in adequate doses under cover of this preparation.

(*i*) 8-*Methoxy-psoralen; "Oxsoralen"* (*Paul B. Elder*).—With a view to encouraging repigmentation of quiescent hypopigmented leprosy lesions and thus remove a distressing social stigma, work has continued with "Oxsoralen", a synthetic furocoumarin, in vitiligo of diverse and unknown etiology, and in leprosy. Results so far are uncertain, and not very encouraging.

(*j*) *Rimino-compound; a substituted Anilino-aposafranin B* 663 (*J. R. Geigy, S.A.*).—The remarkable *in vitro* and *in vivo* anti-tuberculous activity of certain of the Rimino-compounds suggested that they should be tried in leprosy. With the co-operation of the Medical Research Council of Ireland, a small pilot trial comprising six untreated lepromatous patients has been inaugurated. Three are receiving standard Dapsone treatment in addition.

Early results are distinctly encouraging, and a further trial will probably be undertaken in 1961.

(*k*) *Monobenzyl-ether of hydroquinone* (*Boots Chemists Limited*).—An ointment containing this compound has been specially prepared for the Unit by Messrs Boots. The active principle interrupts the complex mechanism responsible for melanin formation, and thus reduces the degree of cutaneous pigmentation.

It will be used, with adequate precautions in view of its sensitising properties, to induce a return to normal in the persistent disfiguring hypermelanotic macules, which may characterise the fixed drug eruption caused by Dapsone, etc.

B.—OTHER INVESTIGATIONS

Studies of fundamental importance and interest continue to occupy much time and attention in the Unit. Some of these studies will be briefly referred to:

1. *Immunology.*—In collaboration with Dr D. S. Ridley, Pathologist, at the (London) Hospital for Tropical Diseases, studies have continued on the histological changes resulting from the intradermal injection of extracts of normal human skin. An essential feature seems to be the early formation of eosinophilic micro-abscesses whose appearance is apparently determined by a fatty fraction liberated in the damaged tissues.

Further work is proceeding on the intradermal injection of inert particulate matter.

2. *Sarcoidosis.*—In view of the many intriguing similarities between certain of the cutaneous lesions of sarcoidosis and various leprosy lesions, a series of leprosy patients having sarcoid-like skin lesions were subjected to the Kveim test with material kindly supplied by Dr Robb Smith, of the Radcliffe Infirmary, Oxford. The results of the histological examination of the biopsies are awaited with interest.

3. *Toxic phenomena* due to various anti-leprosy drugs in common use have been investigated; especially hypermelanosis, parallergic dermatitis, and toxic epidermal necrolysis.

4. As opportunity occurs, investigation of dermatological conditions of interest to the leprologist for various reasons (especially differential diagnosis), is undertaken. Continuing interest is shown in various tropical pigmentary conditions (hyper- and hypopigmentation) in view of their possible bearing on the hitherto imperfectly explained depigmentary phenomena in leprosy.

5. The practical problems of *desensitisation of patients* who are unable to continue treatment with standard anti-leprosy drugs because of severe or recurrent dermatitis, have been given attention.

LABORATORY ASPECTS

The laboratory is an essential part of the work of the Unit, and its maintenance at a high level of efficiency is a primary concern. More good work could be done, and more varied investigations attempted, if staff and equipment could be augmented.

Within the limits imposed, however, the laboratory undertakes the routine procedures necessary for the cover of drug trials, immunology and diagnosis.

(*a*) Skin biopsy, the preparation of sections, clinical photography, tuberculin and lepromin reactions; these are undertaken for research patients, and as necessary for other patients on admission;

(*b*) Laboratory cover for drug trials proceeds according to a standardised schedule involving blood, urine and liver function;

(*c*) Bacteriological examination of multiple smears is carried out routinely on all patients in the Settlement, and on all patients presenting themselves at the diagnostic clinic. All patients under treatment with new drugs are smeared at regular intervals, and the detailed morphology of the *M. leprae* is recorded for each site examined. This information is of great value in indicating degenerative changes presumably due to therapy, even when the actual bacteriological index may show little change.

STATISTICS

There is still a need and scope for further laboratory investigations, particularly in the biochemical and histological fields, but this must await the appointment of suitable qualified staff.

	1959	1960
Patients smeared for M. leprae...	3,142	3,042
Lepromin tests	253	187
Tuberculin tests	157	142
Haematological examinations	3,143	2,197
Urine examinations	4,538	3,731
Faeces examinations	939	763
Sputum examinations	231	107
Biochemical examinations	479	719
Histological examination/Blocks	159	114
Slides	391	336
Kahn test	214	224
Miscellaneous examinations	86	128
Radiographic examinations	153	147
Kveim tests	—	11

TRAINING

The benefits accruing from the short courses of training given in the past for laboratory workers from other Leprosy Settlements in the Eastern Region where drug trials are in progress, and elsewhere, have been apparent during the past year. More trainees have followed these courses during 1960.

The existence of these facilities should be more widely known.

EQUIPMENT

Several valuable items of equipment have been added during the year.

1. A Cambridge Skin temperature reading apparatus.
2. A Selenium Cell Reflectrance Spectrophotometer.
3. A Wood's lamp.

A fluorescent microscope is on order.

PERSONAL

Congratulations are due to Mr B. M. T. Onyenekwe, who passed the Intermediate examination for the Associateship of the Institute of Medical Laboratory Technology during the year.

Mr O. U. Osoagbaka took over the superintendency of the Laboratory on 26th January. His admission to the Fellowship of the I.M.L.T. was confirmed in July.

Mr J. O. Okwuosa was promoted to the grade of Assistant Medical Laboratory Technologist during the year.

Deep appreciation must be expressed for the continued co-operation of Dr Hogerzeil at the Settlement. His assumption of the oversight of the Settlement relieves the Specialist of the bulk of the administrative burden, and his sharing in the clinical work is a valuable contribution to the activities of the Unit.

Mention must also be made of the very valuable co-operation of the Welfare Department, which is organised and maintained by the Methodist Missionary Society.

ACKNOWLEDGEMENTS

It is with real pleasure and a sense of gratitude that we acknowledge the interest of the Federal Government in the work of the Unit.

Grateful thanks are expressed to the British Leprosy Relief Association and to an anonymous friend for funds for the provision of special apparatus, and to the World Health Organisation for the provision of cameras for skin photography and laboratory equipment.

The fruitful and pleasant co-operation of the medical and scientific departments of certain ethical drug houses is acknowledged, in particular: Messrs Imperial Chemical Industries (Pharmaceuticals) Ltd.; Ciba; Bristol Laboratories; Pfizer; Beris Laboratories; J. R. Geigy, S.A.; Boots (Chemists) Ltd.; Paul B. Elder Company.

Tribute is gratefully borne to the junior laboratory staff, to the co-operative patients, and to the medical, nursing and administrative staff of the Settlement. The work of the Unit would be seriously jeopardised, if the standards of any of these integral parts of the activities of the Settlement were allowed to fall.

With the continued co-operation and goodwill of all concerned, the Unit strives to maintain the prestige and usefulness it has achieved under its previous Directors.

VISITORS

In addition to many distinguished non-medical visitors welcomed to the Settlement during the year, the following Medical Visitors have visited the Unit for a longer or shorter period:

Dr W. Bowman	Sierra Leone.
Dr E. R. Stockdale	Cameroons.
Dr E. Petitpierre	Cameroons.
Dr K. Duankaow	Thailand.
Dr V. Reynierse	Itu.
Dr H. Reynierse	Itu.
Dr W. H. Mercer	Belgian Congo.
Dr K. I. Schaller	Ethiopia.
Dr R. V. Coggins	Shell, Owerri.
Prof. P. J. Zuidema	Holland.
Prof. S. Graham	Scotland.
Dr A. Fabiyi	Yaba.
Dr Q. A. K. Usufzai	Pakistan.
Dr E. Odé	Cameroons.
Dr A. Pinto	Portugal.
Dr F. A. Vorst	Northern Region.
Dr D. Leiker	Holland.

PUBLICATIONS

1. Browne, S. G. ... ... Onchocerciasis and Leprosy. Leprosy Rev., 1960, **51**, 9.
2. Browne, S. G. ... ... Hyperpigmented macules occurring during sulphone therapy. Leprosy Rev., 1960, **31**, 54.
3. Browne, S. G. ... ... Onchocercal depigmentation. Trans. roy. Soc. trop. Med. Hyg., 1960, **54**, 325.
4. Browne, S. G. ... ... Bluish coloration in lepromatous lesions during treatment with amodiaquin. Internat. J. Leprosy—in the press.
5. Browne, S. G. ... ... Cantharidin poisoning due to a "blister beetle". Brit. Med. J., 1960, 1290.
6. Browne, S. G. and Ridge, E. Toxic epidermal necrolysis. Brit. Med. J.—in the Press.

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