LEPROSY REVIEW

The Quarterly Publication of THE BRITISH LEPROSY RELIEF ASSOCIATION

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JANUARY 1958

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Edited by DR. J. ROSS INNES, Medical Secretary of the British Leprosy Relief Association, 8 Portman Street, London W.1, to whom all communications should be sent. The Association does not accept responsibility for views expressed by writers.

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EDITORIAL

In the course of the last three months of 1957, the Editor had the great privilege of a visit on behalf of the British Leprosy Relief Association to two countries where active and successful leprosy relief programmes are in progress. These were West Africa and India. Some account of these tours will be given here, with the liberty of returning to the subject more fully in later issues of "Leprosy Review," particularly in the case of the West African tour, which was by far the larger one.

Visit to West Africa

The visit to West Africa comprised 44 days of a schedule as comprehensive as possible kindly worked out by the Governments concerned. It began with 12 days in Northern Nigeria and went on to Eastern Nigeria, the Cameroons, Western Nigeria, and Sierra Leone. It was not possible to include Ghana on this occasion, but it is hoped to make a separate visit to Ghana in 1958.

In Northern Nigeria Dr. C. M. Ross, the Senior Leprologist, very generously gave his personal guidance and fellowship throughout the tour. We began at Kano and visited the Kano Leprosarium of 500 patients, a fine institution of the S.I.M. under Dr. Dreisbach. Each day we travelled many miles by road and visited leprosy work in institutions or district clinics. These included Bindawa: Azare Clinic where there was also residential accommodation for inpatients; clinics at Damagum, Damatura, and Benisheikh; the Bornu Provincial Leprosarium near Maiduguri with 361 inpatients and 1,000 outpatients under Dr. R. Marshall; Potiskum Clinic; Darazo Leprosy Dispensary; the new Zalamga Leprosarium of the S.I.M. with 120 inpatients and 60 outpatients; the Plateau Provincial Leprosarium at Mongo under Dr. F. C. Priestman. Dr. D. Hilton, the leprologist stationed at Jos, took us to visit Gyel Dispensary, a general dispensary which has 210 leprosy cases. From Kaduna, Dr. Ross was able to show Zaria, Provincial Leprosarium under the C.M.S., with Dr. Mess and two BELRA workers, Miss Hardaker and Mr. J. Boyd, with 151 inpatients and 6,000 outpatients; also the leprosarium of the Albarka Fellowship, with Miss J. A. Whittle at present in charge and 135 inpatients and 1,500 outpatients; also the very interesting experience of visiting a class of 60 African trainees in leprosy who were receiving instruction from Dr. Ross. They were a thoughtful and intelligent body of men who left a very favourable impression on the visitor. Dr. G. K. M. Khomo, Superintendent of the Training School for Medical Assistants, also showed its buildings and hostel and facilities: this was an additional cheering experience.

Dr. C. M. Ross will be speaking for himself in this issue of

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" Leprosy Review " in his article on Leprosy Control in Northern Nigeria. The Editor is glad to be able to add his personal testimony as a result of his visit. A large cross-section of the institution and district work was seen, giving the very clear impression of a sensible scheme of leprosy control suited to the country and amazingly successful in the short period of its operation to date. Dr. Ross and his helpers have succeeded in providing leprosy therapy to many thousands of patients, using a system of leprosy clinics and segregation camps staffed by African workers and integrating existing leprosaria into the general scheme. The Editor examined a considerable number of leprosy outpatients under treatment, and was able to be sure that they are getting their treatment regularly and obtaining the expected improvement in their disease. The faithful and competent work of African leprosy inspectors and dispensers was everywhere to be seen: they must have been wisely chosen and carefully trained. The whole scheme rests upon this, and all credit is due to the Government and people and the trainees themselves, in that they responded to the call of Dr. Ross. The peope of Northern Nigeria, if they go on like this, have a sporting chance of eradicating leprosy in a generation.

In Eastern Nigeria 19 days were spent altogether, beginning with kind hospitality from H.E. Sir Robert and Lady Stapledon, and it was possible to see a large part of the outstanding leprosy campaign there, which has attained a degree of success probably unique. The first centre visited was Oji River Area Headquarters with Dr. A. S. Garrett. There is a leprosarium there with all departments, a Training School, and a Social Welfare and Rehabilitation section. The decline in the number of inpatients at Oji River from a former 1,600 to a present 600, and outpatients from a former 14,000 to a present 7,800, is one of extreme interest and can only mean essentially that the leprosy prevalence has been reduced. Dr. A. Zahra, acting Leprosy Adviser, gave information on the proposed scheme in collaboration with WHO and UNICEF to spread a network of health centres throughout the region. These health centres would make a place for leprosy control. Many of the ordinary leprosy clinics were visited, and all in the stage of a reduced volume of work due to successful impact on the leprosy prevalence. As in North Nigeria, the work has been faithful and effective, and the role of the African staff a great one. Some of the new health centres were visited with Mr. Frank Hathaway who is building them. The prospects for the usefulness of these are very great.

The next Centre visited for a stay of some days was Uzuakoli Research Centre and Leprosarium and Headquarters, where Dr.

Frank Davey and his staff showed a most stimulating piece of work. Among other things, the leprosy cases on the drug trial with DPT or SU 1906, and other drugs, were shown by Dr. Davey, who in this issue of "Leprosy Review" publishes his report on 3 years' experience with DPT. It is unusual for an Editor to have seen the cases on which a report is made, so it is worth while recording this fact, and that no point of disagreement occurs with Dr. Davey's assessment of the action of DPT. This new drug probably represents a genuine step forward in leprosy therapy, though much remains to be done. All departments of the work of the beautiful leprosarium were seen, and new buildings provided by BELRA for the children were formally opened (the "BELRA Wallich Feeding Centre "). It was noted that preventive and curative physiotherapy is going strong here, and the services of an orthopaedic surgeon are shortly to become available. The Research Centre was originally a BELRA foundation, and Dr. John Lowe worked here: now the work is in the able hands of Dr. Davey and Mr. S. Drewett. In discussion with Dr. Davey and the staff it was revealed that in that Province (Owerri) since 1937 there have been 16,000 discharges, and surveys have shown that there were 32,000 leprosy cases in 1948, and these were reduced to 15,000 in 1957. This is a remarkable result. Apart from the wisdom and energy and faithfulness of the whole body of leprosy workers, and the support of the U.K. Government and Nigerian Governments, and the help of all Missions and the Mission to Lepers and BELRA and WHO and UNICEF (what a magnificent co-operative effort by many bodies!), we discovered one other very important factor in success. This was the degree of understanding and co-operation which was brought to the leprosy campaign by the people themselves. One does not get great success in a leprosy campaign unless the people co-operate, and in this area undoubtedly they have co-operated.

The younger but active and growing leprosy campaign in Southern Ogoja was the next to be visited, where Dr. A. Macdonald is in charge. The leprosarium at Uburu under the Church of Scotland Mission deals with 300 inpatients and the 16 district clinics cover 2,500 outpatients. Uburu has simple and attractive buildings and the work progresses steadily. With Dr. Macdonald and Mr. Lowes of BELRA we visited Ukawu Clinic, and Yakurr and Mbembe leprosaria. Ukawu has 300 outpatients and 100 resident patients; the leprosaria are about the 500 inpatient size. In all cases it was possible to detect good and faithful work, and growing co-operation by the people.

The famous Church of Scotland leprosarium at Itu was next to be visited under the guidance of Rev. R. M. Macdonald and his

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tine staff, which at the time of this visit included five BELRA workers. The Editor visited this leprosarium in 1947, when the inpatients were 4,000. The present number is 1,300, and the reduction must be ascribed to the waning of leprosy prevalence. The well-organized industrial stability of Itu still persists and has been the basis for the great volume of effective work in the past which continues to this day. Itu was founded in 1928 and many thousands of patients have passed through and returned to normal life. The present discharge rate per annum is about 300 patients; it is a glorious history.

Isoba Leprosarium in Rivers Province was next visited. Dr. M. Corcos is the Superintendent in this area, and Mr. O. S. Wilson the Leprosy Control Officer, and there are two nursing Sisters, Miss Alderman and Miss Boynes. This extremely beautiful and well-planned leprosarium on the banks of the New Calabar River contains 230 patients, and there are 40 district clinics. The whole is a fine piece of work intelligently pursued.

Returning later to Enugu the Editor had valuable interviews with the Hon. E. P. Okoya, Minister of Health, and Dr. S. E. Onwu, Director of Medical Services, and others, was able to express his high opinion of leprosy control in Eastern Nigeria, and to suggest that in the final stage of eradication now ahead the use of BCG might be helpful.

In the Cameroons leprosy work consists of two Mission leprosaria, one at Manyemen and the other at Mbingo, and a growing district work in outpatient clinics. Only partial surveys have been done as yet and the leprosy incidence varies between 7 and 35 per thousand. The work is still young, but the principles of leprosy relief and control as practised in Nigeria are thoroughly understood here and it awaits only an increase of staff and funds and perhaps also better road communications for a broader and deeper leprosy campaign to flourish. We were grateful for the informative and helpful contacts in Victoria with the Principal Medical Officer, Dr. B. L. Green, and also Dr. A. L. McKnight, and were able to travel up-country to stay at the Basel Mission Leprosarium at Manyemen. This is in charge of Dr. Voute, assisted by Dr. Petitpierre, and two nursing sisters, and a manager. The Basel Mission has requested BELRA to provide a replacement for the manager, who had retired, and recently Mr. R. Dunford has been chosen and has accepted the task. Manyemen was founded in 1954; it already has 514 inpatients and 200 outpatients in 6 district clinics. It lies in mountainous terrain, and there are real difficulties over district communications. The buildings are unpretentious but adequate and attractive. The work

has been founded and is being run on sound lines and has progressed a long way in the short period of its existence.

In Western Nigeria we visited the headquarters of the leprosy campaign at Ossiomo Leprosarium, where Dr. Basil Nicholson lives, who is the Senior Leprosy Officer of the Western Region. Dr. S. J. Healy is in charge of the leprosarium itself, and there are Dr. B. Lasisz, Miss Gilon, Miss Paradijs, Miss Vandermensbrugghe, Father O'Regan (the Leprosy Control Officer) and many African staff. The leprosarium contains about 600 inpatients and there is a chain of outpatient clinics and segregation villages. There are 28 leprosy inspectors and at the moment there is a training course in progress which will add 12 more. The leprosarium buildings and facilities are of high standard. Dr. Nicholson was a mine of information on the leprosy problem and the progress of the campaign. Surveys have been completed, but others are needed before a general incidence figure becomes available; it might be 30 per thousand or more. There are two features of the problem peculiar to this region. One is the existence of large native towns. Thus Ibadan has 750,000 people, and there are 6 towns with over 100,000 and 135 towns with over 5,000. A leprosy survey in towns is well-nigh impossible, and there is no real guarantee that the urban leprosy rate will be less than the rural rate. The other difficult feature is the existence of an exaggerated fear of leprosy among certain tribes, which reacts adversely on their co-operation.

We concluded the Nigerian tour by an evening and night in Lagos, not too short a time to receive great kindness from H.E. the Governor-General and Lady Robertson, from Sir Samuel Manuwa, and Dr. Norman Williams. It was also a great pleasure to hear of the resurgence and the flourishing activities of the Lagos BELRA.

In Sierra Leone we spent 4 days on a preliminary visit. Sierra Leone is about to open a modern leprosy campaign. BELRA has lately transferred to their service an experienced worker, Mr. Alan Waudby, and Dr. C. M. Ross of N. Nigeria was expected to arrive on loan in December to begin the necessary surveys and advise on how things should proceed. Dr. T. P. Eddy, the Director of Medical Services, kindly welcomed our visit and arranged many valuable meetings and a stay up-country at Magburaka, where we had the pleasure of meeting Dr. N. G. D. Campbell and Mr. Alan Waudby *in situ*, and seeing something of the country and of existing leprosy work. The Chief Secretary of Sierra Leone, Mr. A. N. A. Waddell, is our old comrade from Solomon Islands days, when he was a tower of strength during our leprosy survey there in 1937. It was very useful to see Sierra

Leone before the main campaign begins; a subsequent visit will be all the more valuable for assessing progress.

Reflections on the West African Leprosy Work

1. The coming of the sulphones offered a great opportunity which has been firmly grasped in West Africa, first in Eastern and Western Nigeria and latterly in Northern Nigeria and contiguous countries to Nigeria. Once it was established that a moderate twice-weekly oral dose of DDS was effective, the way was open to a great extension of the leprosy campaign.

2. Leprosy in West Africa is clinically moderate; the lepromatous rate is between 10 and 20%, and as a whole the disease responds to DDS in not too long a time, and with very few relapses.

3. The stage of opening-up of the campaign was wisely planned, and had the advantage of Lowe and Davey and collaborators working in a Research Centre in Uzuakoli right in the heart of the area, and the fine work at Oji River is also central. The essence of the campaign was henceforth to use oral DDS to treat patients in segregation villages and dispensaries, as well as the leprosaria, and to train a sufficient number of African staff to administer the therapy, keep the records, promote the rules of hygiene and prophylaxis, all under periodic supervision by medical officers. Surveys have been frequent, and close check has been kept on the progress of the campaign.

4. The enlightened co-operation and financial support of many bodies was secured, from Government and WHO and UNICEF to the individual Missions, Mission to Lepers, and BELRA. The success achieved is a credit to all concerned. It does look as if in leprosy work in a given country the policy of "go it alone" is futile, and the co-operation of all interested bodies is indispensable.

5. There is one body whose co-operation is likewise indispensable. That is the people themselves. If it is not forthcoming, time and money and patience must be expended in explanation and persuasion, and the demonstration in sample clinics of the benefit of leprosy relief, i.e., the Propaganda-Treatment-Survey units long advised by Ernest Muir. In Nigeria they were fortunate in obtaining that co-operation and understanding.

6. Another great lesson to be learned from Nigeria is in the matter of personnel. They have shown that a leprosy campaign faced with a lack of national doctors to participate, but possessing a cadre of experienced leprologists, can fill the gap by training educated nationals in leprosy recognition and treatment and leprosy lore generally, and getting them to care for groups of patients under rural conditions. In Nigeria they call these trained laymen " leprosy inspectors." Their work has stood the test. Many

thousands of leprosy sufferers have been relieved of their disease beyond a shadow of relapse. The leprologists, in effect, in addition to being physicians and researchers, and planners and inspirers, become **teachers**. They have been fortunate in finding so many African nationals willing to be taught, and competent in carrying out what they have been taught.

7. Such a big bite has been made into the leprosy prevalence that one dares to think of the last mouthful. Nigeria in particular can begin to think of eradication. The stage preceding eradication is the hardest. Nigeria can be trusted to take another breath and continue to the end, using all hopeful means to augment the the campaign in this difficult last stage. A good sign of this is the development of the idea of Rural Health Centres which will include leprosy in their activities.

Visit to India

The Indian Association of Leprologists invited the Editor, in his capacity as Medical Secretary of the British Leprosy Relief Association, to attend their Third Biennial Meeting, which was to be held in Gorakhpur and followed by the All India Leprosy Workers' Conference. With the goodwill of BELRA, he was able to go to India, and in a short visit of 10 days had a most absorbing and valuable contact with the leprologists and leprosy workers of India, was able to see in Gorakhpur a most attractive and successful piece of leprosy work in progress, and to get an impression of the enormous advances that have been made in leprosy work in India. The Editor had not seen India for 11 years, and can testify to the widening and deepening of the dynamic attack on leprosy that has taken place. There are about 11 million leprosy cases in India, and nowadays this formidable problem is being attacked by a growing regiment of leprologists and leprosy workers, a great deal of thought is being given to the complexities of the problem peculiar to India, and there has been an "opening-up" of the campaign to bring treatment to outpatients as well as to improve the leprosaria and create new ones. Under the stimulus of the wish of their former great leader, Mahatma Gandhi, who had a special care for leprosy sufferers and begged his people to share it, there has been a great growth of an enlightened and humane attitude amongst the peope, fostered and shared by the Government of India and the State Governments.

The Editor arrived in Delhi on 9th December to receive a great welcome from Col. Lakshman and Sardar Balwant Singh Puri of the Hind Kusht Nivaran Sangh (one of the great organizations in India which foster leprosy work), and this welcome was repeated of arrival in Gorakhpur from Dr. K. R. Chatterjee, EDITORIAL

the Honorary Secretary of the Association of Leprologists, Dr. Dharmendra, Director of the Research Institute at Chingleput, and a host of others. Prof. Kanehiko Kitamura of the University of Tokyo also caused great pleasure by his arrival from Japan to attend the Conference. We two were cared for throughout our stay in Gorakhpur by the hospitable Mr. and Mrs. Bhisham Arora, and received endless kindnesses from all.

The Third Biennial Meeting of Leprologists was inaugurated on 13th December by **Sri Hukum Singh Visen**, Minister of Health for Uttar Pradesh. He mentioned the incidence of leprosy in Uttar Pradesh as 80,000 cases, or 1.4 per thousand population, and described the institutional facilities as 17 leprosaria, and the expansion of the work to outpatient clinics. The new control units are of two types, one for study and research, one for survey and treatment. Mobile units are also being tried, and the training of social workers goes on steadily. The training of medical students and graduates is also of highest importance.

Dr. Dharmendra gave the first paper, on The Role of Chemotherapy in the Control of Leprosy, and this subject was also taken up by **Dr. N. Mukerjee.** Both speakers, while recognizing the potential role of therapy, wisely emphasized that some degree of segregation is still needed. Dr. Dharmendra pointed out that the protective value of the sulphones for contacts is still not proved. Dr. Mukerjee insisted on the regular follow-up of healthy contacts as a very important part of control programmes, and on the paramount importance of early diagnosis, as well as the willing and intelligent co-operation of the patients and public, for which a suitable educational campaign is essential.

Dr. K. R. Chatterjee described his studies in the Electron Microscopy and Cytochemistry of M. Leprae and Leprous Tissue. By the comparative use of phase contrast and electron microscopy he found either solid uniformly dense bacilli, or bacilli with alternate light or dark zones: there is a thin enveloping membrane. and a gloea. The electron microscope shows that the bacilli occur in nerve endings in the skin, in tactile corpuscles, in the myelin sheath, in Schwann cells, and in the axons; also attached to nerve fibrils and inside macrophages and foamy cells of leprous tissue. Cytochemical study showed that the nucleus, generally central in location, contained desoxyribonucleic acid, and the cytoplasm contains ribonucleic acid, muco-polysaccharides, and lipids. The polar condensations contain cytochrome oxidase and appear to be the mitochondria. The cell membrane is rich in mucopolysaccharides; the gloea seems to contain complex lipids.

Dr. A. T. Roy gave a paper on General Treatment. Though the usual dose of DDS is 600 mgm. a week, even 300 mgm. a week

has been found to be effective, and he found that 1.0 gm. of sulphetrone daily, and as little as 3 to 4 cc. of 50% aqueous solution of sulphetrone intramuscularly once a week produced clinical results. Thiosemicarbazone is especially good in cases who cannot tolerate DDS. **Dr. D. N. Bose** gave a paper on the same subject. He still finds it an advantage to combine with sulphones the injection of hydnocarpus oil and its derivatives. In lepra reaction he warned against the use of antimony in patients with a history of pleurisy or tuberculosis. Irgapyrin and unalgen are useful and intramuscular streptomycin for tuberculoid reaction, and corticosteroid therapy is valuable in refractory reacting conditions.

Dr. P. Fritschi described in detail Recent Advances in Reconstructive Surgery in Leprosy. He emphasized the prevention of deformities by splinting and bed rest and physiotherapy and described many reconstructive and plastic operations. There has been a great advance in this field.

Major E. J. Somerset gave a paper on Eye Lesions in Leprosy, describing the commoner ocular manifestations and their management, and showed how much can be done to prevent and alleviate eye damage in leprosy.

Dr. F. Hemerijkx described the work of the Belgian Leprosy Centre, Polambakkam. Here the emphasis has been on mass treatment in clinics and hospital, with some segregation where practicable. During the $2\frac{1}{2}$ years of the existence of the Centre, almost 20,000 patients have been treated, and surveys of contacts and local regional leprosy surveys are being undertaken. The staff of the Centre includes 38 leprosy workers, of whom 24 are posted in the villages, and there are 2 doctors and 2 nurses.

Dr. H. Sharma Rao described the Leprosy Relief and Control Scheme in Thirumangalam under the Madras State Government. This scheme covers a rural area with 40 treatment centres which already treat over 4,000 patients, and treatment is often taken to the homes of the patients. Medical officers of general dispensaries provide medical supervision and lay workers are trained. The scheme is capable of expansion as time goes on.

The Sixth All-India Leprosy Workers' Conference began on 15th December, with Sardar Balwant Singh Puri as President. The inaugural address was given by **Dr. Sampurnanand**, the Chief Minister of Uttar Pradesh, who spoke with deep understanding of the problems of leprosy. **Sardar Balwant Singh Puri** spoke of his long association with leprosy work, as he has been the Honorary Secretary of the Indian Council of BELRA since its inception in 1925. In 1950 the Indian BELRA became Hind Kusht Nivaran Sangh, and of this he continues as Honorary Secretary. He pointed

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out that India established the first full-time leprosy research centre. This was at Calcutta over 30 years ago, and this has been associated with the names of Sir Leonard Rogers, Dr. Ernest Muir, Dr. John Lowe, Dr. Dharmendra, Dr. S. N. Chatterjee, Dr. N. Mukerjee, and Dr. K. R. Chatterjee. Dr. Dharmendra has now become Director of the new Central Leprosy Teaching and Research Institute at Chingleput. The work of Dr. R. G. Cochrane was formerly associated with Chingleput and India acknowledges her debt to him. The Sardar went on to describe the expansion of leprosy work in India in his time, citing many other illustrious names. The need for personnel and funds still remains great.

Dr. N. Mukerjee described the Leprosy Control Scheme which is a joint responsibility of the Union and State Governments, and the object is to give a trial to mass treatment with sulphone in the control of leprosy. Already 4 Study and Treatment Centres and 52 Subsidiary Centres have been established, and a further 73 are planned for the second five years, during which also 500 doctors and 2,000 ancillary personnel are to be trained and the sum of Rupees 27,150,000 (£2,036,250) is to be expended. In the 2 years' work so far, in a total population in the project areas of 3 millions, 57% have been examined and 25,000 cases of leprosy detected (an incidence of 15 per thousand). Of known cases the lepromatous rate is 34%. There are 81,000 contacts under observation.

Dr. R. V. Wardekar spoke on the Leprosy Control Work of the Gandhi Smarak Nidhi (Gandhi Memorial Foundation). The work covers 9 control units, by which a population of 192,835 is under observation for the detection of leprosy, treatment, and prevention. Training of doctors and health workers goes on. Because of the difficulty in getting enough doctors, Dr. Wardekar suggested that doctors from the general medical service should be detailed to leprosy work in rotation.

Dr. P. Chandy described the Development of Leprosy Work in Gorakhpur. The Kushta Sevasram at Gorakhpur is a leprosy institution started and maintained by Indian men and funds, and besides being a most attractive and efficient hospital, it has village clinics and a mobile unit and looks outward, and the co-operation of many doctors and social workers is abundant and faithful. It was established in 1951 and has treated 708 inpatients to date. There are 4 outpatient clinics, and a rehabilitation centre. (Members of the Conference later visited the Kushta Sevasram and can testify to the fine spirit and high standard of this work.)

Sri T. N. Jagadishan spoke on the Social Aspects including Rehabilitation. There is some softening of the old prejudice against leprosy, but there is still much prejudice to be overcome, and social assistance for the relatives of the leprosy patient has hardly begun. Rehabilitation measures are growing but need organizing, for those who have recovered without deformities as well as those who are marked. Education of patients to prevent deformities is also needed everywhere. No patient should be discharged without regard to his physical and psychical condition.

Sri M. B. Diwan also spoke on the Social Aspects of Leprosy. He mentioned the small numbers of workers in this field, and asked for enlistment of the interest of every responsible citizen. Vigorous propaganda to remove social stigma, provide family assistance, assist in rehabilitation into society, should be carried on.

Dr. H. K. Lall dealt with Certain Important Questions, about the admission and discharge of patients and medical leave granted to employees who have leprosy. He advised special measures to help in the rehabilitation of discharged cases, including reservation of posts for them, and the provision of land. Two consecutive negative smears at an interval of 3 months should qualify a patient for discharge. Leave for an employee with lepromatous leprosy should be 2 years.

Miss Chandra Manuel discussed Rehabilitation, and called for many Rehabilitation Units with a specialist, physiotherapist, and social workers. Patients with gross deformity should be trained for and provided with "sheltered industry." Those with little or no deformity should also be helped to find employment. Those with medium deformity should be given the aid of reconstructive and plastic surgery.

Dr. Jawhar Lall Rohatgi described Leprosy Legislation for India. It has the defect of applying segregation to all cases, whereas many cases of leprosy do not need this, and also the defect of compulsion of segregation for pauper leprosy patients, whereas segregation, if needed, should be for all social classes. He thought there should be a ban on marriage for infectious cases, because of the great danger to children.

Dr. S. N. Chatterjee dealt with Customs, Laws, and Rules which affect leprosy. Disinheritance in Hindu Law can be imposed for leprosy on the grounds of its being a virulent and incurable disease: this has been amended in 1956 by the Hindu Succession Act: but the Hindu Marriage Act 1955 allows judicial separation for disease virulence, and divorce on the grounds of virulence and incurability of leprosy, and the foundation of this law is wrong, because healthy partners have a natural protection. The Railway Act (1890) also discriminates against leprosy, and under the Motor Vehicle Act (1939) leprosy is the only disease which debars a person from a licence to drive a public vehicle. Nor can a leprosy patient be accepted for life insurance. Also in Military

and other services a leprosy subject is liable to dismissal. A new law should be enacted to guide the public and correct all these unjust anomalies, and this will lead to the reversal of public opinion and make leprosy control easier and rehabilitation of patients the normal thing.

Along with Prof. Kitamura the Editor had the great honour of being made an Honorary Member of the Indian Association of Leprologists. We consider it a very real distinction to be able to count ourselves as integral parts of this Association.

VII International Congress of Leprology, New Dehli, India

Dr. Dharmendra, Secretary of the Organizing Committee, asks that all note his change of address from Calcutta to **Central Leprosy Institute, Chingleput, South India,** of which the cable address is CENTLEPINS. Dr. Dharmendra also provides the following advance information:—

Because of requests from a large number of intending delegates, the **dates of the Congress have been changed to November 10th to 16th, 1958;** registration of delegates will take place on 8th and 9th November. A preliminary information brochure will be sent to all persons and organizations likely to be interested in participation in the Congress. The enrolment form included in the brochure may please be completed and returned at an early date, upon which further literature will be sent to those who enrol.

In New Dehli the conference hall set aside for all functions of the Congress is Vigyan Bhavan, Edward Road. It has facilities for simultaneous interpretation of languages used.

Membership fees. There will be two grades of membership full and associate. A full member will be entitled to take part in all the functions of the Congress, both scientific and social; an associate member in social functions only. The full membership fee will be Rs. 50/- for those who are members of the International Leprosy Association and Rs. 100/- for those who are not. The associate membership fee will be Rs. 25/-. There will be an increase of 20% over these rates for those who enrol after 31st July, 1958. (The rupee is worth 0.21 of the U.S. dollar, and 1/0 sterling.)

Official Languages will be English, French, and Spanish, and there will be arrangements for simultaneous translation.

Themes for discussion include Classification, Therapy, Epidemiology, Immunology, Bacteriology and Pathology, and Social Aspects. The theme of Evaluation of BCG in Prophylaxis will be dealt with by a separate panel (see below), but the findings will be included under Epidemiology and Immunology.

In preparation for the scientific sessions the Council of the

International Leprosy Association has set up panels for the above themes. Each panel will discuss its theme beforehand by correspondence and will arrange for the presentation of the theme to the Congress. This new procedure arises from experience of the previous Congresses and is expected to be beneficial.

Categories of papers on the above themes will be two— "invited" and "proffered," (i.e. spontaneously submitted). The "invited" papers will be those presented in symposia by members of the respective panels; "proffered" papers may be submitted by any member of the Congress. The "proffered" papers will be assessed and arrangements will be made for presentation of those that are accepted.

Submission of Abstracts and Papers. Abstracts of not more than 200 words should be sent (2 copies) to the Secretary of the International Leprosy Association, 8 Portman Street, London, W.I, England, so as to be received not later than 1st August, 1958. Abstracts and papers should be in one of the official languages. It would be helpful if abstracts in languages other than English are accompanied by an English translation. The papers themselves should be addressed to the International Leprosy Association, c/o Dr. Dharmendra, Central Leprosy Institute, Chingleput, South India, so as to be received before the end of September, 1958.

Travel. New Dehli is served by many airlines linking it with all countries, and many international shipping lines touch Bombay and Calcutta. Delegates travelling to New Delhi must hold valid passports and entrance visas for India. Nationals of Australia, Canada, New Zealand, the Republic of Ireland and United Kingdom of Great Britain and Northern Ireland do not require entrance visas.

Hotel Charges. The charges for board and lodging in hotels in New Dehli are as below:—

		Sing	le R	001	n	Dou	ble	Roc	m
Grade	Α	 Rs.	40	to	70	Rs.	60	to	85
Grade	В	 Rs.	30	to	40	Rs.	50	to	80
Grade	С	 Rs.	12	to	2 0	Rs.	2 0	to	25

Rates in Indian hotels include full board and lodging, and normally no reduction is made for meals not taken. The Organizing Committee will arrange for hotel reservations if duly notified.

Climate and Clothing. The weather in Dehli during November is generally fine; the average maximum daily temperature is 30.6 deg. C. (89 deg. F.) and the minimum 13.9 deg. C. (57 deg. F.). Visitors should bring woollen clothes.

Social Functions. Social and cultural programmes will be arranged in a way that they do not interfere with the scientific and business sessions of the Congress. It is proposed to arrange for sightseeing and study tours after the Congress.

LEPROSY CONTROL IN THE NORTHERN REGION OF NIGERIA Dr. C. M. Ross

Senior Leprosy Specialist, N. Nigería.

Since January, 1952, the following factors have been investigated in this region:—

- 1. Data concerning the incidence and public opinion of leprosy, and the reaction of the general population to treatment.
- 2. A scheme within the resources of the country whereby sulphone treatment could be made available to all leprosy cases.
- 3. The development of a leprosy control service which would be of a permanent nature and be a part of the general medical and health services of the country.

Considerable interest has been aroused generally in the successful leprosy control methods of the Eastern Region of Nigeria, which are described by Davey *et al*, 1956, and Garret, 1956. During the first part of this period reviewed from 1940 to 1950, little was known generally in the Northern Region concerning the incidence of leprosy and what would be the response to a leprosy control scheme; the success, however, achieved in the Eastern Region stimulated a desire for organized leprosy work in the North and work was commenced in 1952.

There were many problems to consider, and of these the main ones could be grouped under three heads:—

- 1. The size of the territory and the scatter of the population.
- 2. The climatic and social conditions associated with a large territory, a diversity of people and variety of country.
- 3. The financial resources of the region.

Nigeria has within its boundaries approximately one-sixth of the total African population of the Continent, the Northern Region is three-quarters of its total size and it contains more than half the population: the most sparsely populated areas of Nigeria are found in the North. The 1952 Census revealed a population of almost 17 millions and it is estimated that the figure now stands at more than 18,000,000. The overall density of the population is 60 per square mile and again this density varies exceedingly: the most densely populated provinces of Kano and Katsina show a density of 304 and 157 per square mile as compared with Niger Province which has a density of 25. Great variation in climatic and social conditions can be expected in a region which has rain forest for its southern boundary and the sands and vegetation of the Southern Sahara as its northern boundary. In northern districts, with a rainfall of less than 20 inches, a leprosy control scheme based on

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specialised leprosy clinics and segregation villages is unpractical. The long dry season, scarcity of water, the type of staple foods and the possibility of a poor harvest makes living apart from an organised community difficult. The staple crop of this district is sorghum which requires the participation of male and female to farm and to prepare as food. This fact does not allow the complete segregation of the individual infective case but rather the segregation of families who have one or more members stricken with the disease. In the Southern area this situation does not arise: there is a constant rainfall and the land is well watered, grain and root crops and vegetables are abundant and farming can be an all-season occupation. Consequently segregation villages have been successful in those areas where the people are leprosy conscious. There is also in the Northern Region the problem of a constantly moving population in search for cattle fodder and to conserve food.

The third problem, that of finance, presents the greatest difficulties. It has been found that the majority of leprosy cases in highly organized Provincial Settlements and segregation villages require subsistence. Partial subsistence may be required throughout the whole year and complete subsistence may be necessarv for some time preceding the harvest, and a failure of a staple cron may call for yet more subsistence. If to this expenditure there is added the provision of special buildings, the training and payment of the staff of a specialized leprosy service, with leprosy medical officers whose sole duty is to administer the service, the problem of finance is insurmountable.

Leprosy is endemic in the Region. Surveys of sample areas have yielded varying incidences. Among the Fulani and Hausa people, who with the Kanuri people comprise the main group of the population, survey work in Kano and Katsina indicated a general incidence of 35 per thousand. Higher incidences, varying from 50 to 100 per thousand have been found among the tribal or pagan groups, and in these groups the general pattern of the disease differs from that of the main group. In the main group there is evidence that leprosy is an old and accepted disease: it is not feared as the newer sickness of tuberculosis, and leprosy camps and compounds are a part of the community. It is possible that the disease pattern may be related to the habits of the people, e.g. the lack of clothing and crowded compounds of the tribal groups with a consequent higher incidence and with a high rate of the milder types of the disease. One significant feature is the extraordinary high incidence and the relative absence of burnt out cases found in a single tribe which recently left the hills to farm the fertile foot hills and plains, and the fact that this incidence seems



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to be repeating itself in other districts of the Region. A further indication of the prevalence of the disease is seen in the examination of the school children of ten schools in the Niger Province, where an incidence of 64 per thousand was recorded. It is possible that there are 500,000 leprosy cases in the Region.

A Government Medical Officer was posted to the Region in January, 1952. The work of this officer was to co-ordinate existing leprosy work and organize a leprosy control scheme for the Region. Leprosy work, with the exception of a few leper camps and clinics administered by the local authorities was entirely that of the Missionary Societies. About 10,000 patients were registered at 51 treatment centres, 9 of which were leprosy settlements. It was soon evident, however, that a scheme based on Provincial Settlements, administered by Voluntary Agencies, with surrounding treatment and segregation centres staffed by national personnel specifically recruited and trained for leprosy work was unpractical. Details of leprosy incidence made it soon apparent that to treat leprosy effectively, and as a separate entity, would require a financial allocation, buildings and staff almost equal to the needs of the curative medical services and far beyond the resources available for leprosy control. Furthermore, full-time medical officers were not forthcoming to administer and supervise a separate scheme of this nature.

Following successful experiments in outpatient treatment during 1952 and 1953, one such experiment was described in the "Leprosy Review," April 1956 (Ross); the policy of making treatment available throughout the Region in the Local Authority and Government dispensaries by DDS administered by the existing dispensary staff, was considered practical and possible. During this experimental period active opposition was encountered from those already engaged in leprosy work in the Region on the grounds that the L.A. dispensary attendant was incapable of administering the drug and that the treatment of infective cases who were not segregated was ineffective and could do more harm than good. There was a lack of interest and co-operation among many Local Authorities. One encouraging feature was the increasing interest of Government medical officers in leprosy treatment and its results, and especially of several Medical Officers of Health who volunteered to supervise and carry out experiments in outpatient treatment in Katsina, Sokoto and Kano Provinces. District Heads and Chiefs, although doubtful at the beginning, became co-operative and helpful when they realised the object of the experiment and saw the results of treatment. Special mention must be made of the Emir of Katsina, who from the beginning actively encouraged and sponsored the experiment in his Emirate, and also the District

Head of Riga Chikun, Zaria Province, whose assistance was vital to the establishment of experimental clinics in his district.

A gradual commencement of the scheme was made by the introduction of leprosy instruction into the curriculum of the Medical Auxiliaries Training Schools of the Region: local courses of instruction were also conducted at the central hospitals of medical areas for the dispensary attendants who staffed the dispensaries of the area, and this was followed by the opening of leprosy clinics at these dispensaries. In two years' time the majority of the patients treated in the Northern Region were treated at Local Authority dispensaries or at branch clinics attached to a central dispensary or rural health centre with DDS supplied by UNICEF at little or no extra cost to the Region. In Katsina Province Dr. Butler, Rural Medical Officer, commenced a scheme of treatment through the rural health staff and dispensary attendants in which the patients who regularly received treatment arose from nil in 1952 to about 13,000 in 1956. Valuable information was discovered in this experiment in Katsina and in other experiments. Regular attendance was ensured by having treatment given on market days. It was unreasonable to expect regular attendance from patients who lived more than seven miles from the clinic. Good results were seen in reducing the infectivity of the severe lepromatous cases and patients who had been unable to farm for several years were made able to farm and help to support themselves and their families.

A very important finding was that patients unwilling to seek treatment at the Provincial Settlement or local segregation village, were willing and eager to attend weekly for treatment over a period of years; also it was found that the most regular attenders were lepromatous cases and that about 30% of the registered patients were in many districts lepromatous cases. Toxic effects were negligible and reaction was extraordinarily rare.

The object of this scheme of mass treatment is to treat all leprosy cases in the Region, to reduce the infectivity of all open cases and to prevent early cases by early treatment from progressive disability and from reaching an infective stage. There is some evidence that in districts where treatment has been carried on from 4 to 5 years, a beginning of leprosy control is apparent. There is a gradually increasing number of discharged resolved tuberculoid cases; no lepromatous cases or those of the intermediate groups have been discharged. The percentage rate of lepromatous cases showing marked resolution in the clinics is increasing as the clinics decrease in size. There is a steady intake of patients with early tuberculoid and indeterminate early lesions, with few, if any, new lepromatous cases. The clinics in such districts are becoming smaller and are well attended by the lepromatous cases who are most appreciative of the benefits of treatment. It seems reasonable to suppose that in such districts the treatment of all leprosy cases with an effective drug is more effective in leprosy control than the segregation and treatment of a very small proportion of the highly infective cases.

Segregation is encouraged but is purely voluntary. Settlement and segregation villages have failed to attract the lepromatous cases, who live within easy reach of them in the Northerly Provinces of the Region. In Provinces where 200 to 500 cases were treated at great or considerable expense for some years in settlement and segregation villages, 10,000 to 15,000 are being treated in a province at a fraction of the cost and with good results. Government policy lays down that the lepromatous case, who is unable or unwilling to segregate, must not be refused treatment at an outpatient clinic. There are many excellent segregation villages, especially in the Southern Provinces of the Region, which are administered by Missionary Societies, and as leprosy control increases and staff are trained as leprosy inspectors and assistants, it is hoped that segregation centres will increase. The segregation village for a group of leprosy clinics at dispensaries in a medical area and which is supervised by the Government medical officer of that area, with an assistant leprosy inspector constantly touring the area and visiting the clinics, has been proved successful and is envisaged for the future.

The importance of the Provincial Settlement is fully realised. In each Province there is at least one settlement, administered by a Missionary Society acting as a Voluntary Agency, which receives Local Authority or Government grants for the erection of hospital buildings, treatment and laboratory buildings, and for a piped water supply. Recurrent grants are also given for the maintenance of the settlement. The function of the settlement is that of a leprosy hospital for the Province and as a centre for laboratory work. It is fully realized and emphasized that a settlement working in close co-operation with the Local Authorities and Government is necessary to the efficient working of the scheme.

The leprosy staff, apart from the considerable numbers of staff supplied by Voluntary Agencies in Provincial Settlements, Segregation Villages and Mission Dispensaries, is drawn from Government and the Local Authorities. While the giving of treatment is the work of the L.A. dispensary attendant at the dispensary and the leprosy assistant at the branch clinics, the general supervision is given by the Government medical officer of the area or the medical officer in charge of the Provincial Settlement. The examination of patients and estimation of their progress, the

necessary leprosy instruction and the correct and adequate compilation of returns of patients treated and DDS stock, is the responsibility of the Central Government staff. The establishment of the Central Government staff is as follows:---A Leprosy Specialist and Leprosy Medical Officer; a Senior Rural Health Superintendent and six Rural Health Superintendents, and twelve Provincial Leprosy Inspectors. At present there are two Medical Officers as Specialist and Leprosy Medical Officer, one Senior Rural Health Superintendent (Leprosy), three Rural Health Superintendents (Leprosy) and three Assistant Rural Health Superintendents (Leprosy). There are also several staff in training for Provincial Leprosy Inspectors. The Local Authorities provide the posts of Assistant Leprosy Inspectors and also Leprosy Assistants to visit branch clinics set up to provide treatment in districts where medical facilities are few. A Leprosy Assistant, based on a Local Authority Dispensary, can visit 3-4 branch clinics and give treatment there each week. There are about 10 fully trained Assistant Leprosy inspectors at present in the Region, and there are 24 Dispensary Attendants, who showed themselves capable in giving treatment and worthy of promotion to supervise leprosy clinics in training as Assistant Leprosy Inspectors. A leprosy unit consisting of a lecture hall, a laboratory and store has been built and is attached to the Medical Auxiliaries Training School at Kaduna.

The training of staff is a major part of the scheme. There is an annual leprosy course for Medical Officers, and also courses as necessary for Rural Health Superintendents and Health Sisters. The Dispensary Attendants are taught to diagnose and distinguish the different types of leprosy. They are instructed to treat each patient according to their type, age and physical condition, and to recognise toxic signs, Reaction and Lepra Fever. The institution of treatment is slow and cautious, and suited to each individual patient and consequently toxic signs and reactions are rare. The attendant is limited in the giving dosage of DDS, and doses of more than 4 tablets weekly are prescribed by the supervising staff. The Assistant Leprosy Inspector is employed by a Local Authority to visit their dispensary clinics regularly and ensure that a good attendance is maintained; his training extends over a course of several months at the Medical Auxiliaries Training School and Leprosy Units, Kaduna, and includes instruction in epidemiology, diagnosis, classification, treatment and bacteriology necessary for his work. His work is not confined to the Leprosy Clinic and supervision of treatment, but is directed towards the visiting of all absentees from treatment and lepromatous cases in their compounds and to examine contacts. As the service develops the Provincial Leprosy Inspector will be directed to stimulate interest and leprosy

consciousness in the Province, and to seek and examine contacts, and do survey work in villages and schools.

The Rural Health Superintendent is in charge of a Medical Division and is chiefly engaged in instruction and refresher courses to the Dispensary Attendants. He will work in close co-operation with the Local Authority and the Medical Officer of the area he is visiting. The Specialist and Leprosy Medical Officer will advise the Local Authority, administer the scheme and determine its progress in the examination and discharge of patients.

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Summary

There is put forward a scheme for mass leprosy treatment, which is an integral part of the general medical and health services and not distinct and separate from it. It follows successful experimental outpatient treatment based on the social habits and economy of the country.

The scheme was quickly evolved by making use of the existing medical and health staff at a comparatively small cost.

The importance of training national staff in the classification of leprosy and treatment and of a safe dosage for each type is emphasized.

The general supervision of the scheme, while the normal duty of the Medical Officer of the area, is augmented by specialized staff which is partly Local Authority and Government

An Epidemiological study in different tribes is suggested in (a) the habits of the people related to the incidence and types of leprosy, (b) the pattern of the disease in people who may have contracted leprosy for the first time.

We acknowledge help from the United Nations' International Children's Emergency Fund, whose generous help stimulated and made possible the carrying out of the scheme.

Thanks are due to the Director of Medical Services, Northern Region, Nigeria, for permission to publish this paper.

THE TREATMENT OF LEPROSY WITH DIPHENYL THIOUREA COMPOUND SU 1906 (DPT)

A REPORT ON EXPANDED TRIALS IN NIGERIA

1. A SECOND REPORT ON THE PROGRESS OF THE PILOT TRIAL WITH A REVIEW OF THE FINDINGS IN EXPANDED TRIALS Dr. T. F. Davey

Introduction

SU 1906 is the research reference number given in the CIBA laboratories to a relatively simple compound of diphenyl thiourea, also becoming known as DPT. It is 4 butoxy-4' dimethylaminodiphenyl thiourea, and has the following structural formula.



This substance was found to have outstanding bacteriological activity against *M. tuberculosis* both *in vitro* and *in vivo* by Mayer, Eisman and Konopha (1953) and Konopha, Gisi, Eisman and Mayer (1955), and this prompted its clinical trial in leprosy. Pilot trials in the treatment of leprosy with this substance were undertaken both in East and West Africa. In a progress report written after 16 months' experience of the drug in Nigeria, Davey and Currie (1956) found that it combined a noteworthy freedom from toxicity with chemotherapeutic activity similar to that of DDS. These findings were confirmed in East Africa by Ross Innes, Smith and Harden-Smith (1957).

Another sixteen months have now elapsed since the first progress report was written, and the further progress of the pilot trial in Nigeria is here reported, together with additional information gained from the wider use of DPT. The promising short term findings made it desirable to expand the trials of the drug in three directions, (a) to test its therapeutic activity in larger numbers of lepromatous cases of leprosy, (b) to examine its usefulness in patients whose response to sulphones was unsatisfactory, and (c) to explore its use in combination with other drugs. After preliminary work at the Uzuakoli Research Unit on the second and third of these projects, leprologists in charge of six Settlements in Nigeria were invited to co-operate in expanded trials of the drug, and all willingly agreed to do so. The centres concerned with

Leprosy Service,	Dr. A. S. Garrett	25 patients
Oji River	Dr. K. Ellis	
Leprosy Service,	Dr. B. Nicholson	8 patients
Ossiomo	Dr. S. Healy	
Leprosy Service,	Dr. M. Corcos	5 patients
Rivers		
Catholic Mission Settle-	Dr. E. Fern	10 patients
ment, Abakaliki		
Presbysterian Mission	Dr. M. Phillips	12 patients
Settlement, Itu	Dr. R. Matheson	
Presbysterian Mission	Dr. A. Macdonald	10 patients
Settlement, Uburu	Dr. L. Hogerzeil	

numbers of trial patients at each are as follows-

With 97 patients in various categories at the Research Unit, the additional 70 rapidly brought the numbers of patients receiving DPT either alone or in combination to 167. Apart from a few patients unable to tolerate sulphones all the additional patients were lepromatous cases previously untreated. At all centres laboratory work followed the same routine, and uniformity was sought by providing periods of study for the laboratory technicians of co-operating Settlements at the Research Unit, and by periodic visits to each centre by Mr. S. E. Drewett, Senior Laboratory Superintendent, when independent bacteriological tests were undertaken. Co-ordination in the choice of patients and their controls and in the clinical assessment of progress was maintained through similar visits to each centre by the writer.

Dosage

The drug was originally prepared in the form of coated tablets containing 0.25 gm. It was later found more convenient to use uncoated compressed tablets containing 0.5 gm.

An initial dose of 1.0 gm. daily in the case of adults and 0.5 daily in the case of children has been found generally satisfactory, subsequent increases depending on the weight and liability of the patient to reaction. For the average adult an increase in the initial daily dose by 0.5 gm. at fortnightly intervals is convenient up to a maintenance dose of between 25 and 40 mg. per kilo. At first a rather higher dosage than this was given, adults receiving 3.0 gms. daily as routine, but experience proved that this dose, which represents about 50 mg. per kilo is unnecessarily high, and few adults need more than 2.0 gms. daily, given in a single dose. In practice the lack of toxicity displayed by the drug makes it unnecessary to calculate dosage within narrow limits, but there is nothing to be gained therapeutically by exceeding the suggested

dosage. With prolonged treatment at a higher level than this the antithyroid action of the drug may begin to show itself.

Children tolerate DPT extremely well in the same dosage per kilo as is suggested for adults, which in practice means a daily dose ranging from 0.5 to 1.5 gms. in accordance with age.

The suggested routine for treatment is based on clinical experience. As yet it has not been found possible to establish a rationale of treatment which is based on studies of the absorption and excretion of the drug. For a long time no satisfactory method of estimation was available, and although in recent months we have been advised of two possible methods, technical difficulties have prevented any speedy assessment of their value. The drug has been used in sufficient numbers of patients and in a range of dosage sufficiently wide to enable an opinion on suitable dosage to be expressed with confidence.

Toxicity

The freedom from toxic side effects found in both West and East Africa in the pilot trials of DPT has also been experienced at each of the six new centres where the drug has been used. In the range of dosage used the drug is very well tolerated and causes no gastric or intestinal irritation, promoting on the other hand tranquility and a sense of well-being. Among Nigerian patients there has been no indication of any disturbance of bone marrow, liver, or kidney function for which the drug could be held responsible. No case of dermatitis or drug fever has arisen, the drug has indeed been well tolerated by patients hypersensitive both to sulphones and to thiosemicarbazone. Psychosis has not been seen. It has in fact not been necessary at any centre to remove any patient from treatment with DPT for any cause. The lack of toxicity displayed by DPT is one of its outstanding virtues, and has been the experience not only of leprosy workers, but also of those undertaking clinical trials in tuberculosis. Two conditions which may arise during treatment call for comment.

(a) Hypothyroidism

Thiourea and some of its compounds are potent antithyroid substances, which are believed to act by preventing the combination of iodine with tyrosine and consequently inhibiting the synthesis of thyroxine. The action of DPT in this direction is evidently feeble. Throughout the trial a careful watch has been kept for signs of hypothyroidism in patients receiving DPT, but on the dosage recommended there has been no evidence of any depressant action on thyroid activity. In the earlier stages of the pilot trial the standard dose was maintained at a rather higher level, and during the second year signs of hypothyroidism did appear in one adolescent patient who had been receiving 3.0 gms. of DPT daily for 15 months. It was not possible to determine the basal metabolic rate with accuracy, but signs of impaired thyroid activity which developed in this patient included increase in weight, bradycardia, constipation, dry skin and mental dullness. With a reduction in dose to 1.5 gms. daily and the administration of small doses of thyroid extract these symptoms gradually disappeared and have not recurred. On the same high dosage another patient during the third year began to complain of amenorrhoea which might possibly have been related to the DPT. It has not recurred following a reduction in dose. There is thus some evidence that at a dosage of 50 mg. per kilo there is some risk of mild degrees of hypothyroidism developing after long administration of the drug. This dose appears to be unnecessarily high.

(b) Skin eruptions

When used in the treatment of tuberculosis in doses of 6.0 to 9.0 gms. daily, DPT has been found to cause an irritating skin eruption in some patients. This has not been encountered to any appreciable extent among patients receiving the lower dosage used in leprosy treatment even after prolonged administration. Incidental skin eruptions have occurred from time to time but it has not been possible definitely to implicate DPT as the agent responsible. Other possible causes have always been present, and their treatment brought relief without there being any need to modify the dose of DPT.

THE PROGRESS OF LEPROSY

A. DPT given alone

Here we have to consider the progress of the pilot trial group of patients at the Research Unit, comprising all three main types of leprosy, up to the 32nd month of treatment, with in addition the findings in supplementary groups of 25 lepromatous patients treated for one year at centres other than the Research Unit.

(a) Tuberculoid cases

The eight tuberculoid cases in the pilot trial are all in a residual condition. Four were discharged from treatment after two years, and having been followed up for six months are all fit and well. The other four are being retained under observation, two because of the persistence of neuritis for some time after macules became residual. Additional tuberculoid cases placed on DPT treatment because of severe neuritis have made satisfactory clinical progress and are discussed later in relation to neuritis.

(b) Indeterminate and Borderline cases

After two years or longer, five out of six patients in this group are clinically also in a residual condition. Their progress was, how-



Relative Decline in Bacterial Index. Trial Patients and Controls.

ever, not uneventful. As commonly happens in any form of chemotherapy the immunological instability of this group showed itself in the appearance of recurrent macules in three of these patients at various times between the 7th and the 21st month. Such new lesions were of short duration and tended to be closer in appearance to tuberculoid than the original lesions. Nerve involvement was prominent but not serious in its effects. The sixth patient had a short-lived eruption of similar type at the 24th month.

(c) Lepromatous cases

FIRST YEAR

The pilot trial covered 17 patients. In the first progress report it was stated that these all exhibited an early response to treatment, with satisfactory clinical and bacteriological progress, particularly marked during the first nine months, but with a perceptible falling off in bacteriological improvement in a few cases after that time. This effect proved to be temporary only, and at the end of the first year of treatment it may be said that all cases showed satisfactory progress, particularly gratifying in some individuals, while the group as a whole displayed a degree of resolution, both clinical and bacteriological, rather greater than was found among controls on routine DDS treatment. The same is true of eight other lepromatous cases added later to the original group.

Expanded trials have added a further 25 cases at three centres, and among these identical results have been obtained during the first year of treatment. Resolution has been satisfactory in all respects, and is considered by the experienced leprologists responsible to be at least as good as that encountered in controls on normal DDS treatment, and in some cases to be better.

SECOND YEAR

During the second year of treatment the slowing down in decline in bacterial index which is familiar in the chemotherapy of leprosy became apparent in the pilot trial group of patients, as did the variation in the rate of progress between one patient and another which is also a common experience. Clinical progress was, however, uninterrupted, and in several patients biopsies exhibited the continued shrinking of lepromatous infiltration in the skin, which as Ridley has noted (1956) accompanies satisfactory resolution. As long as this shrinking layer of infiltration contains acid-fast material positive results will be obtained in routine smears, and the appearance of a negative smear is thus evidence of a very advanced degree of resolution. By the end of the second year 3 patients had become negative to routine bacteriological tests, and in all patients with persistently positive smears the proportion of bacilli showing degenerative changes steadily increased with the passage of time. In the group as a whole the advantage gained over controls during the first year was maintained. THIRD YEAR

Twelve patients in this group have now completed eight months in their third year of treatment, and progress continues to be satisfactory. In a majority of them the skin is beginning to assume a normal appearance, with surprisingly little loss of elasticity, while bacteriological progress continues to be gratifying. There are as yet no signs of drug resistance developing.

The group progress in bacterial index of trial patients and their controls is illustrated graphically in Figure 1. This shows that during the first year trial patients showed greater progress than their controls, and that ground gained then has not subsequently been lost.

Complications during Treatment

(a) Erythema nodosum

This common complication in the chemotherapy of lepromatous cases has not been a serious problem in patients receiving DPT. During the first year it was rare, occurring in 3 cases out of a total of 44 treated with DPT alone. Such a finding is not unusual in Nigerian practice, where this condition tends to be more a late than an early complication of chemotherapy, being most prevalent when the Bacterial Index has fallen to the neighbourhood of 1.0 or less. During the second year in the pilot trial group it occurred more frequently, and has again been encountered during the third year. As generally seen it has been mild and easily controlled by a short course of treatment with Fantorin (Stibophen). No case has yet been encountered of peristent erythema nodosum; indeed patients in such a condition following DDS treatment have done very well when the DDS treatment has been replaced by DPT. In one patient severe erythema nodosum was associated with the rare phenomenon of a change in type from lepromatous to borderlinc leprosy and was associated with a severe neuritis with ulnar paralysis which, however, was only temporary. In this patient the reactive condition led rapidly to the disappearance of bacilli from routine smears in the skin. Erythema nodosum is thus not prominent during DPT treatment and has tended to occur rather earlier among trial patients than among their controls.

(b) Neuritis

Apart from the example mentioned above no serious case of neuritis has arisen. Phases of mild or moderately severe neuritis occurred in tuberculoid and borderline cases mostly during the first fifteen months of treatment. In lepromatous cases, neuritis, like erythema nodosum, has not been prominent, and when it has occurred it has not been persistent. It has indeed been found that patients presenting severe nerve involvement when DPT treatment was instituted have made calm and steady progress in their nerve condition as well as in their general infection.

(c) Exacerbation of the disease

Reference has already been made to the appearance of fresh skin lesions during the treatment of borderline cases. These are considered to reflect a changing immunological state rather than indicate an exacerbation of the disease, for without exception the subsequent progress of those concerned on continued DPT treatment was quite satisfactory.

A watch has been kept for any signs of exacerbation of the disease in lepromatous cases. In the first progress report the case was mentioned of a patient who showed some exacerbation at the sixth month following severe influenza. He was the only example of such an occurrence; indeed after the first year there was less variation in consecutive bacterial findings among individual trial patients than among their controls, and no evidence of seasonal influences.

Treatment in special cases

An important aspect of the use of DPT is its value in the treatment of patients in whom sulphone treatment is either difficult or impossible. It has now been used for adequate periods in a number of the conditions which complicate treatment with the sulphones, and the following results have been obtained.

(a) Drug sensitivity

In three patients hypersensitive both to sulphones and to

thiosemicarbazone, DPT has provided an entirely satisfactory form of chemotherapy. No case of drug sensitivity to DPT has been encountered yet in Nigeria.

(b) Psychosis

Three patients with psychosis have tolerated DPT much better than they tolerated DDS. One of them, who developed psychotic signs after only short courses of DDS, has had several months of complete normality during treatment with DPT.

(c) Persistent erythema nodosum

Seven patients transferred to treatment with DPT after long periods of recurrent erythema nodosum during DDS treatment, have settled down very well and been able to tolerate therapeutic doses without difficulty.

(d) Severe neuritis

When it was noticed that neuritis was not prominent during DPT treatment, a number of patients with severe neuritis occurring during DDS treatment were transferred to the new drug, and have in general made satisfactory and more tranquil progress. The same is true of patients presenting severe neuritis on first consultation. For patients with this complication of leprosy DPT has proved itself an acceptable form of chemotherapy. Among 13 patients suffering from neuritis who have received it, no case has arisen of any extension of paralysis which has been more than temporary. The tendency has been in the opposite direction, relief from pain and improvement in motor nerve involvement being commonly encountered.

(e) Unsatisfactory response to DDS

DPT has also been found of value in eight patients whose response to DDS was slow and unsatisfactory. In all of them resolution was expedited.

DPT given twice weekly

The need for daily administration is a serious disadvantage from the standpoint of the wider use of DPT. The study of its absorption and excretion will in due course give information on which a sound rationale of treatment can be based, but it has been thought desirable not to wait for this, but to observe directly the effects in patients of administration on a twice weekly basis. Sixeen patients at the Research Unit have now had twice weekly treatment for periods up to seven months, the dose employed commencing at 1.0 gm. and rising by I gm. at fortnightly intervals up to a maximum of 4.0 gms. twice weekly. This is a little less per week than the dosage recommended above, but 4.0 gms. was considered to be as much as patients could be expected to take as routine.

ILLUSTRATIONS TO ELECTRONMICROSCOPY

Article by R. KOOU, M.D. on page 56



Fig. 1. Lepromatous Leprosy. Untreated Leprosy bacillus attached to a saline crystal. Magnification 36,000 x.



Fig. 2. Lepromatous Leprosy. Treated with DDS and Isonicotinic acid hydrazide during $2\frac{1}{2}$ years. Magnification 27,000 x.



Fig. 3. Lepromatous Leprosy. Untreated. Magnification 17,200 x.



Fig. 4. Lepromatous Leprosy. Untreated. Shadow cast. Magnification 13,000 x.



Fig. 5. Lepromatous Leprosy. Untreated Mass of bacilli. Magnification 12,000 x.



Fig. 6. Lepromatous Leprosy treated with DDS and thiosemicarbazone for $3\frac{1}{2}$ years Magnification 36,500 x.



Fig. 7. Lepromatous Leprosy. Treated with DDS and thiosemicarbazone for $3\frac{1}{2}$ years. Magnification 36,500 x.



Fig. 8. Lepromatous Leprosy. Treated with DDS and thiosemicarbazone for 3! years. Magnification 13,200 x.



Fig. 9. Lepromatous Leprosy. Treated with DDS and thiosemicarbazone for 3½ years. Magnification 17,200 x.



Fig. 10. Lepromatous Leprosy. Treated with DDS and thiosemicarbazone for 3¹/₂ years. Magnification 13,200 y.



Fig. 11. Lepromatous Leprosy. Treated with DDS and thiosemicarbazone for 31 years. Shadow cast. Magnification 12,400 x.



Fig. 12. Lepromatous Leprosv. Treated with DDS and thiosemicarbazone for $3\frac{1}{2}$ years. Shadow cast. Magnification 28,200 x.



Fig. 13. Tuberculoid Leprosy. Untreated. Magnification 30,000 x.



Fig. 14. Tuberculoid Leprosy. Untreated. Magnification 30,000 x.



Fig. 15. Tuberculoid Leprosy. Treated with DDS for 5 months. Remnants of bacilli? Magnification 30,000 x.



Fig. 16. Tuberculoid Leprosy. Treated with DDS for 5 months. Remnants of bacilli? Magnification 30,000 x.

THE TREATMENT OF LEPROSY WITH DIPHENYL THIOUREA

One patient complained of some discomfort after this dose. The remainder have made no complaints and are quite satisfied with this form of treatment.

Therapeutically the results in some patients have been good, but an element of uncertainty has been encountered which is absent on daily administration. In five patients after three months, it was felt that progress was definitely less than would be expected on daily treatment, and they were transferred to daily treatment, after which enhancement of progress speedily became evident. The remainder, consisting of two lepromatous, six tuberculoid and three borderline cases, have continued to make satisfactory progress on twice weekly treatment. On the whole twice weekly treatment appears to involve some loss in the efficiency of the drug, though results in some patients may be entirely satisfactory.

B. DPT in combination with other drugs

Once the chemotherapeutic activity of DPT had been demonstrated, it became desirable to examine its usefulness in combination with other drugs. As the drug is not likely to be manufactured very cheaply, much of its practical usefulness may depend on whether it can be combined safely with a cheaper drug to produce materially improved results, particularly if thereby it could be used in rather lower dosage than appears to be necessary when given alone. Preliminary work on this subject has been undertaken in these expanded trials, and findings are here presented after one year's experience of DPT, used in combination with DDS and with INH.

(a) DPT used in combination with DDS

A total of 32 patients have received the two drugs in combination for one year or longer. They fall into three groups.

I.	Full dosage of DPT with full dosage of	
	DDS. 2.0 gm. DPT daily with 600 mg.	
	DDS weekly (given daily or twice weekly)	11 patients
2.	Full dosage of DPT with low dosage of	
	DDS. 2.0 gm. DPT daily with 400 mg.	
	DDS weekly	12 patients
3.	Low dosage of DPT with low dosage of	
	DDS weekly	9 patients
	DDS. 1.0 gm. DPT daily with 200 mg.	

All the patients in the third of these groups were at the Research Unit. Most of the patients in the other two groups were at other centres. In all cases DDS treatment followed standard routine, and was given daily in some patients, twice weekly in others. DPT was given daily at the same time.

Without exception all patients have tolerated the two drugs

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very well, and at the dosage levels used no toxic effects have been observed over and above the minor disturbances attendant on DDS therapy. At these dosages the two drugs may safely be combined. There was also the possibility that a combination of drugs might delay the onset of drug resistance should this be encountered in the later stages of the trial.

Where chemotherapeutic activity is concerned, the progress of these groups has not been the same. Both the first and second groups have made very good clinical and bacteriological progress, better than would be expected under DDS treatment alone, and better than was encountered in controls receiving DDS on its own. In the third group progress was satisfactory but not outstanding, certainly not as marked as in the other groups, but decidedly better than would have been expected on the dosage of DDS alone.

That is all that can be said at present. The combination of drugs appears to give results during the first year superior to those obtained when DDS is given alone, but it is not yet clear whether the combination is superior to DPT alone. Larger numbers, additional groups, and observation over a longer period will be needed before sound judgment on this matter is possible. The important point at present is that when combined with DDS, DPT still contributes both its freedom from toxicity and enhanced therapeutic action.

(b) DPT in combination with INH

DPT has been used in combination with INH in 20 patients for periods of 7 to 20 months at 4 centres. INH alone has not been found generally useful in the chemotherapy of leprosy as its effects are unpredictable. This, however, does not rule it out as a possibly useful member in a drug partnership, and its use in conjunction with DPT commended itself as a possible means of using DPT economically in a combination of low toxicity. The two drugs have been given in doses of 1.0 to 1.5 gms. DPT with 100 mg. and 200 mg. INH daily.

Once again the combination has been extremely well tolerated, and no toxic effects of any description have been detected, patients continuing cheerful and in very good physical condition.

The therapeutic effects have not been quite the same at all centres. All eight patients at the Research Unit have made excellent progress, better than would be expected with DDS treatment, and with little if any difference from that expected with larger doses of DPT alone. At other centres results have been outstandingly good in some individuals but not so good in others, and generally not quite as good as that seen when DPT is used alone in full dosage. Further study is again needed, but results so far make this a promising combination of drugs.

Conclusions

It is the opinion of all those taking part in these trials that in DPT we have an anti-leprosy drug of considerable potential importance, a drug which combines a noteworthy freedom from toxic side effects with chemotherapeutic activity of a high order. In a dosage of 25-40 mg. per kilo its activity is quite as great as that of DDS and sometimes surpasses it, and after 32 months of experience there is no evidence of the development of drug resistance.

Complications during treatment have hitherto not been important, one of the virtues of DPT being the favourable course often taken by patients with neuritis. Drug hypersensitivity and psychosis have not been encountered. On the basis of experience so far DPT is considered to be the drug of choice when an alternative is needed to DDS.

DPT can be combined safely with both DDS and INH, the combination having a very satisfactory chemotherapeutic action during the first year of treatment.

In the treatment of the individual patient DPT promises to be a serious rival to DDS, for it combines an activity, at least as great with the promise of a relatively smooth course uninterrupted by major upsets. It is particularly valuable in children. For large scale use, however, something more is needed than high therapeutic activity and lack of toxicity. The dose of DPT is relatively large, and apart from its inconvenience this adds to the cost of When given twice weekly results though often treatment. adequate are not generally as good as when daily treatment is given. For these reasons DPT is not applicable to many situations. A drug with such outstanding qualities should, however, be within the reach of patients everywhere, particularly those in whom DDS has failed to be all that could be desired. Further study both of it and of closely related compounds is urgently needed with the object of promoting ease of manufacture and greater economy and simplicity in administration.

Acknowledgements

Many workers have co-operated in these expanded trials on DPT, and it is a pleasure to acknowledge the help given not only by medical officers who agreed so willingly to take part and have given most careful attention to this work, but also Mr. S. E. Drewett, Senior Laboratory Superintendent, the laboratory staff at the various settlements, and perhaps above all the patients who so readily volunteered at all centres to take what to them was an unknown drug, and faithfully carried out all that was required of them.

Thanks are also due to the Directors of Medical Services, East and West Nigeria, for permission to publish this paper.

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Grateful thanks are due to Messrs. Ciba Ltd. for continued generous supplies of DPT.

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FINDINGS AT OJI RIVER SETTLEMENT 2. DR. A. S. GARRETT

At Oji River we have carried out our small section of research on DPT under the close guidance of Dr. Davey.

We have had 25 patients, the first of whom started in July, 1956. They have been on a standard dose of 2 gm. daily as with Dr. Davey's other patients.

The previously untreated lepromas have all shown clinical and bacterial resolution as fast as that in their controls and also faster in all cases but one.

Reactions of neuritis and erythema nodosum have been almost absent and no eye reactions have occurred.

The group of patients given DPT because of previous reactions on dapsone have all had less reactions and some markedly less than before.

The group given DPT to accelerate slow resolution of tuberculoid leprosy has succeeded in its aim.

No case of toxicity to mind or body has been noted.

These few notes are to stress that my findings are identical with what Dr. Davey reports. There is nothing to add to his findings.

It has previously been strongly held by some people, that all effective anti-leprosy treatment commonly causes reactions. DPT points to a reversal of that view. Investigation of the biochemistry of DPT and Mycobacterium leprae may reveal that, in killing the bacterium. DPT fixes a toxin.

FINDINGS AT OSSIOMO SETTLEMENT 3. DR. B. NICHOLSON

Eight patients have been treated at Ossiomo Settlement with DPT for periods ranging from 121 to 151 months. Of the eight, four had diffuse lepromatous leprosy, three had macular leproma, and one was a borderline case with areas of diffuse infiltration. They include four adult males, one adult female, one male child and two female children.

On admission the Bacterial Indices ranged from 2.2 to 3.8 with an average of 3.2.

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Dosage

Started in all cases at 0.25 gm. daily. In adults it was increased to 1.5 gm. daily over a period of four weeks and in the children to maxima of 1 gm. Recently doses in a few cases have been increased to maxima of 2.0 gm. daily.

These doses have been maintained without difficulty, except in the cases referred to below.

Attitude of Patients

All patients who have been treated with DPT have welcomed it at all stages of the test. No patient has made any complaint about it.

Toxicity

No toxic effect of any kind has been noted in any patient. A sense of well-being has been evident in several cases.

Progress of Leprosy

Every one of the eight cases has shown marked improvement. Clinically there has been general resolution of infiltration and nodules have disappeared.

The Bacterial Index now ranges from 1.1 to 3.2 with an average of 2.1.

Complications

One extremely severe case of diffuse lepromatous leprosy in rather poor general condition suffered repeated attacks of low fever in the early months of treatment. The dose of DPT was reduced but not abolished and the attacks subsided after about six months. They may not have been directly due to the treatment.

The single patient with borderline leprosy had typical crythema nodosum leprosum after having been free of complication during treatment for 12 months. This subsided in a short time after reducing the dose. He is now again on full dose.

Comments

Improvement was seen in every case clinically and bacteriologically. This was distinctly better than is to be expected from similar patients treated with Dapsone in this area. The psychological calmness of these patients while on treatment with DPT is especially noteworthy.

4. EXPERIENCE AT RIVERS SETTLEMENT Dr. M. Corcos

Five patients have now been on DPT for the following periods.

No. 1	Male Adult	 	18 months
No. 2	,, ,,	 	18 months
N•. 3	,, ,,	 	17 months
No. 4	,, ,,	 	16 months
No. 5	,, ,,	 	14 months

All were lepromatous cases previously untreated. The dosage in all cases has been:—

Weeks	I—2		0.5 gm.	daily
,,	3—4		1.0 gm.	daily
,,	5 onwards		1.5 gm.	daily
Raised	after 3 mont	ths to	2.0 gms.	daily.

All the patients liked the drug and there have been no complaints of any symptoms attributable to it. No case of toxicity attributable to the drug has been noted at any time.

Therapeutic activity has been as follows:---

- No. 1. Severe diffuse leproma with some nodulations of ears. Marked clinical resolution after 18 months. Smears at the beginning of treatment were all 4+. After 18 months of treatment, skin smears were 2+ though ears were still 3+and left side of nose 4+.
- No. 2. A moderate diffuse leproma. Has much improved clinically. Skin smears at the beginning of treatment were all 2+. After r8 months' treatment, only scanty bacilli were found except in ear lobes which still showed 2+.
- No. 3. Active diffuse leproma with early nodulation. Extremely marked clinical improvement after 17 months of treatment. Skin smears at beginning of treatment 3+—present time 2+ and 1+.
- No. 4. Diffuse leproma. Steady clinical improvement. At beginning of treatment skin smears 3+. After 16 months of treatment from 2+ to scanty.
- No. 5. Diffuse leproma with faint maculation—much improved after 14 months of treatment. Skin smears at beginning of treatment 4+ and 3+. After 12 months' treatment 2+.

Complications during treatment have been notably absent so far. Case No. 5 who complained of nerve pain in the left ulnar nerve (which was grossly thickened) when starting treatment lost this in a few weeks without any radical local treatment. The pain has not recurred though the nerve is still somewhat thickened. There have been no true lepra reactions, but case No. I, after 15 months' of treatment, showed a slight almost symptomless erythema-nodosum-like reaction which lasted for about two months. Treatment has not been interrupted.

It was not at all easy to match exactly these patients with control of the same severity. Moreover, since all the controls had received previous Dapsone treatment the state of their leprosy at the beginning of their treatment did not necessarily correspond with the state of the leprosy of the experimental cases at the beginning of the experiment **and** of the treatment; the controls were selected on the basis of similarity to the experimental cases, of clinical condition and bacteriology at the time of matching. Thus the controls were usually more severe cases of leprosy than the experimental cases, but as mentioned had already been under treatment. Controls I and 3 particularly were considered unsatisfactory.

- Control I. Diffuse leproma—relapsed in 1953 following Hydnocarpus treatment. Treated with Dapsone since then. Smears 2+ and 3+ at beginning of experiment, and unchanged 10 months later.
- Control 2. Previous treatment 15 months. Diffuse infiltrated leproma. Steady clinical improvement. Skin smears at beginning of treatment 2+. At beginning of experiment 2+. After 15 months experimental period smears very scanty + and acid fast granules.
- Control 3. Nodular leproma, I year and II months previous treatment with DDS. Smears at beginning of treatment were 4+, at beginning of experiment 2+ and after 9 months very scanty +.
- Control 4. Previous treatment I year II months. Diffuse leproma with slight maculation—steady clinical improvement on Dapsone. Skin smears at beginning of treatment 4 + . beginning of experiment 3 + . After 14 months smears were - ve and very scanty + ve.
- Control 5. Treatment with hydrocarpus oil from 1948 to 1949. Very irregular treatment with DDS, thereafter until beginning of experiment. Skin smears in 1949 were 1+, at the beginning of the experiment they had become 4+. After 12 months of regular DDS, although there was marked clinical improvement, skin smears were still 3+ and 2+.

Within the limits of the experiment it was considered that the progress made by the five experimental cases in the 1st year of treatment was fully up to that made by DDS treated cases.

5. EXPERIENCE AT ABAKALIKI SETTLEMENT Dr. E. Fern

It is now 16 months since 3 of our 10 trial patients began receiving DPT. Two started treatment 14 months ago and the remaining 5 began treatment this year.

1. Dosage

Six patients are receiving DPT and DDS. The initial dose of DPT was 1.0 gm. daily (6 days a week) with low dosage of DDS, 200 mg. twice weekly. This dosage was given for a month. It was then raised to 1.5 gm. daily and continued for three months. Thereafter, it was raised to 2.0 gm. daily. This dosage, along with 200 mg. of DDS twice weekly, has been maintained throughout.

Four patients are receiving DPT in combination with INH. Three of these patients showed hypersensitivity to sulphones and to thiosemicarbazone. After consultation with the specialist they were transferred to treatment with DPT. The fourth patient had received no treatment previously.

2. Attitude of patients to DPT

All patients have continued cheerful and in fairly good physical condition. All are satisfied with the treatment. Several who are hypersensitive to DDS and thiosemicarbazone desire to be transferred to the new drug, after seeing the promising results in the above three cases.

3. Toxicity

The drug has been well tolerated. There have been no complaints of headache, nausea or malaise. No dermatitis and no drug fever have been noted. Two patients who showed hypersensitivity to thiosemicarbazone and DDS were transferred to treatment with DPT and INH while they were still in acute lepra reaction. No untoward effects were observed. One was given Cortisone. Both recovered from the reaction and have continued in fairly good condition. Blood and urine examinations have shown no pathological changes in all cases.

4. Therapeutic activity, clinical and bacteriological

Clinical improvement was noted as early as 6 months in some cases, but after 8 months when a second report was submitted clinical and bacteriological improvement was seen in most cases. In the two cases of macular lepromatous group, the patches had faded considerably, more so than in the control patient. Two cases of the nodular group and one of the infiltrative group showed resolution earlier than did the control patients.

The earlier bacteriological response was better, as changes were noted sooner. Now, however, the bacteriological picture changes slowly and although still positive in all cases, the bacteria show degenerative changes in most cases.

5. Complications during treatment

One case of the nodular group, on DPT and DDS, developed erythema nodosum. The first attack was mild and prolonged. The second attack began four weeks ago, and was associated with neuritis of the ulnar nerve. This has since subsided. He is receiving Anthiomaline injections. The patient has been afebrile and ambulatory. DPT and DDS were continued throughout.

Another case of the nodular group, on DPT and INH, developed neuritis of the ulnar nerve, not as mild as the former. He is receiving Fantorin injections. Treatment with DPT and INH is being continued.

The patient, who was transferred to treatment with DPT because of repeated lepra reactions, had yet another reaction last month. It was not as prolonged nor of such severity as marked his previous attacks. He responded to a course of antimony injections. He is now afebrile, ambulatory, in fairly good con-

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dition and quite cheerful, whereas formerly he was always apathetic.

b. Comments

From the foregoing it will be seen that all ten patients have tolerated the drug well, apart from the three just mentioned, who developed complications. Even then, these were mild, compared to those patients who are being treated with sulphones and thiosemicarbazone. No toxic effects have been observed so far. In conclusion, it may be said that these TO patients have benefited by the use of the new drug.

6. **EXPERIENCE** AT ITU SETTLEMENT

Dr. R. Matheson

Comments on Drug Trials with DPT

There were twelve patients in all treated. Seven were treated with DPT and DDS for fifteen months, while one was treated similarly for eleven months. Dosage was—DPT 2 gms. daily and DDS 100 mgs. daily. Three patients were treated with DPT and INH for nine months, while one was treated with DPT and INH for eight months. Dosage was DPT 2 gms. and INH 100 mgs. daily. Patients seemed happy and there were no complaints about treatment.

Toxicity was nil.

All patients progressed markedly while on treatment. Those on DPT and DDS made faster progress than their controls.

There was little difference for a long time between those on DPT and INH daily and their controls. In fact the controls seemed to be making better progress. In the last few weeks the trials have been making greater progress.

There was little in the way of complications. One of the DPT and DDS groups had slight erythema nodosum after a year on treatment, but soon recovered. Another, after a year on treatment developed macules of the borderline variety and has made good progress since.

DPT has certainly proved very effective in the cases here.

7. EXPERIENCE AT UBURU SETTLEMENT

DR. A. MACDONALD

Report of a trial of DPT used in combination with Dapsone and INH.

Selection of Trial Cases

At this centre six lepromatous cases were chosen for the trial of combined DPT and Dapsone treatment, and five for the trial of combined DPT and INH treatment. All were patients previously untreated for leprosy, and all were of active lepromatous type in varying degrees of severity. At the outset all were lepromin negative.

Controls

Controls, who on first admission corresponded closely in respect of type and severity of the disease and bacterial index, were selected for each patient in the experiment. All controls had for

			TABLE I			
	I	61	З	4	, Qi	9
Name	Nneze	Nwokporo	Odum	Ivo	Nwochulo	Ori
Duration of Treatment (months)	16	16	16	15	15	6
Clinical effect of therapy	Rapid early im- provement main- tained.	Excellent response apparent after six months.	Excellent response apparent after six months.	Slow steady im- provement.	Slow, not dram- atic improve- ment.	Good, steady res- ponse.
Compared with control	More rapid res- ponse.	Much better res- ponse.	Better.	Not much better.	Not better.	Not better.
Bacteriological effect of therapy	After 6 months rapid reduction in bacilli.	Steady slow re- duction in No. of bacilli.	Steady slow re- duction in No. of bacilli.	Satisfactory.	Satisfactory.	Steady reduction in No. of bacilli.
B.I. fall Compared with control	2.7—0.3 Better response.	3.3—2.0 Better.	2.7—1.0 Better.	4.0—2.5 Parallel response	3.3—1.2 Parallel response	3.3—2.0 Parallel response
Control's B.I.	3.0-1.7	3.7-3.3	3.0-2.3	3.0-1.3	4.0-1.3	2.7-2.0

			LABLE II		
N	I	6	3	4	5
Duration of	Otu	Uho	Emmanuel	Amos	Chima
Treatment (months)	14	14	н	Q	IO
Clinical effect of therapy	Excellent rapid response.	Rapid early res- ponse.	Excellent early response.	Response evident after six months.	Good response apparent after six months.
Compared with control	More rapid res-	Better.	Better.	Not better.	Not better.
Bacteriological ffect of therapy	Rapid reduction in No. of bacilli maintained.	Rapidly became negative.	Very good.	Slow effect.	Steady good res- ponse.
B.I. fall Compared with	4.0—0.6 Much better.	2.0—0 Better.	3.6—0.7 Better.	3.0—2.4 Not better.	4.0–2.0 Not better.
control ontrol's B.I. fall	3.0-2.3	2.3—0.6 —	2.3—1.3	2.3-1.0	3.6—1.3 (in 15 months)

the corresponding period of treatment received 3 mg. oral Dapsone twice weekly.

Reactions, Toxicity, Complications, etc.

None of those taking DPT showed any dislike of the drug. (One, No. 10, absconded for reasons unknown after 7 months' treatment.) Nearly all were appreciative of the steady improvement effected in their condition. None showed any signs of toxicity due to the drugs. Only one (No. 3) showed any of the complica-

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tions of leprosy during the period of treatment; this man developed erythema nodosum leprosum in the fifth month, which was quickly controlled by the administration of Fantorin. His control, a case of very similar type, began to have frequent recurrent erythema nodosum leprosum after fifteen months with increase in the Bacterial Index and polyneuritis. Case No. 6 died of cerebral malaria after nine months of treatment.

Combined DPT/Dapsone treatment

(a) Dosage

Cases Nos. 1-5 were after 2 to 3 months gradual increase in dosage receiving 2.0 gm. DPT daily with 300 mg. Dapsone twice weekly. Case No. 6 (a girl) received a maximum dose of 1.0 gm. DPT daily with 200 mg. DDS twice weekly.

(b) Therapentic Effect

In all these severe cases the response to therapy was good excellent in cases 1, 2 and 3 as compared with the much slower response of their controls on Dapsone. Cases 4, 5 and 6 showed a response to treatment very similar to that of their controls on Dapsone alone.

Combined DPT/INH Treatment

(a) Dosage

In all cases the dosage was quickly increased to a maximum of 2.0 gm. DPT daily with 200 mg. INH daily.

(b) Therapentic Effect

This was excellent in cases 7, 8 and 9 as compared with that of their controls. Cases 10 and 11 showed a slower response not better than that of their controls.

Conclusions

All the patients treated with DPT in combination either with Dapsone or INH showed a satisfactory response to the therapy. More than half showed excellent rapid improvement which compared favourably with that of their controls who received Dapsone only. The general impression from this small series is that DPT used in conjunction with other active drugs in this way evokes a very satisfactory response both clinically and bacteriologically, and prevents residual scarring of the skin and disfigurement.

Acknowledgements

We are grateful to Dr. Davey of the Research Unit, Uzuakoli, for the opportunity of taking part in the extended trial of these drugs, and for his encouragement and advice. Mr. Drewett undertook the training of one of our laboratory assistants and we thank thank him for this valuable help. Dr. L. M. Hogerzeil was responsible for selecting the patients for DPT treatment and their controls, and we are grateful to him for his careful recording of the initial findings in each case.

THERAPEUTIC TRIALS IN LEPROSY USING SERIAL BIOPSIES Dr. D. S. Ridley

Hospital for Tropical Diseases, London

Therapeutic trials in leprosy are beset with two difficulties: (1) clinical impressions of progress are subjective, and photographs are not amenable to statistical analysis; and (2) various bacterial indices are in use which, having no mathematical basis, are inconvertible one to another; none of them reflects accurately either the clinical or the total response to chemotherapy. Neither of these difficulties was an impediment to the finding of an active drug when there were no alternatives; now that there are many new drugs to be compared with one that is proved, better methods of testing are needed, especially since the number of untreated lepromas suitable for trial is becoming limited.

The fallacy of the bacterial index of skin smears is that it reflects the density of bacilli in the leprous lesion from which it was made, but not the size of the lesion (Ridley, 1955). The point is crucial since, as can be shown by serial biopsies, response to sulphones proceeds partly by solution of the leprous granuloma (which is apparent clinically), and partly by a reduction of the bacilli therein (which is noted in skin smears), and the two processes are independent; soemtimes one, sometimes the other is predominant according to the race of the patient and the stage of treatment. It would be desirable therefore to have an index not only for bacterial density but for size of lesion; but it is not possible to measure size clinically or from smears: the whole of the leprous infiltration would have to be scraped out, spread to a uniform thickness, measured, and its area multiplied by the bacterial index, in order to determine the number of bacilli.

Serial biopsies provide the basis of an index which takes account of both size and density of the bacterial mass (Ridley, 1957). It was found that the mean rate of fall of this index in a group of lepromatous patients on sulphone therapy was remarkably constant at all stages of treatment, irrespective of the initial severity of the infection; if confirmed this observation would provide a basis for an absolute comparison of different drugs. For European and Eurasian patients on sulphones the mean rate of fall of the index in each period of 6 months was about 25% of the index at the beginning of the period. The results have since been extended and reassessed by a slightly modified system, and the rate remains the same as before from beginning to end of treatment. The progress of individual cases is erratic; the mean rate of improvement of individuals in this series varied between 18% and 40% per 6 months period. By contrast with these figures 8 similar patients on izoniazid progressed at a mean rate of 9% per 6 months; while 3 patients in the sulphone group, who were excluded from the trial because their treatment was interrupted by prolonged spells of severe erythema nodosum, made no progress: their indices fell 0.5% per 6 months. The results are given in more detail in the earlier paper.

The procedure and the methods used, slightly modified, are here described in detail in the hope that the system will be given the wider trial which is necessary to establish confidence in its reliability.

Calculation of the Biopsy Index

In sections of uniform thickness stained for acid-fast bacilli, the density of bacilli in the parts of the section occupied by leprous granuloma is estimated in much the same way as in a smear; areas of healthy dermis are ignored. For this purpose Cochrane's (1952) index has been modified in such a way that each figure represents 10 times as many bacilli as the figure below it; the scale is defined as follows, according to the number of bacilli in a field of view under the 1/12th inch (2 mm.) objective:

2 + 1 or more bacilli, on average, in 10 fields

1 + 1 or more bacilli, in 100 fields.

Sometimes the density of bacilli in different areas of one section is not uniform, in which case the density in each part of the granuloma is estimated separately, and the mean taken.

To obtain the bacterial index of the section, "biopsy index " for short, the figure for the bacterial density is multiplied by the fraction of the section occupied by the leprous granuloma. This fraction is estimated by observation of a haematoxylin-eosin section under a low power magnification: a 11 inch (32 mm.) objective is ideal; by considering whether the granuloma occupies much more or less than one quarter, half or three-quarters of the dermis, it is possible to estimate the fraction to the nearest 1/10. with fairly good agreement between different observers. Excised lesions should be divided and each half examined for this purpose. If the entire dermis is occupied by leprous infiltrate the factor is I; the theoretical maximum for the biopsy index therefore is 6.0; if the bacterial density is 5 + in a granuloma which occupies 7/10of the dermis, the index is 3.5, which is an average figure for a fully developed untreated leproma. If the initial index is 4.0 and after 6 months' treatment it falls to 3.6, the improvement, 0.4 out of 4.0, is 10%; if after another 6 months it falls to 2.4 the improvement is 1.2 on 3.6 or 33%; mean $21\frac{10}{2}\%$.

Plan for a Therapeutic Trial

Cases are selected for the trial according to the usual criteria. The only experience of the biopsy index so far has been with lepromatous cases, free from any borderline features. Although one would prefer to use untreated cases, I cannot see that any serious error would arise from the use of previously treated patients provided the trial was arranged to commence 3 months after the change of drugs. If treatment is seriously impeded for any length of time by reactions the case is excluded from the trial; otherwise reactions are ignored.

The selection of sites for biopsies is important and should be undertaken by the same doctor throughout the period of trial. The lesions chosen should be the most active that are also representative; solitary ulcers and exceptional nodules should be disregarded as comparable lesions will not be available later.

The most useful period for observations is 6 months. The published results were based on biopsies taken every 3 months; and to minimize random variation between one biopsy and another they were subsequently paired and the means taken to provide a 6-monthly analysis; even then there were many ups and downs in indices. In order to find out whether it is always necessary to base each idex on two biopsies, I have made separate analyses of the results on the basis of (I) double biopsies at 6-monthly intervals, (2) single biopsies at 6-monthly intervals, and (3) single biopsies at 3-monthly intervals. Surprisingly, whereas there was good agreement between the results based on single and on double biopsies at 6-monthly intervals (they are summarised in the table), the means of results at 3-monthly intervals, based on the same sets of indices, were discrepant; the reasons for this are made apparent later. The conclusion is that single biopsies at 3-monthly intervals are unsatisfactory, but that single biopsies at 6-monthly intervals should give a good index of progress for a drug provided (1) each case is observed for at least 2 periods, and (2) a total of at least 50 periods of observation is obtained from all cases, e.g. 20 cases observed from 12-18 months. If it is desired to obtain a result in 6 months, or from a very small number of cases, it is necessary to make a pair of biopsies in each period of 6 months. It is necessary that each biopsy should be made within I month of the date it is due.

The termination of the trial may be either by set period of time, or by cure of the cases; even in the first method some cases may become bacteriologically negative before the termination is due. As far as can be seen in sulphones the index falls at a constant rate, in a group, until bacilli are no longer to be found; but very low indices cannot be accurately estimated, and it is necessary to decide

TABLE

Comparison of Results based on Single and on Double Biopsies at 6-monthly intervals

Case	I	2	3	4	5	6	7	8	9	10	II	12	13	14 al	Mean 1 cases
Initial Index	4.5	4.4	3.9	3.5	3.5	3.3	3.0	2.5	2.2	2.0	1.5	1.0	0.9	0.8	
Previous treatment	_		_		+	+	÷				+		÷	÷	
Duration of trial in months	48	30 42	18	36	18 30	36	30	12	1.8	30	12 24	12 24	12 18	12 18	
% Mean improvement (Double biopsies)	19	26	20	$22\frac{1}{2}$	39	23	18	38	19	28	37	22	$21\frac{1}{2}$	$20\frac{1}{2}$	25.3
% Mean improvement (Single biopsies)	18	23	23	23	45	18	16	33	20	30	36	27	22	22 <u>1</u>	25.5
Trial completed (C) or incompleted (I)	С	С	Ι	С	С	С	C	Ι	Ι	С	С	С	С	С	

on some point beyond which the trial of any patient will be discontinued. If an index figure, say 0.2, is taken as the signal it will be found that the last period of observation, on average, will produce a greater fall in the index than it should, since each case will be terminated by a significant fall; to avoid this error a figure is chosen beyond which one more period of observation will be made, and the trial of that case then terminated. The procedure I have used is to wait till the index falls to 0.4 or lower and then to terminate the trial after the next biopsy, which may be higher or lower than 0.4; but if in any biopsy there are no bacilli, or the area of the lesion is estimated to occupy less than one tenth of the skin, the biopsy is discounted and the trial of that case is stopped immediately. The termination of the cases in the Table was different in many cases according to whether the analysis was by single or double biopsy; in the latter case account was taken of all biopsies (which happened to be at 3-monthly intervals), but in the analysis of single biopsies only every other one was noted and the first signal of 0.4 was sometimes missed. This explains the double set of figures in column 4 of the Table. Even so the discrepancies are not great. The trials of 3 cases were not completed: one patient discharged herself and two others were progressing when the analysis was made.

Analysis of Results

The 14 cases in the Table include all lepromas which have been observed by serial biopsy for at least 1 year. The mean improvement in all 6-monthly periods of observation was 24.3%per period. The mean of the mean rates of progress of the cases, assessed individually, was 25.3% per period (25.5% with single biopsies). The difference of 1% is accounted for by the bias in the former instance due to the fact that more observations were recorded from slow cases than from those who made a quick response; the bias, however, appears to be unimportant and the mean of this series can be taken as 25%. It would be interesting to see whether other workers with patients of different race obtain a comparable figure for sulphones. This mean is the only figure that need be calculated to determine the result of the trial; but there are some other points of interest.

Individual biopsies vary considerably, as would be expected. A simple comparison of two biopsies is never of any value. At 6-monthly intervals much of the irregularity in the movement of the biopsy index is due to the ups and downs of the patient's progress and the effect of reactions, although when the index reaches a low figure inaccuracies of estimation make their mark; in general, however, the progress of the patient outweighs other factors. At 3-monthly intervals random irregularities become preponderant and lead to curious results; an example is the progress of case 13 during the last 15 months of the trial:—

Index 0.6 0.9 1.05 0.25 0.4 Total fall, 0.6 - 0.4 = +33%% Fall -33 - 14 76 -38 Mean % fall, 76 - 85= -2.25%

It will be noticed that when the index goes up instead of down, the rise is expressed negatively as a percentage of the index at the end of the period instead of at the beginning; this usually leads to a sensible answer: 0.6, 0.9, 0.6 gives percentage movements of -33 + 33 which cancel each other, just as do the movements of the index. But in the exceptional instance given above the three negative percentages outweighed the single positive fall which was actually the greater: several small steps, expressed as percentages, outweigh one large one. This did not happen with biopsies at 6-monthly intervals.

Although the mean improvement of 25% applies to all stages of treatment, this figure does, of course, represent a greater absolute fall in the index at the beginning of treatment than at the end when the value of the index is smaller. The index is multiplied every 6 months by 0.75; at the end of I year it would be expected to be 0.75^2 times the initial figure, and at the end of 4k years (9) periods) it will be multiplied by 0.75^9 (Log 0.75 = -0.125; ×9 = -1.125; antilog = 0.075); this answer (0.075 = 7.5%) represents an improvement of $92\frac{1}{2}$ %. The formula to express the progression is $x^n = b/a$, where a = the initial index, b = the final index, x = the multiplication factor for each period, and n = the number of periods; it can be applied to individual cases or to means, and will give the expected improvement, theoretically, for shorter as well as for longer periods, e.g. if the ratio of b to a is 0.75 to 1 for 6 months, it will be the same for 2 periods of 3 months, and the factor x for 3 months will be found from $x^2 = 0.75/1$; then .75 = 0.866, which represents an improvement of 13.4% per x =3 months.

Technical Methods

No special virtue is claimed for the methods described except that of simplicity. A full description of the removal of skin tissue for biopsy is given by Khanolkar (1951), and by Freudenthal and Haber (1951) who describe also some refined histological processes.

Excision of Skin. The operator wears gloves which can if necessary be kept on the hands and soaked in dettol in between operations. The skin is disinfected with a colourless antiseptic. The part to be excised is surrounded by sterile towels—the number is reduced to one by using a towel with a circular hole in the centre. To avoid a wait for the local anaesthetic to take effect,

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Dr. W. H. Jopling, at the Jordan Hospital, Redhill, mixes hyaluronidase (1500 unit ampoule) with only 1 ml. of 2% procaine or similar preparation and injects it under the skin to be excised; the effect is immediate. A suture is inserted but not tied and the ends are carried up through the shaft of a punch; he finds that for firm or infiltrated skin a punch of 5 mm. diameter is satisfactory and its incision can be closed usually by a single suture; for soft skin overlying fat a punch of 6-7 mm. is needed, and it will require 2 to 3 stitches. Some prefer a scalpel. Whatever instrument is used it is important that the incision should extend down to the subcutaneous fat, and should be square with the skin surface, not sloping. After the incision is made the tissue is held up by the loose suture for excision.

Fixation and Embedding. The specimen is dropped into 3-5 ml. of the following mixture (Lowy, 1956): 40% formaldehyde 10 ml., Mercuric chloride 2 g., glacial Acetic acid 7 ml., water 100 ml. After about 3 hours (not more than 4 hours) the specimen is transferred without washing to about 10 ml. 70% alcohol, in which it can be kept for several weeks, and if desired despatched to a central laboratory. Alternatively, Zenker's fixative gives good results but is not quite so simple or flexible. The suture is pulled out, and the specimen divided in half; later, the two halves are embedded in the same block. Dehydrate in alcohol as follows: 70%, overnight; 90%, 2 hours; 95%, 2 hours; absolute, 2 changes of 2 hours each. Transfer to cedarwood oil overnight, wash in benzene 30 minutes and impregnate with paraffin wax at 56° C., 3 changes in 4 hours, and finally embed.

Section cutting. A sharp knife is more important than the type of microtome, and sharpening the knife is perhaps the most skilled operation of all. The best hone is a Belgian yellow stone; the best strops are impregnated with jeweller's rouge on one side while the reverse is plain or lightly oiled for finishing. A small knife needs frequent stropping. Sections should be of uniform thickness; 7μ is satisfactory.

Staining of sections for bacilli is done by the method of Lowy (1956), or Wade (1952) which is probably simpler:

- 1. One part paraffin oil in 2 parts pure turpentine, 2 changes in 15 minutes. Blot.
- 2. Lugol's iodine, 5 minutes. Wash.
- 3. Sodium thiosulphate (5%), I minute. Wash thoroughly.
- 4. Concentrated carbol-fuchsin (do not heat), 20 minutes. Wash.
- 5. Differentiate with 20% sulphuric acid (about 30 seconds), until the connective tissues are a pale pink. Do not overdifferentiate. Wash.

- 6. Counterstain (about 30 seconds) with 0.1% toluidine blue to give a pale purple-blue background. This shows up nuclei and structure better than methylene blue.
- Blot, and dry in air. (Do not use alcohol.) Clear in xylol. Mount in synthetic medium or balsam.

Two sections of each block are stained for bacilli and the better is used for calculating the bacterial density. Another section is stained with haematoxylin and eosin. Alternatively the section stained for bacilli can be counterstained lightly with Ehrlich's haematoxylin (about I minute, and no differentiation) and the same section is then used for calculating both parts of the index.

Conclusion

The technique of assessing the progress of leprosy patients by the use of serial skin biopsies, which has been fully described, appears to offer the best method available at present of estimating the activity of an anti-leprous drug.

The expected improvement factor obtained by this system for sulphones is constant at all stages of treatment because acquired resistance to these drugs by *M. leprae* is a rare event. This may not be so with other drugs.

The performance of serial biopsies need not be arduous, but requires organization; in compensation the need to use large numbers of patients is obviated. As a matter of opinion I can see no necessity to undertake serial skin biopsies and smears in parallel; after an initial examination by each method, biopsies are the most useful method of assessing progress until the patient is nearly better; thereafter multiple smears are needed as a test of cure.

Acknowledgements

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TUBERCULOID LEPROSY IN IDENTICAL TWINS J. A. KINNEAR BROWN, M.D., B.SC., D.T.M. and

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M. M. STONE, S.R.N., S.C.M.

In a general paper on leprosy, Ryrie referred to a particular instance of this disease in twins. He did not say whether they were identical twins, and from his brief description it appears that one had tuberculoid leprosy and one lepromatous leprosy. Keil wrote specifically about hereditary factors in leprosy and gave several instances of twins in contact with infection, both of whom or neither of whom developed the disease. Rotberg and others have from time to time referred to a constitutional factor which determines the onset of clinical disease and which was probably hereditary.

Twins, who from all appearances were identical, aged 10, were seen by one of us (M.M.S.) at a rural treatment village in the Teso district of Uganda, and admitted to the Kumi-Ongino settlement in July, 1957. They had already had several months' sulphone treatment, and the patches were repigmented. The initial lesions had appeared about the same time in each child in 1955. They consisted of typical hypopigmented areas. In one twin they were more extensive, involving both legs anteriorly and posteriorly above and below the knee. The other twin had more limited areas affected on the limbs and one discreet patch on the back just above the right iliac crest. Bacteriological examination was negative but a biopsy in each child confirmed the diagnosis of resolving tuberculoid leprosy: the Mitsuda or late lepromin reaction was 3 mm. in each child.

A visit was paid to their home 55 miles further north, and the various members of their family seen, together with the local chiefs who had been instrumental in calling them together. Reliable details of great aunts and great uncles were difficult to ascertain, but the following information was obtained and is regarded as reasonably authentic:—

Of the grandparents, the grandmother on the father's side had leprosy, and from the description it was probably the lepromatous type. She died **before** the twins were born.

The father had five brothers, but no sisters. One of the brothers had tuberculoid leprosy and has now been discharged after three years' treatment. The mother had two sisters, one of whom had tuberculoid leprosy. She had no brothers. There was a monogamous marriage and neither the father nor the mother of the twins had been married before. By this marriage there were twelve children, three of whom died in infancy. Of the survivors,



Genealogical Tree showing infected members of the family.

four were older than the twins, three younger. Only the twins developed leprosy, and it was of the same type.

Two interesting points arise. In the first place, in this part of Uganda the population density is approximately 90 to the square mile, or one individual to seven acres. There are no villages and each family homestead is centred in the middle of its farmland in comparative isolation. Thus, a family of ten or twelve would probably live 500 yards from its own boundaries, or at least half a mile from its neighbours' houses. Infection with leprosy in childhood in Uganda is therefore nearly always the result of contact within the family. The only family sources in this instance were an aunt on the mother's side, and an uncle on the father's side, both of whom had tuberculoid leprosy. To those unfamiliar with the country, ingenious explanations may suggest themselves of why and how two children out of nine should contact the disease, explanations perhaps more in line with the views that association with an open case is necessary for infection. It is difficult to believe, however, that the twins had any more exposure to infection than the other seven children, and as it is not customary for a household to include aunts and uncles, whatever contact took place must have been limited and not of the prolonged intimate type often asserted to be necessary. The prevalence of the disease in this part of Uganda is around 20 per thousand, and the lepromatous rate is less than 10%. In the average one open case can be found in every five square miles. The simplest explanation is, therefore, that the twins derived their infection within the family by contact with an aunt and uncle, both of whom had tuberculoid disease.

Secondly, and particularly, the interest of the disease occurring in identical twins is demonstrated in the genealogical



Tuberculoid Leprosy in Identical Twins.

tree. In three generations, only a minority contracted the disease although all were exposed to a similar risk of infection. In the third generation only two out of nine siblings have so far developed leprosy, and they the identical twins.

It has been suggested elsewhere by one of us (J.A.K.B.) that there are many anomalies in the epidemiology of leprosy. Conjugal infection is relatively uncommon-only a fraction of the children of infected parents develop the disease; the majority of people living in constant relationship with patients do not develop leprosy whilst others do so after brief or trifling contact. These anomalies are most easily explained on the assumption of a constitutional factor that is transmitted genetically and which determines whether successful invasion will take place. The occurrence of leprosy in these twins, particularly of the same type, is regarded as confirmatory evidence of this hypothesis. Patients with leprosy belong to a race within a race, they come to light as a result of contact: but those who are not infected because they never meet infection, continue to transmit the constitutional factor to some of their progeny. It is not suggested that this factor is a single gene, indeed it is far more probable that it is the presence or absence of components of a polygene. In a country so rural as East Africa where there is no herding of the population into artificial communities, this is the simplest explanation of the haphazard occurrence of patients who stoutly and rightly deny any memory of the disease within their families, and any but the most accidental contact with infected persons. In the epidemiology and aetiology of leprosy, and in the organization of control, as much prominence should be given to the hereditary factor in susceptibility as is usually given to the bacillus.

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STUDY OF THE MORPHOLOGY OF MYCOBACTERIA LEPRAE BY ELECTRONMICROSCOPY* R. Kooij, m.d.

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Studies of the morphology of leprosy bacilli have been carried out by Bishop et al.¹, Haedicke et al.², Malfatti and Jonguieres ³, Yamakoa⁴, Brieger and Glauert⁵ and by workers in India⁶. Because leprosy bacilli cannot be cultivated, the material for examination under the electronmicroscope must be obtained from lesions of leprosy patients. These lesions must be excised, minced with scissors and ground in a sterile mortar with 0.85 per cent saline. To obtain good pictures of the leprosy bacilli, this emulsion of bacilli must be made as free as possible of tissue cells, proteins, debris, etc., by repeated centrifugalisation. Lepromatous lesions rich in bacilli from patients with little or no previous treatment were first chosen for this purpose. Besides examining bacilli from lesions of untreated patients, we also examined bacilli from lesions of patients who had been treated for more than three years. Furthermore bacilli from bacteriologically postive lesions of patients with tuberculoid leprosy were examined.

It is possible, by means of the electronmicroscope, to study the internal structure of bacteria. By means of shadow casting with tungsten oxide, the surface of the bacilli can be seen.

Materials and Methods

After testing several methods, we found the following useful (mainly according to the method of Akiro Yamaoka⁺ and F. W. Bishop *et al.*¹).

A lesion, which was positive bacteriologically, was removed aseptically. It was then minced with scissors, and ground in a sterile mortar with from 3.0 to 5.0 ml. of an 0.85 per cent saline solution. After thorough grinding, it was then freed of coarser tissue particles by filtration through several layers of sterile gauze. The resulting suspension was centrifugalized for 5 minutes at a low speed. After that, I cc. of the supernatant fluid was taken and centrifugalized for 20 minutes at a high speed. Then the supernatant fluid was removed and discarded. To the sediment, I cc. saline was added and this again was centrifugalized for 20 minutes at a high speed. The supernatant fluid was removed a second time and discarded, and I cc. of distilled water was added to the sediment and resuspended by shaking. A loopful of this suspension in distilled water was placed on the specimen carrier of the Philips electron microscope and examined. A few specimens were shadow cast, with tungsten oxide showing the bacilli in a three dimensional way.

* Illustrations to this article are between Pages 32-33.

Discussion

The interpretation of the electronmicrographs is very difficult. The pictures are presented with the aim to collect more data which might further our knowledge of the morphology of the leprosy bacillus.

Figs. 1 and 3 show leprosy bacilli from an untreated patient. They are not homogeneous but contain irregular arrangements of dense material.

Fig. 2. Leprosy bacillus from same the patient of fig. 1, however now treated with DDS and Isonicotinic acid hydrazide for $2\frac{1}{2}$ years. The bacillus seems to be swollen and transparent. Many similar bacilli were seen by electronmicroscopy of this specimen.

Fig. 4. Shows a leprosy bacillus from an untreated leprosy patient in a three dimensional way (shadow cast).

Fig. 5. The leprosy bacilli are swollen and transparent. No limiting membrane is visible. The bacilli are probably held together by a substance called "gloea." This formation might be called a globus or mass. According to Denney four different interpretations concerning the structure of the globi are given. Some observers considered them to be intercellular colonies; others have considered them clumps formed within the lymph spaces, mechanically compressed into spherical or spheroidal forms; still others have expressed the opinion that the masses represent colonies of individual rods bound together as a zooglea. A fourth view is that they may be characteristic colonies growing within an as yet unidentified membrane. Denney takes the last view. Brieger and Glauert showed pictures of groups of leprosy bacilli with and without a limiting membrane. Our picture would be more consistent with the third view. Chaussinand distinguishes between an " amas " or " mass " and a globus. In the " mass " the bacilli are not necessarily arranged parallel to one another and are still distinguishable. In the globus they should lie end to end, in parallel array and are so tightly packed that it is no longer possible to distinguish them from one another. According to Chaussinand's definition our picture shows a mass. Probably we are dealing with different phases of development of the leprosy bacillus in the human being.

Figs. 6, 7 and 10 show a leprosy bacillus from a patient with lepromatous leprosy, treated with DDS and thiosemicarbazone for $3\frac{1}{2}$ years. They appear swollen and transparent. In the screen of the electron microscope similar pale swollen leprosy bacilli from those treated patients were observed. However, as can be seen in figs 8 and 9, darker types of leprosy bacilli in these treated patients occur. The leprosy bacilli of fig. 8 suggest transverse division. The leprosy bacilli of figs. 8, 9, 10 and 12 show a peripheral halo. Malfatti and Jonquieres state that the peripheral envelope surrounding the isolated bacillary **units** and **globi**, which is always observed in preparations from untreated patients, is an index of cellular vitality and consequently of the virulence of the leprosy bacillus. Our findings show that these envelopes can still be seen in **isolated** bacilli from patients treated for more than three years. Besides in the pictures of the isolated leprosy bacilli from our untreated leprosy patients (figs. 1 and 3) there is not much evidence of a halo. The possibility that the halo is caused by shrinkage cannot be excluded. However, Indian research workers report that comparable forms were seen with the electronmicroscope, the phase contrast microscope and with routine microscopy of leprosy bacilli, from the same source. Figs. 11 and 12 show leprosy bacilli in a three dimensional way from patients treated with DDS and thiosemicarbazone for 3½ years.

Figs. 13 and 14 show pictures of leprosy bacilli obtained from an untreated patient with tuberculoid leprosy in reaction. There appears to be no obvious difference from the bacilli from lepromatous patients.

Figs. 15 and 16 suggest remnants of leprosy bacilli from a patient with tuberculoid leprosy in reaction, treated for 5 months.

Summary and Conclusions

Bacteriologically positive leprosy lesions are excised, minced with scissors and ground in a sterile mortar with 0.85 per cent saline. To obtain good pictures of the leprosy bacillus, this suspension must be as free as possible of tissue cells, proteins, debris, etc. This is obtained by repeated centrifugalizing. Several micrographs were taken of shadowed and unshadowed samples from untreated and treated patients with lepromatous leprosy. Magnifications of up to 36,000 times were used. The leprosy bacilli from the untreated patients appear in most cases to possess more of the dark granular structure than do the bacilli from treated patients. The latter generally were more swollen and transparent. Micrographs were also obtained of bacilli from patients with tuberculoid leprosy. They did not differ from the bacilli of patients with lepromatous leprosy.

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LETTER TO THE EDITOR Government Leprosarium,

Makete,

The Editor,

" Leprosy Review."

P.O. Tukuyu, Tanganyika. 2nd December, 1957.

Sir,

May I submit a strong plea for caution in accepting the view expressed in your Editorial¹ that erythema nodosum leprosum is a beneficial reaction?

There are three very good reasons why these reactions should always be controlled:—

- 1. The patient is usually ill and in pain.
- 2. The tendency is for the reaction state to become subacute or chronic, with the supervention of neuritis and neuropathies.
- 3. As far as the Bantu of East Africa are concerned—and Davison² has reported this finding from South Africa most lepromatous cases satisfying the standard criteria for discharge from treatment are those who have had no, or very few, reactions; while patients who have had repeated reactions are comparatively slower to become bacterio-logically negative.

The most effective means of aborting the reaction, in my experience, is intravenous sodium antimony tartrate, given in doses of gr. $\frac{1}{2}$, gr. I and gr. $I\frac{1}{2}$ on alternate days—an old-fashioned remedy, to which over 90% of our cases respond promptly. We give alkalis and sedatives in addition.

Repeated reactions, becoming chronic, are, in my view, due to **overdosage** with oral DDS. Control is achieved, though seldom immediately, by changing over to a more slowly acting preparation, such as 50% aqueous sulphetrone by injection, or thiosemicarbazone.

Three types of E.N.L. can be differentiated:-

- I. That occurring in the early stages of sulphone treatment. This is frequently only a solitary attack, particularly if aborted within the week. I have seen several cases in which there has been a striking improvement in the bacteriological index in the first year of sulphone therapy following such a reaction, but whether it is the reaction per se or its prompt control which has been beneficial is a moot question.
- That occurring later—after one to three years' treatment which is usually repeated at intervals as short as two or three weeks. Repeated reactions are characterised by

severe constitutional disturbance, loss of weight, anaemia and general debility and misery, the coalescence of subcutaneous leproma to form painful, tender, leathery plaques, and severe neuritis involving, particularly the ulnar nerves and often necessitating surgery. Eye reactions are rare, fortunately. These cases develop a gradually lower and lower threshold of tolerance to oral DDS. On the other hand, stopping all treatment for longer than the period of the acute pyrexial phase does not prevent recrudescence. Hence the value of small doses of sulphetrone by injection, thiosemicarbazone or INH.

3. That occurring in what you, Sir, once described to me as the "last fling" of the disease. Here one finds very little systematic upset and skin smears from the E.N.L. lesions are negative or show only a few, granular bacilli. The end result is persistently negative skin smears and the patient qualifies for discharge. This is the type of reaction evoked by potassium iodine when used as a "test of cure." Its significance is uncertain.

As far as I know, there is no satisfactory explanation for the seasonal variation in the incidence of E.N.L. Here it is much more common in the coldest month of the year, July. A beneficiat reaction with such a seasonal peak of incidence is, surely, an unusual phenomenon?

On the other hand, however, there exist two classes of cases which, although in the minority, indicate the futility of dogmatism in considering this complex problem:—

- Those who have no reaction and improve considerably on sulphone therapy, but reach a stage when they stick, and remain stationary both clinically and bacteriologically. Possibly the artificial induction of a reaction has a place in such cases. I have not attempted it.
- 2. Those who, after a period of E.N.L. and neuritis, finally necessitating surgical stripping of both ulnar nerves, show marked improvement and very scantily positive skin smears, becoming negative after one year or so.

Possibly cases of this type are more frequent in other parts of the world, while those liable to develop harmful reactions are less frequent.

I am, etc.,

H. W. WHEATE.

[Comments invited from readers, please.—Ed.]

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REVIEWS

La Lepro. Official Organ of the Japanese Leprosy Association, 28, No. 2, March, 1957.

K. Takeda contributes two papers on the *endocrine-autonomic nervous system* in leprosy and the *byaluronidase spreading reaction* in relation to it. He finds an instability of the system in leprosy patients, and similarly the HSR is influenced by this system and in leprosy shows a characteristic distribution. Inhibition of the HSR was caused by injection and transplantation of ox hypophysis, by ACTH and cortisone, by operation, and by administration of ovarian hormone: insulin increased it.

K. Yanagisawa and M. Maeda, in conjunction with the workers of three national leprosaria, report on their studies on *the diluted lepromin test*. On 1,687 patients they tried various dilutions of lepromin, a half, a quarter, and an eighth dilution of the Mitsuda or Dharmendra antigen. The intensity of the reaction weakened with the increased dilutions, regardless of the type of antigen or the type of reaction (early or late).

K. Yanagisawa, N. Asami and S. Ishiwara give a first report on their work on *BCG in leprosy prevention*. They think it is effective. They studied a separate populations of school children, and found that BCG by scarification or intracutaneous vaccination could convert more than half of the total subjects to a positive lepromin carried out 8 to II weeks after the vaccination. For the first group it was 56.5% in II weeks, for the second group 77.4%in 8 weeks. They also found a high correlation in the size of the erythema in the reactions to lepromin and tuberculin.

S. Nishimura and T. Masuda report on the action of *chemo-therapeutic agents in murine leprosy*. They use the screening method of Nishimura-Isawa, which enables them to assess the action in 3 months. The agents studied were isonicotinyl hydrazones and a few antibiotics and the results were slightly better than INAH for the former and negative for the latter. Non-chemotherapeutic agents were also studied, without striking results.

K. Minami reports on his experiments in the serum reaction in *leprosy*. The agglutination method of Ogata using equal parts of cardiolipin and lecithin as antigen gave a high titre in his experience. Minami, however, finds low titres in all cases, and that 64% of all cases are positive, and among these lepromatous leprosy were positive in 75%. For other sera 12% were positive, and 9% of syphilitic sera. The author thinks there is enough positivity in the test to guide us in the diagnosis of leprosy, if we take account also of the clinical features. He also tried the slide agglutination method with antigen of cardiolipin-lecithin-cholesterol

in proportions 1/34/30 and 1/1/18 and found strong reactions but not superior to the ordinary agglutination method.

K. Takigawa reports on *statistics of leprosy patients in Japan*. From the beginning of 1953 to the end of 1955 there were 1,232 leprosy patients reported in Japan. The ratio of males to females was 1.7-2.3: I, with no difference for the lower ages. There was a higher age at which the disease showed itself, and the 30 to 44 year period was the most frequent. Most of the cases were of tuberculoid ("maculoneural") type, and most cases came from rural districts and the warmer districts. Most of the cases in the younger ages were admitted to the leprosaria, and a lesser proportion of those in the higher age groups, and the time between diagnosis and admission was very short for most patients.

East African Medical Journal, 34, 7, July 1957, is a Special Number containing the proceedings and papers of the Tuberculosis and Leprosy Conference held at Dar Es Salaam in January 1957, and organized by the East African Council for Medical Research. In default of the space to review this at the moment, attention is directed to this very valuable and stimulating number of the E.A.M.J., which devotes II8 pages to its report and the papers.