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LEPROSY REVIEW

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EDITORIAL

The VIIth International Congress of Leprology was held in Tokyo, Japan, from 12th to 19th November, 1958. Such congresses are held under the auspices of the International Leprosy Association in conjunction with a host country, at intervals of five years. The previous congresses were Berlin, 1897, Bergen, 1909, Strasbourg, 1923, Cairo, 1938, Havana, 1948, and Madrid, 1953.

This particular Congress was to have been held in India, but insuperable difficulties arose there at the last moment and the International Leprosy Association was very glad to receive a warm invitation from the Japanese Leprosy Foundation (Tofu Kyokai) to hold the Congress in Tokyo at about the same time it was to have been held in India. This gallant offer was accepted and in the event everything went very well and the unanimous opinion was that the VIIth Congress in Tokyo stood out as the most effective and enjoyable Congress that could be imagined.

Dr. E. Muir, the secretary of the International Leprosy Association, and Dr. J. R. Innes, the medical secretary of BELRA, who was acting as assistant secretary to Dr. Muir, arrived in Tokyo on 28th October, and Dr. H. W. Wade, the president of the International Leprosy Association, arrived a little later. Prof. K. Kitamura and Dr. K. Hamano of the Tofu Kyokai and their staff and members of the Japanese Leprosy Association showed an organising talent and capacity for hard work that made it certain that the Congress would be properly arranged. Also, Mr. A. Saita, the liaison officer of the Ministry of Health, was a tower of strength.

The Japanese Leprosy Foundation, or Tofu Kyokai, was founded under the inspiration of the late Empress Teimei, mother of the present Emperor. She it was who composed the beautiful Japanese ode which one finds inscribed on her memorials in every leprosarium in Japan.

"Tsurezure no
Tomo to narite mo
nagusameyo
Yuku koto kataki
Wari ni kawarite",

which can be rendered as follows in English:

"Comfort them as our true friends,
On my behalf, I beseech you,
In their day to day living,
As my presence with them
May not always be possible".

It was natural, therefore, that, at the opening plenary session of the Congress on the 12th November, Their Imperial Highnesses, Prince and Princess Takamatsu, should be present and that the beautiful ode of the Empress Teimei should be sung.

Dr. K. Kitamura was the president of the Congress with Dr. H. W. Wade as vice-president. The secretary of the Congress was Dr. E. Muir and the vice-secretary, Dr. K. Hamano. In this Congress, what proved to be a very effective system of panels and technical committees had been introduced. This meant that each subject had been considered for about a year by a small panel and at the time of the Congress extra names were added and the panel was converted into a technical committee, so that the subject was presented to the Congress and then thrown open to submitted papers and discussion on them.

Full opportunity was given to members to see something of the beautiful Japanese country and various aspects of Japanese life and to visit research institutes and leprosaria. The hospitality of our Japanese hosts will always leave a warm and gracious memory. There were 43 countries represented at the Congress, and the number of members approached 300. It was notable that scientific sessions of the Congress were fully attended.

Early in the Congress, the presentation of the Damien-Dutton award was made to Dr. H. W. Wade by the Bishop of Yokahama. This is the second award, the first being to Sister Hilary Ross, of Carville, and the ceremony was watched with the greatest of pleasure by all. The veteran leprologist and secretary-treasurer of the International Leprosy Association, Dr. E. Muir, laid down his office at the close of the Congress, and in his place Dr. J. R. Innes was appointed. Dr. Wade continues as president of the International Leprosy Association, and the three vice-presidents are, Dr. J. M. M. Fernández, for the Americas; Dr. K. Kitamura, for the Eastern section; Dr. R. G. Cochrane, for the Western section.

The International Leprosy Association received with great pleasure an invitation from the Government of Brazil for the holding of the next congress, due in 1963, and accepted it with great appreciation.

This issue contains a personal record of the Proceedings of the Congress made by the Editor, and though the record made by one man is bound to be imperfect, it will be useful to give it here in anticipation of the publishing of the full transactions of the Congress by the Tofu Kyokai.

Dr. Davey's Latest Report on ETIP, or 'Etisul'

In the therapy section of the proceedings of the Seventh Congress it will be noted that Dr. Davey gave a report, among other drugs, on ETIP. His first progress report for publication has just arrived at the time of printing. Because it will be convenient to all workers to have this information provided in the same issue which records the Congress, it will be found on page 61.

BACTERIOLOGY AND PATHOLOGY

13 NOVEMBER, 1958
9.15–12.00

Chairman: DR. J. H. HANKS

Rapporteur: DR. R. J. W. REES

DR. HANKS described the preliminary work of the Panel and Technical Committee, and reported that in *Bacteriology, immunology and pathology* there were limited contributions; but there has been progress in many ways:—

Bacteriology

1. Methods for counting bacilli have been developed and are of great value. Techniques were described by Rees, Hanks and others.
2. Cultures of bacilli have recently been partially successful. Other mycobacteria, e.g., of tuberculosis also have difficulties in cultures. Tissue cultures are more successful in *M. leprae*. Dr. Rees will discuss this. Two problems in culture: to find tissue cells of other host systems to substitute for natural ones: or to modify the nutritional or hormonal balances. Assessment of results is difficult. Enumeration of bacilli and histological assessment can be used. Microbiology and genetics and electron-microscopy are proving helpful. These must have other mycobacteria as comparison.

Pathology

Superficial nerves and skin and endothelial system in leprosy are prominent. There is an effect of bacteriaemia. Pathology is also important in prognosis and therapy. Great progress has been made in histology, using Fite-Faraco process for demonstration of bacilli in sections.

Diagnosis consists of demonstrating

(*a*) acidfast bacilli or host cell

(*b*) cellular invasion or around the nerve fibril

(*c*) histological studies for classification and prognosis

i Tuberculoid—focal infiltration of epithelioid or lymphocytic cells.

ii Lepromatous—granulomatous infiltration of lymphocytic cells not reaching into subepidermal zone.

iii Intermediate types—a mixed picture but requires more clarification.

Histology in treatment is valuable to study behaviour of cells and bacilli—an Index can be compiled (Ridley). This should be taken up by pathologists and agreement reached.

Early histology of nerves may be studied to find out if this is earliest region of invasion or not.

Lepra Reaction Erythema nodosum type, and reactional type: they are not bacillary in origin, but reaction of the body. Further study much needed.

DR. R. J. W. REES: (U.K.)

The Study of Rat Leprosy in Tissue Culture

Previous attempts at culture having failed, studies of other strains should be useful. Rat leprosy is chosen because in many ways it is similar, and *M. leprae murium* has not previously been cultured and would provide a model system. A tissue culture system is a hopeful system for growing it for many reasons. Serum concentrations should be reduced, and generation time discovered. The latter has been found to be 10–12 days (*M. tuberculosis* 24–30 hrs. *in vivo*). Bacilli may persist alive or dead and lead to error. Methods of counting total numbers of bacilli before or after culture have been developed by us.

Monocyte culture after 80 days: no multiplication but viable bacilli seen.

Spleen explants offered a hopeful method of culture and limited multiplication was shown. Addition of streptomycin to INH inhibited the multiplication.

Similar results from separated spleen cells.

Fibroblast cultures have given best results so far. The bacilli do multiply, as shown by enumerations, up to 60 days. This may be a basis for advance.

DR. HANKS said his own work coincides with that of Rees. An important point is not to count the cells but to count the bacilli. A disappointing feature is that the multiplication is so limited: an essential component still seems to be lacking and we do not think vaccines from cell cultures will ever be possible. But cell culture is a tool for analysis of many problems.

DR. J. H. HANKS (U.S.A.):

Evaluation of Physiological State of M. Leprae by Cytology

Methods of evaluation of *M. leprae* and its physiology have been developed. We first used tetrazolium compounds. The amount of pigment produced indicated metabolic activity, and could be used to say if bacteria were alive or dead. Tetrazolium was used to stain bacteria, and blue granules meant there was metabolic activity. With pathogenic species the proportion did not agree with *pathogenic activity.*

Saffranin was added to tetrazolium: *permeation by dye means no metabolic activity*, but 5% remain a mystery. Other enzymes and solvents were tried but would not modify permeability except in presence of heat. The impermeable bacteria were the active alive ones. Pathogenic bacteria do not admit the tetrazolium agent which therefore will not be useful to us.

Dyes have been studied: pathogens have a wider range of permeabilities: some produce DNA granules, especially *crystal violet*. *M. leprae* have non-permeable types to a dye at 37°C. There are great variations in permeability of mycobacteria: the saprophytic type are permeated readily, *M. leprae* very slowly. Capsulation seems an essential factor: electronmicroscope shows a definite envelope.

Use of dyes in presence of heat is therefore a useful test of metabolic activity of mycobacteria. The malachite green method illustrates this: it attacks DNA.

Discussion

DR. CHATTERJEE said: "The impermeability of the cell wall of leprosy bacilli, described by Dr. Hanks, may possibly be due to the presence of complex calcium bound carboxylic groups not only in the cell wall but also in the gloea around each bacillus. This cell wall contains oxy-fatty acid insoluble even in petroleum ether.

"However, by hydrolysis with 0.1 N HCl for about 12–15 minutes at 56°C or with N HCl for 10 minutes at 37° C, often many bacilli are rendered permeable due, probably, to the removal of some of the loosely bound calcium from the cell wall and gloea."

DR. HANKS replied. He said he found he could not stain the capsules and was glad to hear Dr. Chatterjee's contribution.

DR. D. H. BINFORD (U.S.A.):

Histiocytic granulomatous mycobacterial lesions in golden hamsters inoculated with M. leprae: negative results in 10 experiments in other animals.

He reported inoculation experiments in animals, and described materials and methods. He thinks that *M. leprae* selectively affects the cooler parts of the human body. On inoculation of golden hamsters the characteristic picture was a *histiocytic granuloma* (in histological section of testis). There was always a pattern of increased histiocytes. Some contained bacilli. One animal had a nodule on one ear: it had numerous intracellular bacilli.

Intratesticular and intra-auricular inoculations showed similar results, the histocytic granuloma.

Small nerves also showed numerous bacilli. The lesions were of slow progress. No foam cells nor globi were seen but the bacilli intracellularly were numerous. Nerves were invaded. The work will continue.

DR. K. R. CHATTERJEE (India):

Experimental transmission of human leprosy to a hybrid strain of black mice

He first acknowledged his debt to Dr. Hanks, Dr. Fite, and other workers. The root of the problem was to find a new experimental animal and to introduce some human factor along with the inoculation of the bacilli.

The animal was the laboratory crossbred black mouse, very young, 10–15 days old. He chose the black because of fancy only. After thirteenth generation only black come. He has used 106 such

animals: 6 lost, so 100 left. More than 50% took up infection by 14 months, a heavy infection.

He separated the bacilli by differential centrifugalization and counted them and gave only 1 inoculation of 20 million bacilli subcutaneously in various regions of the animal. After 6 months he found multiplication in the animals. Animals which died were examined. There were dryness of skin, loss of hair, some nodules, spleen and liver were enlarged, inguinal glands enlarged. Microscopically fuchsinophil cells in tissues were early to be found, before bacilli were seen. Later bacilli became numerous inside liver cells, and round blood vessels, in spleen (great number in spleen), cells and globi numerous everywhere, numerous in lymph glands and testis, nerves, etc. Could it be a saprophyte? Various media were used for culture—all negative. Lepromin by Dharmendra technique was tested against the inoculated bacillary lepromin and found parallel in reactions.

Inoculation of *M. leprae* to these mice thus seems to be successful.

Discussion

DR. BINFORD commented how he urged Dr. Chatterjee to come to the Congress because of importance of having a laboratory animal to which leprosy can be transmitted. He asks if the black mouse could be made available in other parts of the world.

DR. WADE. "From the reports by Drs. Binford and Chatterjee that we have heard, and of other reports by Dr. Bergel of Argentina which have been published (one of them now in press in the International Journal), it would seem that at long last there has been a break-through in the problem of producing bacillus-loaded granulomatous lesions in animals with inocula from leprosy lesions. Animal granulomas such as have been shown could not have been produced with heat-killed leprosy bacilli. Chatterjee and Bergel have reported inability to obtain cultures from their experimental lesions, and also lepromin test with suspensions of such lesions with results (negative in lepromatous cases and positive in tuberculoid cases) such as are obtained with human lepromin. These results are highly encouraging and if confirmed will mark a new phase of the experimental study of leprosy.

DR. REES commented: "I fully support Dr. Binford that every attempt should be made by instructed groups to repeat these successful transmission experiments reported this morning. With this object in mind I should say that I have, in the past four years, been occupied in attempts to transmit human leproma to mice, with completely negative results. I have used albino mice and like Dr. Chatterjee attempted to separate bacilli from the lepromatous tissue. My negative result may therefore suggest either (1) my unsuitable mouse strain, or (2) unsatisfactory separation of tissue. Could Dr. Chatterjee therefore say how important the mouse strain may be? Has he tried any other strains of mice and with what result?"

DR. CHATTERJEE replied: "I have used white, and mice of other colours but without positive results. It is the black strain only. I hope it will be possible to supply the animals to other workers interested in this type of experiment. A formal request may kindly be made to the Director, School of Tropical Medicine, Calcutta–12, India."

In reply to Dr. Rees he said: "We have often tried other animals also. Of these, laboratory-bred Syrian hamsters have been found to take up infection to some extent. The lesions generally remain localized for quite a long time after which generalised dissemination of a mild type has been observed in a small number of hamsters; only few of them showed moderately heavy infections when the animals survived a long period after inoculation. So far the number of hamsters which take such infection is so small that it does not justify any definite conclusions. It may therefore be said that till now only the black mice have been found to be susceptible to infection with human leprosy."

DR. AZULAY, Brazil asked about control groups and Dr. Chatterjee replied: "Control groups have shown negative results. Our inoculum contained 1 to 20 million bacilli only and the animals sacrificed after about 8 months and later showed the tissues crammed with innumerable bacilli, which indicated definite multiplication of the organism in them."

DR. BINFORD replied to a question on controls in his work: "Controls of heat killed inoculum were given: such showed nothing but the carbon ink in the control inoculum: no granulomatous process was seen."

DR. D. S. RIDLEY (U.K.):

Observations of prognosis of different classes of leprosy in different races

Difficulty arises in clinical estimation of progress (under treatment) of different races. There are errors even in using the bacillary index because of where one reaches in the skin with taking material for a smear, so one may miss the improvement or bias to a reading of lack of improvement.

But *biopsy* is more useful. The granulomatous part of the lesion can be identified and the bacilli counted as well, and arithmetical factors given for each of the two important criteria of progress (bacillary count and histological picture).

In different regions of the world lepromata differ and they may even differ in parts of those regions. Bacterial index also varies in typical cases. But the new serial biopsy gives fall at standard rate, *i.e.*, 25% in Europeans in 6 months; Anglo-Indian rate is the same. The other races—not enough figures are obtained yet. This all applies to leproma and there is remarkable uniformity. Histologically the estimation of the figure for the picture is quite easy and practicable. Borderline and intermediate cases are harder to estimate. Lymphocytic reaction is less in E. Africa than in W. Africa. Fibrosis in a lesion represents rapid resolution. Lymphocytic infiltration is often followed by fall in bacterial density. Borderline respond to treatment twice as fast as lepromatous: It is a matter of individual resistance.

Discussion

DR. HANKS: "Dr. Ridley's paper gives a new view, and the use of his serial biopsy index should be studied widely."

DR. WADE: "During the last several years at Culion I have been observing a nonfoamy-cell variety of leproma (which I call 'histioid' because it resembles superficially an organized tissue rather than a granuloma) which might be well represented by the slide which Dr. Ridley described so heavily infiltrated with fibrocytes. It was impossible, as hoped, to prepare a formal paper on the subject for presentation, but through the courtesy of Professor Kitamura several photomicrographs are on exhibit in the demonstration room, to which the attention of interested members is invited. The most interesting features are the spindle shape of the histiocytes, the general resemblance of the chronic lesions to fibrous or fibromatous lesions, and above all by the fact that although the histiocytes are crowded with bacilli there is—typically—no production of gloeal substance and consequently no globi or foamy cells."

DR. MONTESTRUC: "In Martinique the lepromatous cases do show a fibromatous element in histology, in cases which respond very well to sulphone treatment."

DR. HANKS: "Afternoon session will be at 1 p.m."

BACTERIOLOGY AND PATHOLOGY

13 NOVEMBER, 1958
1.20 P.M. TO 3.30 P.M.

DR. C. C. SHEPARD (U.S.A.):

Tissue Culture of Mycobacterial Pathogens

Various tissue cultures and techniques are described. Serum content (horse serum 10 or 11%) is used to make the virus techniques suitable for bacteria, on the monolayer system. Intracellular growth rates bear a direct relation to the growth rate of the species in culture. Work on *M. leprae* was inconclusive.

DR. R. F. NAYLOR (Uganda, East Africa):

Study of Action of Sulphones on the Metabolism of Mycobacteria

He conducted studies on *M. phlei* and *M. ranae* of DDS by tissue respiration. The results show only a modest depression of oxidation of substrates and little effect on growth. There is a bacteriostatic effect but no bactericidal effect. Production of PAB by the bacteria antagonizes action of sulphones. There is no evidence of sulphone-resistant mutants.

Resistant forms do not readily arise.

Dehydrogenase activity as index of viability as shown by Hanks was tried in some experiments with *M. leprae:* it was found to be present and to persist a long time under treatment.

DR. J. R. MCFADZEAN AND DR. R. C. VALENTINE (Malaya):

An attempt to determine the morphology of living and dead mycobacteria by electron microscopy

Studies on *M. leprae murium* and *M. leprae* by the electron microscope showed electron-dense bodies with an almost uniform electron density. These were untreated. The treated forms showed shrunken cytoplasm and empty cell membranes. Thus viable forms can be distinguished.

DRS. R. J. W. REES, R. C. VALENTINE AND P. C. WONG (U.K.):

Electronmicroscopic appearances of mycobacteria

They studied mycobacteria to confirm McFadzean's observations (in previous paper). For tubercle bacilli the same appearances were found and correlated with viability. There are 3 types, normal, degenerate, and segmented. The difference is based on the internal structure as seen by the electron microscope. The same was found with *M. leprae murium* and with *M. leprae* obtained from lepromatous tissue. The segmented form is referred to by some as spores, but no evidence of life was found in their experiments. They gave INH as therapy and found 73% degenerate (13% in untreated): later the degenerates rose to 95%. They use this in tissue culture systems to detect living and dead bacteria.

DR. S. OKADA (Japan):

Murine leprosy bacilli in electron-microscopic studies

He studied untreated bacilli, stained bacilli, those treated with chemicals or ferments, also ultra-thin sections of murine leprosy cells and bacilli.

He found that *M. leprae murium* has cell wall which is 10–20 mμ in thickness and a cell membrane, at least in part. There are also some granules which are electron-dense and may be mitochondria. The density increases at a zone of apparent cell-division. In the cytoplasm there are also microgranules 14 to 20 mμ in diameter, which can be isolated by centrifuge. These granules contain DNA and protein and are gram-positive. He thinks these microgranules are minimal structural units, and have chemical activity and produce the gram-positivity.

DR. S. W. A. KUPER (U.K.):

Skin reactions to lepromin and tuberculin: effect of BCG on histology

Tuberculin and lepromin tests in large series were done. In 105 healthy and 52 with lepromatous, etc., no correlation was found, but in tuberculosis a distinct correlation between the 2 tests was found In histology of lepromin injections in 150 patients there is only histiocyte proliferation in the lepromatous, but tuberculoid cases show a characteristic lymphocytic infiltration, often along with giant cells and tubercles. One could classify the disease quite well from the histological picture of the lepromin reaction.

BCG was given to see if it altered the reactions to lepromin. There was nothing much in normal subjects and tuberculoid cases, but in lepromatous leprosy 22 out of 30 patients showed an altered response, in the shape of a distinct trend towards the lymphocytic type of reaction, which suggests that a systemic immunological response had been elicited. The sensitivity to lepromin is a lymphocytic phenomenon.

Dr. Kuper and Dr. J. Robert May demonstrated their technique for the detection of Acid-Fast Bacilli by fluorescence microscopy. The equipment was set up in a demonstration room of the Congress and Dr. Kuper showed the results and described the technique. They use auramine-rhodamine. The bacilli appear brilliant orange in colour.

DR. Y. HAYASHI (Japan):

Phagocytosis of leprosy bacilli by leucocytes of leprosy patients, and phagocytosis of other acidfast bacilli

This study was to find out if leucocytes from leprosy patients have specific phagocytic power on leprosy bacilli. The results were obtained on 141 patients of all types of the disease and 20 healthy subjects. *The leucocytes from lepromatous* patients were found to be the strongest in phagocytosis (70% of an average), and least in polyneuritic (neural) patients, in whom it was 42.8%, and intermediate in tuberculoid patients (60.5%). In normal subjects the phagocytic activity was much weaker than in leprosy patients.

In an experiment with non-pathogenic acidfast bacilli, the lepromatous patients again were found to have the highest phagocytic activity, with tuberculoid and 'neural' least.

These findings can be useful to help in diagnosis, and are of interest in immunology.

DRS. T. YAMAMOTO, N. NISHIURA, N. HARADA AND T. IMAEDA: (Japan)

Electronmicroscopy of lepromatous and tuberculoid lesions

Ultrathin sections of lepromatous and tuberculoid lesions were made from skin and peripheral nerve trunks. In the lepra cells there were opaque droplets and foamy spaces between them; this leads to the 'foamy cell'. In tuberculoid lesions, in early stages of the reactional lesions, there are a few small opaque droplets in the phagocytes loaded with leprosy bacilli. The bacilli look identical in both tuberculoid and lepromatous leprosy. In tuberculoid leprosy the bacterial cell membrane is broken down, and mitochondria and microsomes escape from broken cells into the extracellular body fluid. In peripheral nerve trunks the Schwann cells seem to be active and bacilli lie in the endoneural spaces. There is Wallerian degeneration, tubercle formation, and bionecrosis in the nerve trunk, and necrosis. The electron transparent zones around *M. leprae* are a kind of biostabilizer for the bacilli.

DR. TOMOSABURO OGATA (Japan):

The Disease Types of Leprosy Studied from the basis of experimental pathology

Lepromatous lesions show a reaction similar to that of a foreign body; the tissue action is similar to that from a small foreign body. When the bacillary toxin escapes, we get the tuberculoid picture. The body resistance is always weak but stronger in tuberculoid and there are intermediary cases.

DR. P. BRAND (India):

Association between damage from leprosy and temperature

Dr. Binford's observations in pathology correspond with Dr. Brand's findings in surgical pathology. The author took many biopsies and studied tissues. Every tissue is affected by leprosy, except perhaps muscle. First comes infiltration, then granuloma. This process does not occur in infected tissues which are deep and away from the skin, even by a few cm. The maintenance of constant body temperature also seems to protect against infiltration and granuloma. Parts of body subject to cooling are those most subject to damage. On a tendon, macroscopically the damage looked like a fungus growth and would not be on the deep surface of the tendon but on the upper surface of it. Also where tendons cross, the deepening from the surface protects from infiltration. Some nerves never get paralysed, those that are deep, away from the surface of the skin, but the true criterion is that of infiltration. This occurs according to vertical distance from surface of skin. Another factor is ischaemia following infiltration of bundles of fibres: so thickness comes into it: a thick superficial nerve is more liable to be paralysed.

DR. JIRO MINATO (Japan):

Peripheral nerve involvement in upper limbs of leprosy patient (clinical)

The distal peripheral nerves are most often affected in sensory changes and most often the median nerve. Most motor paralysis is found below elbow and wrist. An order of frequency is given for thumb and hand paralyses and of individual flexors and extensors.

DR. GAY PRIETO AND DR. F. CONTRERAS (Spain):

Classification of Disability

They were surprised by lack of data of percentage of patients with deformities, so they attempted a classification on patients in Spain. This sort of information will be useful in evaluating the campaign. They had 3,600 patients under this sort of review and classified them according to disability. In 1,877 patients they found 40.8% in hospital. There was 53% disabilities in the hospitalized, this much less in those not hospitalized. In French West Africa there is a classification, such as perforating ulcer, loss of vision, etc. In our cases, mutilations were 25% in men, 15% in women (in the first grade of our classification). The significance of mutilation is obvious. The cost of dealing with them would be great everywhere. Even after eradication of the disease, there would be plenty of mutilations to be dealt with. We should think of this task.

DR. J. CHARDOME AND DR. M. LECHAT (Belgian Congo):

Arteriography of the feet in mutilated cases of leprosy

They found in mutilated cases of leprosy states of arteritis, arteriovenous communication, or arteriolar spasm. The drugs hydergine and priscol were effective. The conditions occur especially after prolonged sulphone therapy. It seems mutilation goes on in spite of sulphone treatment. The earliest sign seems to be decrease in blood flow, as shown by filiform appearance of the arteries.

DR. T. V. BANG AND DR. N. D. TEIP (Veitnam):

Arterial angiography in perforating ulcer

They have done 45 arteriographies in perforating ulcer. They found 43 with normal clinical pictures. For the artery in the abnormal cases, there was incomplete obstruction; or constriction of the calibre of the artery or distension of same; or enlargement of the collateral artery.

DR. S. LAI (Taiwan):

Experimental transmission of human leprosy to monkey by frequent long-term implantation

His first report on this work was in *Int. J. of Leprosy*, Vol. 23, No. 1, 1955. He now reports on lepromin reaction, bacillary examinations, sensation tests, and X-ray of the bones. This is all quite similar to human leprosy.

DR. J. H. HANKS (U.S.A.):

Enumeration of M. leprae for the standardization of lepromin

The author has devised an easy means of enumerating bacilli in lepromin. The bacilli must first be declumped and dispersed without protein precipitation or destruction of bacilli. This can be done by flowing 0.02 ml of chloroform beneath 0.2 ml of aliquots of well shaken lepromin: shake vigorously for 3 minutes. Then add 1% serum in water and use a standard platinum loop to transfer to clean slides in small droplets in rows. They are dried, formalized-stained, counted and assayed.

The Chairman, Dr. Binford, suggested discussion can now begin in the final few minutes, or comments be made on previous papers.

DR. ROLLIER (Morocco) congratulated the authors of the papers on arteriography and thinks they will lead to significant discoveries, and to linking up with other arterial diseases and to finding a treatment for perforating ulcer.

DR. K. R. CHATTERJEE(India) commented on Dr. Naylor's paper. Chatterjee used Kedrowsky bacillus and found the same result of bacteriostasis only. Also osmium fixation for electronmicroscopy he suggests. He suggests Sudan 3 technique in demonstration of lipids.

Dr. Chatterjee continued: "As far as the excellent paper by Drs. Prieto and Contreras is concerned, I would like to point out that in India proper classification with gradation of deformities in leprosy has been in practice for a long time. Epidemiological studies have shown that such types constitute about 5 to 10% of the total number of leprosy cases. In presulphone days occurrence of such deformed cases was more common especially in leprosaria, and progress of these could not be checked satisfactorily. But nowadays cases receive treatment before the development of deformity."

DR. REES (U.K.): "Dr. Chatterjee suggested osmium was a better fixative than formalin for looking at bacteria in the electronmicroscope. Our experience and we have compared them both, is that they are equally good for fixing whole bacilli. In fact for this work no fixative is really required for looking at freshly recovered organisms. We use formalin in order not to contaminate the apparatus with a potentially virulent organism. On the other hand addition of formalin is essential if leprosy bacilli cannot be worked at soon after recovery from the tissues in order to 'fix' the state of the bacilli. Without formalin the bacilli will transform to the degenerate form."

DR. BRAND (India): "It is important to distinguish arterial changes that may lead to ulceration, from arterial changes that result from ulceration and consequent scarring. In most ulcerated feet there is already a loss of sympathetic nerve and therefore a vasodilation. The loss of blood supply is likely to be due to local mechanical factors such as scarring and chronic oedema."

DR. BINFORD closed the meeting at 4.30 p.m. and thanked members for papers and cooperation in timing of papers.

THERAPY

14 NOVEMBER, 1958
9.30 A.M.

Chairman: DR. J. M. RODRIGUEZ

Rapporteur: DR. T. F. DAVEY

DR. J. M. RODRIGUEZ (Philippines):

Relapses after sulphone therapy in lepromatous leprosy

There is a great need for a follow-up of treated cases, but data are hard to get. Prejudice of the public often hinders getting a follow-up. Relapses are very important, especially in comprehensive mass treatment schemes. Plans should be included to check relapses. The question of the duration of the treatment is bound up with knowledge of relapses. The relapse rate should be calculated each year, and the campaign guided by that. In Philippines sulphones were not in general use until 1952. Follow-up began in 1955. Relapses in arrested negative cases:in Culion 1955–58, 469 negative cases had 29 relapses. Most cases were advanced lepromatous. The longer the periods of negativity, the less the relapses. Each country should undertake study of relapses like this. In another leprosarium in Philippines there were 15% relapses over a duration half that of the Culion observation. In 3 other sanatoria of 1,382 patients: out of 80 negatives only 3 relapsed after ½–1 year. The longer the treatment, the less the relapses. Follow-up should be for long periods. In clinic patients among 101 negatives there were only 3 relapses, patients who had taken irregular treatment.

Taking these data as a whole, there were only 4% relapses.

It is hard to make a good study unless by a full time leprologist with adequate staff.

The earliest study of relapses is by Erikson at Carville, who found 45% relapses in short-treatment cases. Also Lowe in E. Nigeria found 0.8% of relapses up to 5 years. Lowe had a larger group and different length and periods of treatment, and the disease is milder in Nigeria: neural involvement is greater.

A minimum period of 5 years of treatment by sulphones seems to be indicated.

Discussion

Dr. T. F. DAVEY (E. Nigeria): He met Dr. Rodriguez at Cairo Conference and acknowledges his inspiration and help. He has been studying follow-up and summarizes as follows:

1. Criteria for discharge are rigorous—repeated negative smears for 1 year and no neural symptoms. For non-lepromatous, negative smear for 1 year and no symptoms.
2. 631 discharged 1949–1958 and 90% were seen up to 6 m.; 80% up to 1 year, and 42% up to 2 years after discharge. Many kept on coming after this.
3. In these 9 years, 36 cases of relapse (6% of all discharges). Of these 9 arose more than 2 years after discharge. Up to 2 years relapses were 10%.

4. Relation to type: Lepromatous show rare relapse, dimorphous show common relapse (some of Lowe's cases were borderline);
more relapse among borderline than lepromatous;
tuberculoid with many lesions relapse quite a lot, whether major or minor.
So the sinister group is the borderline.

5. In relation to treatment.
19 relapses in 412 cases: 3 had inadequate treatment: exclude these: this leaves 4% relapse rate.
after thiosemicarbazone in 41 cases there was 22% of relapses—an unsafe drug.
DDS plus thiosemicarbazone in alternation—out of 171 cases only 5 relapses, the best results so far: may be factor of alternation of drugs.
in relapse, puberty, lactation, and malnutrition have been prominent conditions.
in therapy, regularity of treatment is the most important factor (600 mgm per week).

6. Study of outpatients shows similar results (injection of DDS has a bearing here).

DR. S. TAKASHIMA (Japan):

Sulphone therapy in Aisei-en

Dr. Mitsuda was first director. All the regular drugs have been used: DDS, etc. Comparative studies have been made.

Clinical findings *on DDS* up to 1958: graded by nodules: showed 72% much improved. The diasone group was much the same and somewhat less than in Doull's cases (1952). Studied from cutaneous lesions and nerve lesions, the former are a better index. Lesions other than skin lesions also are much improved; keratitis, corneal leproma; perforating ulcer to some extent, but lepromatous ulcers of the body are soon improved.

Bacillary findings were by Doull's criteria: an index was worked out. The results were good, a five-fold improvement in 7 years. There have been a few complete negatives.

Histological findings showed regression of the tissue reaction which was steady in all types, but with tuberculoid some scarring, degenerated nerve branches, and atrophy of sweat glands.

Lepromin test was used in 430 lepromatous for 2 years (Mitsuda and Dharmendra antigens were used). There was a high proportion of conversions of lepromin to positive. There was an increase in negatives in 5 cases so a weakening of resistance must have occurred in these, in spite of arrest of the disease. A longer period of observation is needed in this matter.

Lepra reactions appeared in early stages of therapy by sulphones. We do not know if they are beneficial or harmful. They interfere with the therapy.

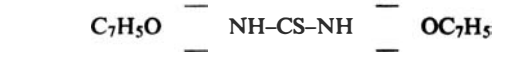
Anaemia: there was no marked anaemic effect resulting from the 5 years of sulphone therapy.

Discussion

DR. HAYASHI (of the National Leprosarium, Tama Zensho-en, Japan), commenting on clinical observations of some new diphenyl-thiourea derivatives, stated: "Ten years have passed since promine was first used for leprosy treatments in our leprosarium. There are, however, some patients who became resistant to the treatment in the course of sulfone therapy.

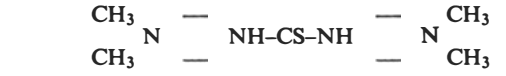
"Clinical trials of some new diphenylthiourea derivatives synthesized at the National Institute of Leprosy Research, Japan, are being carried out for such promine-resistant and non-treated patients, although these are small in number.

I. On diethoxydiphenylthiourea



Clinical experiment on this compound has already been reported by Professor Buu-Hoi and others. In our four cases, patients are given daily dose of 0.5–2 g. Skin eruption disappeared and the bacilli decreased in number without appreciable side effects on the liver and hematopoetic functions.

II. On di-(dimethylamino)diphenylthiourea



O.5 g of this compound is administered daily to four patients. Those cases responded favourably without side-effects.

III. On the dichlorodiphenylthiourea

In three cases at the Rakusen-en leprosarium, the administration of this drug was given up owing to the development of side-effects, particularly disorder of liver function, anaemia and cyanosis."

DR. OJIMA (of Japan): "Of 85 cases on promine for 5–10 years 15 cases have shown new growth of nodules (m 3.9%). The dose was lower than the usual dose. They were given 5 cc daily doses of promine. In treatment with lower doses there are exacerbations."

DR. DHARMENDRA (of India) was interested in conversion of lepromin test during treatment and asked for findings of other workers.

DR. RODRIGUEZ: "The explanation may be that Dr. Takashima is using 3 mm reading as a positive."

DR. K. R. CHATTERJEE (of India) said: "In India we use Dharmendra's refined lepromin, to note early reaction (24 hrs. and 48 hrs.) A positive lepromin reaction is indicated by erythema 10 mm or more and induration 3 mm or more. In our experience we have seldom come across positive lepromin reaction in lepromatous cases showing improvement under sulphone therapy, who were lepromin negative at the outset of treatment."

DR. H. W. WADE (of Philippines) says the point is an important one. Dr. Takashima's figures on positive lepromin findings seem too incredibly high. He has reported 80% positives in lepromatous after treatment.

DR. BECHELLI (of Brazil) referred to the histology and is surprised at the results in Japan.

DR. BACCAREDA-BOY (of Italy): "Our work shows few positives in lepromin conversion, very few."

DR. K. R. CHATTERJEE: "A recent unpublished report of a Japanese worker showed that Mitsuda reaction, recorded at the end of third week, gave positive reading in cent per cent of tuberculoid and 42% of lepromatous cases. It is probably due to the material obtained for the preparation of lepromin, or to the preparation technique itself. It may, however, be possible that lepromatous cases under sulphone treatment are gradually changing their tissue reactivity which may be responsible for such high percentages in lepromatous cases."

DR. GUINTO (Philippines): "Dr. Takashima's figures are really high, but it may be a matter of the lepromin. By concentration a high number of positives can be obtained, even in previously negative cases."

DR. R. MIQUEL (of Thailand): "May we record similar contradictory 'L-T-result' shown between lepromatous cases under DDS therapy in the Thailand leprosy programme as these being shown in Japan. Our L-Tests have been done with Dharmendra antigen among 300 lepromatous cases who received DDS therapy for 1–2 years. But the lepromin reading has not included the early Fernandez reaction because of the obvious difficulties arising in the rural domiciliary schedule of our WHO-assisted project of Thailand for follow-up of that kind of research test."

DR. TAKASHIMA (of Japan): "I used all accepted criteria in the test but it may be due to the antigen. The problem needs investigation."

DR. T. F. DAVEY (E. Nigeria):

Progress with New Anti-leprosy Drugs

He described type of patient and set-up in E. Nigeria. There is heavy leprosy prevalence but great cooperation and interest from the people. They subscribe money to the campaign. They come early. Florid lepromatous cases do occur but are comparatively few. Previous dimorphous condition leads to lepromatous by evolution in our area.

In drug trials we had very good results with DDS, but we found some intolerant to DDS and we wish to shorten the period of treatment. Our patients willingly serve as "guinea-pigs" and we only try drugs in strict laboratory conditions, and the new drugs for pilot trials must be assessed beforehand on animals. We use as many safeguards as possible to avoid bias. Histology and photography are not to be relied on by themselves too much. We put major reliance on the bacterial index of smears at multiple sites, with a good experienced technician in full charge, who is unaware which treatment is being given; he is supervised by the doctor if necessary. Control groups are used in all cases: it suffices if we use the standard expected of DDS as a basic control. Randomization does not work for a long-term trial: so we have built a standard DDS treatment graph for a large group over many years, a minimum of 4 years and with regular smears every 3 months (a graph was shown of this standard, based on bacterial index). We also record type of bacilli as well as number. The proportion of degenerate types can be estimated, and can be entered along with bacillary index on a chart of the body. The progress of the patient can be compared with the average of the group. The number of normal bacilli diminishes consecutively, along with decrease in total number.

REPORTS ON 3 DRUGS

1. Ciba 1906 or DPT:

Widely tested in Nigeria over 3 years 9 months, 200 patients have had the drug, some in combination. Found it a very valuable drug

almost free from toxicity, action like DDS or sometimes better. Graph shows that up to 33 months it follows DDS curve but is more active than DDS in first 6 months. But in 4 patients some signs of exacerbation have been noted, which may mean drug resistance. Twice-weekly dosage not so effective as daily. It is good in neuritis and psychosis. Combines well with DDS. Mild hypothyroidism in 2 patients. Daily dose is needed. It is full of promise and needs further research.

2. DDSO, first studied by Buu-Hoi

After 11 months to 33 months on 400 mgm daily in 49 patients its action is as good as DDS. In some cases, very good results. It is potentially toxic on skin, liver, and kidneys. It is effective in twice weekly doses (600 mgm twice weekly).

3. Diethyl dithiol isophthalate: an oily substance derived from ethyl mercaptan

Effective in tuberculosis in mice (Davies and Driver): is absorbed by macrophages and is effective inside them. Cannot be given by mouth—causes abscesses. It can be given in an ointment by inunction. Most cases show rapid change in the bacilli in morphology.

DOSE: 3 cc twice weekly. Some surprising results. A rapid fall in bacterial index to 0 in four months in one borderline case occurred. Much variation occurs in action. This drug ought not to be given alone for drug resistance appears in 3 months. By adding DDS or DPT the progress is much better than average: we have used these in early stages as additions. This new drug could be used as initial therapy and with the hope of shortening total periods of treatment.

Photos shown of patients on this new drug, which demonstrated remarkable clinical changes in a short time.

DR. P. BRAND (India):

Treatment and Prevention of Deformity

This does not always need a surgeon: preventive measures can be used by anyone. Most leprosy deformity can be prevented. Hands are deformed and damaged in 5 different ways:

1. Damage from wounds received by anaesthetic hands in daily occupations, such as wounds from tools, burns, pressure of wooden handles, etc. Burns may be due to holding hot cups of coffee, or in cooking, or in smoking cigarettes. Thorns get buried in the fingers, so inspect the hands. Rats eat the fingers, so keep a cat.

2. Lack of pain leads to continued harmful use of the damaged hand: so inspect anaesthetic hands frequently. Sepsis in such hands s very destructive. Every single wound should therefore be splinted n addition to the ordinary dressing, for every anaesthetic limb.

3. Improper degrees of force, unrealized, cause subcutaneous damage. The force of the grasp is perceived in the skin, by pressure on the skin (not on the muscle spindles, as taught wrongly by the physiologists). The pressure force reaches 4 or 5 times the normal in those with anaesthetic skin, without correction by the person. Another trouble is the finger-tip holding-grip in anaesthetic hands: they carry things with finger tips. So huge forces come to be applied to small areas. Educate the patients about these things and inspect hands. All tools should have large handles.

4. In dimorphous leprosy the bones become very fragile in the subarticular cancellous bones of the fingers, with osteoporosis and absorption. Fracture and crumbling occur from the most trivial injury. Recalcification can take place after the acute phase if the bones are protected during lepra reaction and certain stages of dimorphous leprosy. The coconut splint is very valuable during such phases, and should be worn for a while.

5. Disuse can lead to damage. The patient gets discouraged by loss of normal work and does no work at all. Secondary changes take place, contractions of skin, tendons, soft tissues, joints. Joints sometimes subluxate. To prevent all this teach a daily routine of use of the fingers, including an inspection of the hands back and front, rubbing the hands with vegetable oil or lanolin, moving the fingers passively through whole natural range, exercises for special muscles, splinting the hand in the over-corrected position to the contraction to encourage return to normal. The last can be done by plaster of paris splints of overcorrected state. Reconstructive surgery can restore many of the worst results which were not prevented (but could have been). These matters have a high priority in thinking for the sake of the patient.

Discussion

DR. K. R. CHATTERJEE (of India): "Dr. Brand's paper on the prevention of deformity in leprosy is very instructive.

"I wish to enquire whether the coconut shell splint for the fingers can be replaced by a tennis ball which has a downy feeling and would provide some slight movement of the fingers.

"Regarding the preventive treatment of destruction of nasal septum we obtained good results with 1% iodised hydnocarpus oil. Swab soaked in the iodised oil is kept in each nostril twice daily about half an hour each time. This gave very satisfactory results in the prevention of destruction of nasal septum. We consider this worth trying elsewhere."

DR. G. L. FITE (U.S.A.) says Dr. Brand has brought out an important point, the interest and education of the patient being so highly necessary; also deformities in limbs are parallel with mental deformities, and these can be avoided as well by education.

DR. WARDEKAR (India): "Leprosy workers in India have become conscious of Dr. Brand's work and we have now started a training programme of lay workers in physiotherapy of leprosy. We believe that the best way of giving this information on care of hands and feet to larger numbers of patients is to utilise trained para-medical workers."

DR. BRAND replied: " The tennis ball is good, like the coconut splint: *rest* is the principle. The physical state is parallel with psychical state, and attention to the former might prevent damage to the latter."

THERAPY

14 NOVEMBER, 1958
1.30 P.M.

Chairman: DR. GAY PRIETO
Rapporteur: DR. J. CONVIT

DR. K. SCHMIDT (Switzerland):

Thiocarbanilides, a new class of chemical compounds in leprosy

He showed slides of a selection of thiocarbanilides; Compound 1906 was especially interesting. He studied absorption and excretion. Radioactive labelled material was used in rabbit and dog (slides of preparation shown).

Maximum blood concentration is reached soon after injection and remains for 24 hours. By mouth, 3 to 6 hours are needed for maximum concentration. Urine concentration is maximum in three hours after I.V. injection.

Distribution in organs. After I.V. injection it was found in wall and lumen of intestine, so part is excreted per intestinal wall. The same occurs if given orally.

Bile concentration. After subcutaneous injection 40% is found in urine and faeces. There is no evidence of a cumulative effect in the tissues.

Most important findings: Absorption occurs after oral administration. Metabolites in bile and intestinal wall are found. Metabolites in urine are found.

DR. R. L. MAYER (U.S.A.):

Antituberculous and antileprosy activity of Ciba 1906

The study was started in 1941; he found antifungal and antimycobacterial compounds especially among the thioureas. Various selected thioureas were chosen (formulae shown). The antituberculous *in vitro* activity varied. The *in vivo* activity more or less corresponded. The evaluation was in mice. Compound Su-1906 was by far the most active. It was 40 times more active than PAS, and twice as active as streptomycin, but less active than INH (in mouse experiments). Resistance emergence was much slower than for any of the other antituberculous compounds.

DR. E. DEL PIANTO (Italy):

Thioethyl compounds in therapy of leprosy

DDS is too slow so other compounds may be sought for. Sodium ethyl thiosulphate (ET) has been used by us in pilot trials. An easily breakable ethyl-thio group is essential for therapeutic activity in leprosy. There were 33 patients of 3 groups of 11 patients. One group received 1.2 g. of ET daily, another had DDS added, and a third had DDS alone. All patients treated with ET had very good improvement. The total daily dose by mouth was given in pills, for 6 days each week. For combination with DDS the dose of each was smaller.

Ethyl mercaptan is the active part of the molecule: the drug is broken down in the liver and lung. Toleration was very good, even for a patient with previous hepatitis. There was no complaint of garlic smell. There were no complications. In the combined group leaving out ET led to intense itching and irritation on DDS alone. On the group with DDS alone there were 2 cases of lepra reaction. Gamma globulins fell on treatment with ET. The period of trial was 1 year. This drug ET is effective, safe and quicker than DDS. Electrophoretic analysis of sera confirms its activity.

Discussion

DR. FERNANDEZ (Argentine): "I congratulate Dr. Davey for his interesting paper about 1906 Ciba compound in the treatment of leprosy. We have been trying this drug for two years in a group of 40 patients of L. and I. type. We have observed good results from the clinical point of view. Tolerance was good in every case. We shall publish the results of our experience very soon."

DR. W. H. JOPLING (U.K.): "It is very encouraging to hear of Dr. Davey's good results with the diphenyl thiourea compound, Ciba 1906, especially as it is so remarkably free from toxic effects. His reference to the 4 patients who appeared to develop resistance at about the fortieth month is important, and all of us who are using this compound must be watchful for this positive development. I am finding Ciba 1906 of particular value in patients in the borderline (dimorphous) group who suffer from severe neuritis when given DDS even in small doses such as 25 mg twice a week. Such patients would be certain to develop deformity (such as in the hand) if DDS were continued. On changing to Ciba 1906 these patients have had no recurrence of neuritis.

"Regarding DDSO, I would urge that no further time be expended in investigating new sulphone compounds (apart from the important task of finding a long-acting sulphone for intramuscular injection). Experience with sulphones to date has shown that there is little to choose in effectiveness between the many sulphones which have been used in leprosy. It is more important that those of us who have facilities for therapeutic research should concentrate on compounds with a different chemical structure, or on such compounds in combination with sulphone. In this respect we need more observations on Ciba 1906, and I would like to see a trial of the Swiss drug Vadrine on which I published a preliminary report, in conjunction with Dr. Ridley, in *Leprosy Review* of July of this year. Especially I would like to see a trial of Vadrine combined with sulphone, for the five patients I have been able to place on this combination appear to be making very good progress.

"Dr. Davey's reference to ethyl mercaptan is most intriguing. To be able to get a significant fall in the Bacterial Index within 3 months is something entirely new, but it seems that resistance develops after this short period of treatment. I would like to ask Dr. Davey if he has any patients who have proved disappointing on mercaptan therapy."

DR. MIYAZAKI (Japan): "Photosensitizing dye stuffs in leprosy are also of value. They stimulate all body cells and strengthen resistance. Dose is small, 1 mgm daily, in a course of treatment limited to 2 weeks. They may aggravate the condition if given too long. They can be a main treatment of leprosy, or an adjuvant to other drugs."

DR. DHARMENDRA (India): "We used Ciba 1906 in Chingleput, 12 cases and a control group under DDS, all untreated lepromatous. Trial now has lasted one year, and I confirm Dr. Davey's results in general. But a few cases worsened in both groups. It compares with DDS but is so far not superior to DDS."

DR. RAMON MIQUEL (Thailand): "Whilst we have not carried out so far any therapeutic trial with ET or DPT, we have a lot of experience on INH, and therefore we object to Dr. Pianto's statement that INH is ineffective on leprosy. Both Dr. Dharmendra, and ourselves in Thailand, have tried and experienced

INH *alone* as a most effective anti-leprosy drug with particularly favourable action in the general and clinical status of the patient, and with selective application on reactional phases and intolerant cases to DDS during at least 6–12 months. INH is also particularly effective, without developing bacteriological resistance, combined with Dihydrostreptomycin. In this connection, Dr. Rodriguez, recently, has reported in the International Journal of Leprosy a most favourable therapeutic trial with INH and Dihydrostreptomycin in a selected group of Philippines patients."

DR. MAYER (U.S.A.): "One point: all sulphur containing compounds found since thioureas have apparently similar mode of action. It appears that the resistance between them is interchangeable. So if resistance develops, do not substitute one compound by another of this group, but look for compounds with complete difference in mode of action which does not have CS group. Cross resistance does not apply to DDS."

DR. DOULL (U.S.A.): "In our fourth series of clinical evaluations we included Ciba 1906. There are large matched groups in several places, blind trials. They have completed 72 weeks. Amodiaquine has no advantage. Ciba 1906 shows no great difference to the sulphones. The trial will continue."

DR. DEL PIANTO (Italy): "I did not use INH so do not understand your reference to it, Dr. Miquel."

DR. MUNGAVIN (U.K.): "Resistance is the price of the activity of an anti-leprosy drug. Ring the changes on chemical groups, as Dr. Mayer said."

DR. GAY PRIETO (Spain): "Price is important, especially for a mass campaign. I went to Uzuakoli and in Spain we tried these drugs, and I advise UNICEF on these drugs. DDS is 14 times cheaper than DPT: the daily administration is a trouble. But I have advised its use in certain cases, resistant and intolerant and weak cases. Five patients were intolerant of all former drugs. We used 1906 on them and corticoid, we got great improvement in 3 which persists. My own experience shows cases which improve better on DPT. DPT has a calming effect and the patients become more social. For patients with lesions of face which cause shame I suggest injection of corticoids into disfiguring lepromata."

DR. DAVEY (E. Nigeria): "I thank the Chairman and agree with him on DPT. Re the isophthalate compound, there is much variation in results. A new long-acting sulphone is also now available. Dr. Cap will speak himself on that."

DR. CAP (Congo Belge): "DDS suspended in ethyl chaulmoogra is long-acting, given at 2 weeks intervals. We have used all suspensions, oily or aqueous. We find 3 cc (6 mgm DDS) injection keeps up a satisfactory blood sulphone level. Therapeutic results are good. The injections are mostly painless and 77% of patients attend for their injections.

"We prefer the aqueous suspension: we also use the oily suspension. Attendances are good for both. The needles block if used too much. We used a pulverized suspension also, also guiacolated suspensions which are painless and absorb well. About 80% of these get absorbed. The ICI preparation in aqueous form seems the best."

End of discussion.

DR. BACCAREDA BOY (Italy):

Treatment of Leprosy with Viomycin Pyrazinamide, Cycloserine

All patients were lepromatous: given 1 gm viomycin per day by intramuscular injection: pyrazinamide was also given to others: also cycloserine. Those given viomycin or pyrazinamide showed no improvement. Marked improvement with cycloserine.

DR. ROLLIER (Morocco):

Treatment with Cycloserine

"Our experiment included 6 cases with DDS, 6 cases given cycloserine plus DDS: all lepromatous. In histology there were early marked cellular changes and in bacilli counts there was a rapid strong effect, but after 1 year it was not better than DDS. Side effects from cycloserine were not more than trivial. On the whole, cycloserine has no real advantage over DDS, though it could be used as an alternative drug."

Discussion

DR. BONNIOL (Madagascar): "Cycloserine is expensive. I was disappointed in its clinical action."

DR. MONTESTRUC (France): "Chardome and I found with cycloserine a tissue permeability to it, and various reactions to it."

DR. LECHAT (Congo Belge): "Cycloserine can be interesting in certain cases, but it must be less expensive to be useful to us."

DR. BANG (Vietnam): "Cycloserine in 12 patients with us (lepromatous mainly) gave speedy clinical results but only 2 really showed much improvement. Reactions occurred (lepra reactions). Histological change was not marked. Psychic disorder occurred only mildly in 2 cases. It is an active drug against recent cases, but is costly."

(Twenty minutes intermission from 3.5 p.m.)

DR. S. V. KIBBY (Hawaii):

Physical Therapy in Hansen's Disease

He reviews the literature on this since 1929: physical therapy includes infra-red rays, massage, contrast baths, diathermy. All have varying value in certain conditions. Splinting was early advised, and also passive and active exercises. There may be a special department and specially trained staff, or not. Much can be accomplished with little in the way of equipment. In Kalaupapa we had little equipment, some of it old, but we got good results. We taught massage and passive movements and introduced contrast baths. The patients have to be urged to keep it up. A resident physiotherapist is a great boon, not only in treatment, but in training. Occupational therapy should be linked to the physiotherapy, and other rehabilitation procedures tried.

DR. K. IKEDA (Japan):

Reconstructive Surgery of Deformities in Leprosy

The deformities of hand and foot need physiotherapy and reconstructive surgery. We have performed 233 operations (191 in hand, 42 in foot) of various reconstructive procedures. We have backed our work with experimental studies in dogs.

Functional results have been good in most cases though partial in some. In the foot, arthrodesis and ostectomies were useful in some cases.

Fusion in leprosy is delayed in comparision with arthrodesis for polio and other conditions.

It is important to understand the physiology and pathology of the leprosy deformities, such as the effect of osteoporosis and infiltration and lack of nerve control.

DR. C. VELLUT (India):

Lepra reactions in a mass treatment centre and their management

These findings are from a large series of patients, about 15,000 in S. India. They are all on DDS. Reactions occur in about 40%. There were 60% who never had reactions. Reactions are often repeated. They are less in children. January to March every year form the season when there are most reactions, the driest and coolest period of the year. Reactions come early in treatment. Treatment is by potassium antimony tartrate, cortisone and derivatives, and chlorpromazine. Temporary hospitalization is used very often. The DDS is temporarily suspended and three quarters could soon be restored to DDS. Potassium antimony tartrate is quite effective. Cortisone is useful in small doses, even for a long time, but we prefer it for short term therapy. Outpatient treatment is possible for lepra reactions. Dr. Hemmerickz is my helper and guide in this work.

DR. G. FARRIS: (Italy)

Antigen Marianum in Treatment of Leprosy

We think research should be continued on this. We tried it in 41 lepromatous and 4 tuberculoid. We injected 10.0 ccm monthly for 6 months. There was an ulcer and later a scar, and most had fever. So 13 patients refused to go on. The results were a marked clinical improvement but no bacteriological improvement.

DR. K. YANAGISAWA: (Japan)

Kanamycin in murine leprosy

This is a new antibiotic from *Streptomyces kanamyceticus* discovered by Umezawa. We compared it with streptomycin and controls in 30 rats inoculated with *M. leprae murium.* The nodules of rat leproma responded to both kanamycin and streptomycin. The order of effectiveness of these two drugs is the same, on 5 mgm per day in rats infected with murine leprosy. The control group showed progress in the disease.

DR. N. P. BUU-HOI: (Vietnam)

Use of isonicotinylhydrazones in chemotherapy of leprosy

These show better results than INH in tuberculosis and are less soluble in water. INH has poor lipoid solubility and is less effective. The isonicotinylhydrazones have definite chemotherapeutic anti-leprosy activity according to our tests, though this is lower than

DDSO and also than 4:4′-diethoxy-thiocarbanilide. They have fungistatic properties which are associated with antimycobacterial activity (Mayer). The hydrazones have been tested against fungi and were found active.

DR. J. TOLENTINO (Philippines):

Clinical evaluation studies of the Leonard Wood Memorial

They showed that the sulphones are not the last word in therapy of leprosy, so other drugs have been added to the trials. Only lepromatous cases are used, and groups of subjects chosen at several centres, and parallel investigations are possible. Controlled clinical trials are thus made possible. The patients are assigned to groups without bias. Records and assessment are also unbiassed. In the results for bacteriological smears, (1) diamidin 72.4% were improved in 48 weeks. (2) In the Diamidin plus INH, 70.7% were improved. (3) In the INH plus dihydrostreptomycin, 71.1% were improved. The three groups are thus much the same in the results. They think that much of the bacteriological improvement is due to factors other than therapy.

Discussion

SISTER HILARY ROSS (Carville) Re paper of Dr. Farris: "We gave Marianum antigen a good trial at Carville: it does not have a place in therapy."

DR. MERKLEN (France): "Results with Nivaquine in lepra reaction in our cases show rapid action in many cases. We use it in all reactions now, as it is inexpensive. Dose up to 100 mgm a day for DDS could be maintained. Dose of Nivaquine is 600 mgm a day for 4 or 5 days. Mode of action is perhaps cortisone-like, i.e. anti-inflammatory."

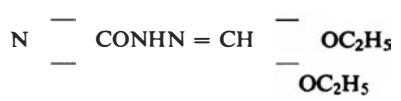
DR. CAP: "Nivaquine with us was not so wonderful but quite good, and had a prophylactic action."

DR. VENKATESWAR: "In reactions watch ESR and make patient fit, removing intercurrent diseases and malnutrition. Corticotrophine I found to be best in severe lepra reactions."

DR. LECHAT: "In lepra reaction we use prednisone and ACTH with good results, and regular treatment with sulphones."

DR. HIRANO: "I conducted the suppressive experiments by isoniazid derivatives and found that isonicotinoyl-3-methoxy-4-hydroxybenzal hydrazone (Phtivazid) possesses more marked supressive effect on the leprous infection than that of isoniazid.

"It was also found that isonicotinoyl-4-hydroxybenzal hydrazone was less effective than the former drug. In the light of these facts it appears that the introduction of an OCH-group into benzene ring may increase the effect against murine leprosy. Recently I found that isonicotinoyl-3,4-diethoxybenzal hydrazone possesses the most striking effect on murine leprosy. This drug is less toxic. A daily oral administration of 3 mg of this drug for three months resulted in the total disappearance of acidfast bacilli at the inoculated site in many cases. The treatment of human leprosy of this drug is still under trial. I think that if this drug has some value in the treatment a new method of chemotherapy of leprosy might be opened up. This drug is also very effective on tuberculous guinea pigs. The chemical structure of this drug is as follows:



DR. ROLLIER: "Corticoids are most valuable in reactions and can be used in outpatients."

DR. BONNIOL: "I use corticosteroids also, mainly ACTH type."

DR. NISHIMURA: "To discover new agents for the treatment of leprosy by using murine leprosy, it will be necessary to screen many hundreds and thousands of derivatives and antibiotics. The method of screening therefore should be as simple and short as possible. For this purpose, the following conditions were examined and on the basis of the results, a screening method was devised.

"The conditions studied were: (1) the most appropriate strain of murine leprosy bacillus; (2) the most suited animal; (3) the best site of inoculation; (4) the optimal dosage of inoculum, and (5) the simplicity of evaluation and ease of reproducibility.

"The screening method is as follows. The dosage of inoculant was 0.2 ml of 10^{-2}, 10^{-3} or 10^{-4} suspensions and it was injected subcutaneously in the lower abdomen. The results were evaluated by measuring the size of the leproma which developed at the site of inoculation with a micrometer gauge. Measurements were made 2 times a month over a period of 3 months and the average of each group group taken. In addition, the animals were observed beyond 3 months after termination of medication for occurrence of relapses.

"Up to now, the effect of certain agents has not always been in agreement due perhaps to differences in method of testing. It is my opinion that a universal standard test, such as the one I have described, should be adopted so that identical results will be obtained with the same agent, no matter who conducts the test. By this, time and effort will be spared and the tempo of research speeded up."

DR. BLANC: "We use corticosteroids in lepra reaction. Some produced a violent lepra reaction."

DR. LAVIRON: "Regarding general therapy: we have many compounds now. They should be used with care and individual attention to the patient. Mass campaigns require non-toxic products for easy administration and cheap in cost. Channel research to depot retard-preparations."

DR. PIANTO: "Mass therapy is not to be solved only by retard-injections. I point out that sodium ethylthiosulphate is much cheaper than DDS and can be used where patients are under daily control."

DR. MAYER: "The search for the perfect drug should not be tied to cheapness first of all. The toxicity and action are our first thoughts. In DPT there are certain advantages that neutralize the higher price, as Dr. Gay Prieto pointed out."

DR. CONTRERAS: "The drug of greatest interest is the one which is most effective and most well tolerated."

DR. B. RUBIO: "The ideal drug for leprosy reaction has not been found, but there is great gain in using sulphones at lower dosage, and in antibiotics. Corticoids are erratic."

DR. PRIETO: " Re lepra reaction, I find corticoids in moderate dosages the most useful, as DDS can be kept on. Find the lowest effective dose which can be well tolerated. I have used corticoids in some cases for 18 months. Use them with intelligence and care."

CLASSIFICATION

15 NOVEMBER, 1958

9.15–12.30

Chairman: PROF. K. KITAMURA

Rapporteur: DR. R. G. COCHRANE

The Chairman said that he had replaced Dr. Arnold as Chairman of the Panel and Dr. Dharmendra had been on the committee.

PROF. K. KITAMURA: (Japan)

The Japanese System of Classification

He summarized the Madrid Classification and its main features Now he would like to describe the Japanese classification. It is simple, There are two types, LM and TM and two subtypes, LN and TN. and stages p, r and q.

Type L has bacilli, globi, lepra cells, thickened skin, loss of eyebrows, lepromin test negative.

TM or tuberculoid macular has the macular hyperaemic lesions: no bacilli: epithelioid and lymphocytic and giant cells: positive lepromin test. Lesions are hypopigmented and anaesthetic.

TN is tuberculoid neural (polyneuritic). There is a *group* as well, A, including atypical cases which do not clearly belong to the other types. The stages are: *progressive*, *retrogressive* or *quiescent*. The atypical group contains cases which under observation may be moved into one of the more definite groups.

DR. R. G. COCHRANE: (U.K.)

A critical appraisal of the classification of leprosy

He reviewed the history of reviews of classification since Manila. A classification acceptable to all should be possible. It should be simple and clear and take histological and all factors into consideration. He thought that the Indian classification should be accepted as a good basis. It is simple and logical. It divides all cases into *Lepromatous* and *Non-Lepromatous*. It can include all clinical features of leprosy. We should, like them, use 'macule' in its true sense as a flat lesion. Borderline and similar lesions are included, and maculo-anaesthetic and neuritic leprosy. In the former there is some loss of skin sensation, and the lesions are not raised, so it is truly maculo-anaesthetic. The lepromin test is only of value if negative or strongly positive. In histology the picture also should be kept clear. There is a special place for the neuritic lesions. The histology of these is more often dimorphous. The borderline group is a phase through which all leprosy passes. *M. leprae* first causes a simple inflammatory response which leads to a definite response (tuber-

culoid leprosy), or to a transformation (through borderline to lepromatous). Reactional tuberculoid is a true borderline lesion. Clinical and histological and immunological knowledge is all needed for classification.

DR. DHARMENDRA: (India)

Classification of Leprosy in India

The Indian Association of Leprologists has evolved a system which I present to this Congress for consideration and approval. I agree there are no unsurmountable difficulties in reaching an agreed system of classification. The chief difficulty lies in choosing the original terms and in expressing the process of evolution of the disease.

We think that the basis should be clinico-bacteriological. Next, histology and immunology should be brought in. Next, the system should have a minimum number of classes.

Next the system should be simple enough for the field workers yet contain room for refinements by experts. Re the Madrid Classification we found two discrepancies (1) the flat macule of leprosy, (2) polyneuritis without clinically being tuberculoid (having tubercles). In Madrid the polyneuritic forms are split up and put in either lepromatous or tuberculoid type. We solved this problem by forming two more classes, the maculo-anaesthetic and the neuritic. Dr. Wade has helped in this synthesis. We have thus six forms.

Discussion

DR. GAY PRIETO: "We suggest the structure can have a scaffolding and we need not insist too much on retaining the scaffolding. Leprosy is a living and changing disease. The instability of certain forms prevents a rigid classification. The borderline stage is one of the fluid concepts. I find Cochrane's borderline cases exist but we name it differently, as an evolutionary phase to lepromatous. Change the other way is rare. Indeterminate is a useful term, because it means we reserve classification. Maculoanaesthetic types are not always macular; some have papules. The ideas join us, the words separate us. But I do not accept the positive Mitsuda in lepromatous reaction as described by Kitamura: it is perhaps an isolated isomorphic phenomenon."

DR. K. R. CHATTERJEE: "The Indian workers start with defining the clinical groups, and by clinical features define the main groups as we see them. Clinical signs of lepromatous and non-lepromatous are sufficiently clear.

"In Pondicherry I found over 2,800 cases in a recent survey, of which lepromatous were 12.2%. Polyneuritis was 4.3%, borderline 0.2%. For a field worker clinical findings are all-important, and the Indian Classification works in practice. Then we go from the field to the laboratory, as I did, and I find that even there the Indian Classification works, and can contain refinements born of histology and immunology in the existing frame. The histology fits in quite well."

DR. BECHELLI: "I agree with Cochrane that macules are not elevated. The atypical group of Kitamura contains many typical types. We do not get positivation of lepromatous leprosy lepromin tests, as in Japan. I agree the classification must be clinical in the first place but do not agree that it should not be scientific as well. We must use all knowledge in any scheme of classification: it must always be scientific. I disagree with Cochrane that Mitsuda strong positives or negatives alone are significant: a mild positive does mean something. 'Macular tuberculoid' term is perfectly feasible. Elevation of a macule is a secondary feature and can apply to a macule or anything else. I do not like the term 'maculo-anaesthetic' but can understand it. Teaching of the existing classification presents no real difficulties."

DR. H. W. WADE: "I endorse Dr. Gay Prieto that leprosy is in flux: we define the case as it is today. There is a broad spectrum. There is a place for every case in it. Every case should be classified differently. I endorse Cochrane's insistence on using 'macule' for a simple flat lesion, though in the histology I disagree with Bechelli. Experts with all facilities have a responsibility of extreme accuracy, but on the field there is plenty of latitude. The truth is that histology is absolutely essential to placing certain macular lesions. In listening to the discussion I am confused by running indeterminate and borderline together: the indeterminate group has its own features, the simple macule which may go one way or another. I also am at sea in the 'dimorphous polyneuritic lesion'. Dr. Cochrane please explain what a clinician should see in a dimorphous lesion."

DR. AZULAY: "I agree with Cochrane, Dharmendra and Chatterjee in what they said in their opening remarks. But enough discussion has not been given to this matter. I want to be on the Committee on the next Congress and I am sure we shall reach agreement. The Latin-American point of view this time has been neglected. Our classification was based on clinical as well as pathology and bacteriology and immunology and we feel it is logical and sound. Our classification works perfectly well clinically in the field. We should bring patients or slides of patients to the next discussion.

"The main disagreement this time is on 'maculo-anaesthetic' and 'polyneuritic' but they are already in our classification under another name. We use day to day histological checks. I admit the polyneuritic does create difficulty. In Brazil we do find it can be either part of tuberculoid or lepromatous leprosy. I must add a Mitsuda positive can exist in a lepromatous case and I have seen many such cases. It is a real fact."

Intermission of 15 minutes at 10.45 a.m.

I. TAJIRI

DR. J. TOJIRI (Japan):

On Acute Infiltration of the lepromatous type of leprosy

This is an acute infiltration which emerges after a patient has been a long time in the resorption stage in lepromatous leprosy. It is one of the several reaction types and should be separated from them. It is not the 'Akuter schub' of tuberculoid leprosy, but something like that occurs in lepromatous leprosy. Nor is it erythema nodosum leprosum. Acute infiltration has an exanthem with a remittent fever of 37° to 39°C. The eruption is macular or papular (like erysipelas), and there may be anaesthesia. There is a moderate lymphocytosis. Bacilli are much fewer than in lepromatous nodules: the Mitsuda is negative but turns to positive soon after, or even when the eruption is present. The reaction may convert to negative later but many remain positive. Histologically the picture is the same as tuberculoid macular with some lepromatous features: both lepra cells and giant cells may be seen and epithelioid cells. The prognosis is good for those whose Mitsuda becomes positive, so the phenomenon must be due to a rise in immunity state of the patient.

Discussion

DR. ANDRADE (Mexico): "Changes occur in classification every five years, depending on where the Congress is held. Statistical analysis is thereby made difficult, and this should be borne in mind. The local national element thus goes against the fact that leprosy is one single international disease. We should be cautious."

DR. M. C. ESTRADA (Mexico): "We must remember the two polar types. Remember that we are dealing with individuals, not diseases. Make room for

many variations and keep an open mind. In Mexico we take smears often, and do not like the idea of pure neuritic types. Remember the factor of varying resistance. Dimorphous cases may contain a large tuberculoid element."

DR. HIDAKO (Japan): "Reactions in tuberculoid leprosy lead to improvement. Reactions in lepromatous leprosy may not lead to improvement, which in any case is slight. There is a whole involvement of body organs and tissues in many reactions. Sarcoidosis resembles tuberculoid reaction in leprosy, clinically and in the laboratory. There is an epithelioid cell granuloma. I base a whole system of classification of leprosy on these reactive states."

DR. M. NISHIURA (Japan): "Madrid Classification of leprosy has a certain weak point from the theoretical point of view. That system is solely based on the different attitudes of phagocytes towards the invasion of leprosy bacilli. But there are two other cell kinds which have an important relationship with leprosy bacilli. And they are the 'spinal ganglion cell' including axon and 'Schwann cell'. Certainly their behaviour towards leprosy bacilli differs considerably from that of phagocytes. I would like to ask all members of ILA here present now. Is there any difference of the cellular resistance of spinal ganglion cell and Schwann cell in different types of leprosy? I think these points should be studied vigorously."

DR. BARBA RUBIO (Mexico): "In all Congresses there is most debate on Classification, because we use different words. We all agree on the fact of lepromatous and the other polar type (tuberculoid). The trouble arises over the case which shades between.

"We tend to make many groups of these. A special committee of leprologists should be made to visit all countries and formulate an agreed consensus on classification."

DR. VENKATESWARA: " In India the flat hypopigmented macule is a reality. Dr. Cochrane's idea of all leprosy being borderline in origin gives us something to think about."

DR. MORGADO (Mozambique): "In Mozambique we know the Madrid Classification and have no difficulties with it, even in the jungle. It works, why change it? It is practical and quite scientific."

DR. CAP (Congo Belge): "I plead to maintain the existing classification. It suits clinical features, and with us our physicians are not leprologists. We do not want confusion for them."

DR. MARSHALL (Okinawa): "One cannot reconcile all these classifications. We need a practical one for public health purposes."

DR. BONNIOL (Madagascar): "Simplification of classification is important in under-developed countries."

DR. A. W. F. RUTGERS (Indonesia): "I agree with Dr. Cap: We want to maintain the existing classification. We give the name tuberculoid to both flat macules and elevated lesions. The benign group. I want to preserve that."

PROF. K. KITAMURA (Japan): "The term 'macule' or 'macula' means skin lesion only with change in skin colouring (in dermatology). But such maculae can change and show other features, in leprosy as in dermatology, such as erythema or elevation. I thing we should use the word, but conditionally."

DR. R. G. COCHRANE: "There are many points to answer. I take a few—

"1. We are trying to retain the Madrid Classification as far as possible.

"2. We must adopt Dr. Azulay's suggestion of sitting down together with slides, but in the meantime we need a base-line.

"3. Dimorphous leprosy is to me a *zone* of leprosy which covers lesions which look like tuberculoid as defined in Madrid: in histology the subepidermal zone is not free; but such lesions are not stable, but in a state of flux. True tuberculoid is rare, but the commonest is this whole spectrum of dimorphous leprosy.

"4. The Schwann cell deserves closer study. Dr. Weddell has already begun this. *M. leprae* is seldom seen in spinal ganglia because there are few Schwann cells there."

DR. DHARMENDRA: "We do not want frequent changes in classification. Yet that is just what we have been doing. Change from tuberculoid to leproma is a concept too vague to fit into practical experience: it does not happen. I insist on basic clinical criteria but that does not rule out the laboratory being used."

EPIDEMIOLOGY AND CONTROL SYMPOSIUM

17 NOVEMBER, 1958

9.15 A.M.

Chairman: DR. J. A. DOULL

Rapporteur: DR. R. V. WARDEKAR

DR. DOULL made a statement on the subject, presenting the unanimous report of the Technical Committee of Epidemiology and Control.

Important points were given emphasis:

1. *Leprosy surveys:* statistically designed sampling surveys are advised. Even limited surveys are worth while, limited in time or area or to school children.
2. *The frequency of evolutionary changes in leprosy* is urgent for study. A modified life table procedure should be used.
3. *Relative infectiousness of lepromatous and tuberculoid types* should be studied to solve the epidemiological enigma where tuberculoid cases seem to carry on the endemic.
4. *Evaluation of effectiveness of clinic treatment* is also urgent for study. There are various indexes which could be built up.
5. *Controlled studies of effect of sulphones* on nerve damage and on tuberculoid type in general.
6. *Subclinical infection* is a subject requiring study.
7. *Methods of transmission.* Insects are still not culpable.
8. *Resistance.* Mitsuda positivity in relation to resistance needs long-term field studies: also natural reactivity to lepromin.
9. *BCG vaccination in resistance to leprosy:* long-term studies are in progress but are very difficult. Secondary factors can be studied.
10. *Possible relation of diet to leprosy* has never been thoroughly explored, and should be done in suitable countries (nutritionists should be co-opted).

In Control

(1) *Educational*
(2) *Medical*
(3) *Social*
(4) *Legal*

Early diagnosis and treatment are essential to control. The patient and his family should be given full explanation of practical matters relating to the disease. Contacts should be sought for and given explanation and reassurance. There are many other practical points for patients and contacts. The public should also receive education and explanation.

It is more important to reduce infectiousness in many cases than to eliminate infection in a few: this from an epidemiological point of view.

The careful search for contacts is of major importance.

Social assistance to leprosy patients and their families is an inescapable duty.

Legal restrictions on patients have little value in the control of leprosy, but reporting the disease to the health authorities is reasonable. Discretionary authority should be given to the health authorities to impose isolation in troublesome cases.

Dr. Doull also mentioned the need for close study of relapses and gathering of statistics on it, also that there was no reason why leprosy patients should not be admitted to general hospitals if necessary. Preventoria should be converted into general child-care institutions. BCG should be used for child contacts.

DR. R. V. WARDEKAR (India):

Success of Case Detection Campaign in Sulphone Therapy

He reported field work in India in the last seven years.

He reported the important part played by 'para-medical' workers in securing the growth of the clinics and the growth of care of the patients. They work under medical supervision. Most patients take the treatment and results are excellent. The cases are detected in early stages of the disease, and this early detection has a marked effect on the prevention of deformities, as well as on a high arrest rate for the disease. The clinical clearing of lesions is surprisingly high. Over six years, only 23% of bacillerous cases remained positive.

Widespread case-detection campaigns are the only solution for poor countries, using para-medical workers who are specially trained. Each patient per year in a leprosarium costs $100.00: the out-patient costs $9.

DR. E. MONTESTRUC (Martinique):

BCG in the Prophylaxis of Leprosy

There are only 300,000 inhabitants: the leprosy rate is 7 to 8 per thousand. We have given BCG to the newborn children of leprosy patients, and can now give the results of the experience of 22 years. None of these children has shown any sign of the disease, whereas 10 children living in leprosaria have developed the disease. We have now extended the BCG vaccination to all children 0–15 years of age. Also in a large special group of children, controlled and uncontrolled, we had 2 cases and 54 cases respectively. We think the effect of BCG in prophylaxis is very clear and justified for wide and general use. A large number of children are sensitive to leprosy and tuberculosis. A positive Montoux in many goes with a lepromin negative: they can be given BCG with advantage, after a clinical and radiological examination for tuberculosis. Why should we not try to secure both

tuberculosis and leprosy prevention in all children? A prophylactic sulphone course is of some use as well, against leprosy.

DR. O. DINIZ (Brazil):

The new programme of leprosy control in Brazil

In Brazil leprosy is a widespread problem with 5,000 new patients annually, and a total of 100,000 patients. For 25 years we compulsorily segregated infectious cases, and 36 leprosaria were built, containing 25,000 patients. There are 31 preventoria, with 5,000 children. There were less than 100 dispensaries, most of them in large cities. The results were bad: there was no decrease in the endemic. Lepromatous type was over 60%. Since 1956 we abolished compulsory segregation and opened up the campaign to take in out-patient work. We formed 'task forces' in each area, using specialist leprologists and general doctors and public health workers: there are even general practitioners. There are now 102 such task forces for the total population of 17 millions. They now have over 10,000 patients. More and more cases have been discovered, reaching 6,600 new and often early cases, and an estimated 60% of the patients have been reached. The campaign has an educative value and we hope it will be successful.

(Intermission for 15 minutes)

Epidemiology and Control

Discussion

DR. N. D. FRASER (Hong Kong): "Dr. Doull's paper was weakest on the contribution of the community and governments and public health authorities. Voluntary agents and the patients also have a part to play. All must work together."

DR. GAY PRIETO (W.H.O.): "I congratulate Dr. Doull on his complete report. Will he add 3 points: (1) Approach to a complete survey is not impossible, using campaigns for other disease to provide part of the information needed. (2) Change slightly the remarks on sampling to include the recommendation to include pilot areas. (3) Chemoprophylaxis is effective and should be added, e.g., Laviron's work, Figuredo in Bombay, Ramon Miquel in Thailand. BCG prophylaxis is still in doubt. In Spanish Guinea there is high prevalence of leprosy along with BCG positivity. The transmission of leprosy may well be by the borderline cases."

DR. K. YANAGISAWA (Japan): "BCG is effective in preventing murine leprosy. We studied tuberculin-positive and negative children who had received BCG. The results are favourable to BCG in both cases. Lepromatous contacts were found to be more dangerous to the children: in these the tuberculin-negatives were more susceptible. The length of contact is important."

DR. CHATTERJEE (India): "Outdoor treatment centres and surveys were started with us by Dr. Muir in 1934. We have continued and amplified these. In 1935 we found 4.9 per thousand in Bankura on a sample survey. Sample surveys are practicable and valuable. Prophylaxis by sulphone is more doubtful: it does not enter the nerves. In treatment the proper dose must be found for tuberculoid cases. We did BCG vaccination in certain areas from ages 2 months to 15 years. To 2,329 children up to 15 years of age we gave BCG in 1953 and in 1958 we found 0.7% of leprosy incidence; it was 17% in unvaccinated children. In another group it was 2.4% against 52.4%: this group was of lepromin-negative children."

DR. CONVIT (Venezuela): "Referring to Dr. Montestruc's work about BCG vaccination, I would like to say a word about our experiences in this particular field.

"We have done intradermal BCG vaccination in a leprosy focus in our country since 1950. We divided the population in groups, one was vaccinated with BCG and the other remained as control. We published the first five years of experience and found on this occasion 26 patients in the group not vaccinated, approximately 45%, and only 3 patients in the vaccinated group, 5.6%.

"A few months ago one of my collaborators, Dr. Albornoz, and I reviewed this study which has now almost eight years of experience and found that the results confirmed the previous study. In relation to the type of leprosy there were no cases of the lepromatous type in the vaccinated; in contrast, we found several cases of this type in the non-vaccinated group."

DR. LANDSBOROUGH (Formosa): "I have been told that compulsory segregation is still in force in Japan, and that amongst male leprosy patients sterilization is made compulsory. I would like to ask our kind hosts whether these two points are true, and whether they think such measures are still necessary in this country."

DR. ISHIMARU: "There has been no compulsory enforcement in recent years. Vasectomy is not enforced by law but is advised for those about to get married."

DR. RAMON MIQUEL (Thailand) referred to the limited but most valuable experience and results achieved in the leprosy village, established near the leprosy control project headquarters at Khon Kaen pilot area, Thailand; this represented an additional contribution to the Laviron preliminary experience in Bamako on preventive sulphone applied to child contracts as a most safe method of prevention.

None of the 184 children contacts who received preventive sulphone in Ban Noi Leprosy village has shown any symptoms of leprosy so far during 3 years of close follow-up and observation.

Ninety-six children received prophylactic sulphone treatment during 1956 and 88 during 1957.

Up to about 750 children contacts are also receiving domiciliary prophylactic treatment in the southern zone of the pilot area but the follow-up and observations have not been so close and sufficient to present valuable data.

The administration method for prophylactic treatment to child contacts applied in our pilot project has been the long-acting injectable 'Laviron one', i.e., every fortnight intramuscular injection of DDS suspension in chaulmoogra ethyl esters.

Our dosage is as follows: For children from 2–7 years: 1/2 cc of the DDS suspension, i.e., 125 mg every fortnight. For children from 7–15 years: 1 cc, i.e., 250 mg DDS suspension every fortnight.

The length of prophylactic treatment is as follows: 6 months for child contacts of non-lepromatous patients. 12 months for child contacts of lepromatous patients.

DR. RICHET: "Dr. Doull laid stress on the role of fixed teams. In French Africa (600,000 patients to be dealt with) and in underdeveloped countries mass campaigns are necessary. We brought 120,000 under treatment and will soon reach 50 or 60% of arrested cases. In French West Africa we also brought large numbers under treatment by mobile teams: i.e., 127,000 patients. We use 100 vehicles, many supplied by UNICEF, and the treatment is injectable sulphone. There are also 500 bicycle circuits for distribution of DDS tablets. The distance covered by mobile teams and bicycles is enormous."

DR. W. FROELICH (Taiwan) described survey work in Taiwan. Surveys for general diseases included leprosy. The cost of a combined survey is cheaper in proportion and yields higher populations.

DR. AZULAY (Brazil) congratulated Dr. Doull on the report. Reference Dr. Wardekar's comments, he says his sort of campaign would suit the richer countries too. He had suggested BCG in prophylaxis in the Havana Congress but it was accepted in the Madrid Congress. "I agree with Dr. Yanagisawa's paper. I think there are basic reasons for continuing with BCG as a prophylactic. It must be recommended."

DR. BACCAREDA-BOY (Italy): "In Italy tuberculosis is widespread, and the lepromatous type predominates in leprosy. It is because there is plenty of time for them to become lepromatous. We used BCG prophylactically in contacts and secured complete protection. Sulphone prophylaxis we think is doubtful."

DR. BLANC: "Mass campaigns alone are not enough. They are still pretty costly. Integration in public health services should not be forgotten. Mass campaigns should also include survey and treatment for other diseases, and in Indonesia we obtained good results. Also our ordinary dispensaries treat leprosy."

DR. BECHELLI (Brazil) praised Dr. Doull's report which he considered is very balanced. Re 'Index of Cure', we should not use the word 'cure', but 'arrest'.

"Re prophylactic treatment, why not use repeated lepromin tests? In Montestruc's paper, were the BCG group and the control group comparable? To Azulay I say that not all data are in favour of BCG. I think we have to wait longer, and be prudent about BCG."

(Session adjourned 12.00 noon)

EPIDEMIOLOGY AND CONTROL

17 NOVEMBER, 1958
2 P.M.

Chairman: DR, PAUL BRAND
Rapporteur: DR. J. GARROD

DR. A. SOBUE (Japan):

Epidemiological Study of Leprosy in Aichi Prefecture

In the 50 years up to 1957, we recorded 1,946 leprosy cases in Aichi Prefecture, a rate of 0.2 to 2.4 per 100,000 population. The stress of war and poverty brought the rate to 1.4–2.0 per 100,000 in the first half of this 50 year period. After 1952 it dropped to less than 0.5.

There were 59% lepromatous type, 17% macular, and 33% neural, and latterly the lepromatous type tends to become rarer. The age of onset was 25 in the first 4 years, but 40 between 1951 and 1955. Males are 260/100 to females. Patients hospitalised were 77% but the average wait before admission was 7 years. However the author thinks that patients unregistered are twice as many as those on the registers, and there is no cause for satisfaction. The Prefecture contains over 3,700,000 population, and a density of 774 per sq. kilom. It is said to have the heaviest incidence of leprosy. Over 29 new cases are found every year. Enforced BCG vaccination was introduced by a law of 1949.

DR. J. LEW AND DR. CHUNG (Korea):

Epidemiological Studies of Leprosy in Korea

Surveys were made 1947–1957. The present-day estimate of leprosy in Korea is not less than 100,000. There are now 8 leprosaria with about 20,000 patients in them. Dr. Cochrane in 1955 estimated 150,000. Most patients come from the four southern provinces, but the endemic is spreading northwards. Lepromatous type is about 30%; males are double the number of females; the age of onset is under 35 years in 55% of all cases. Contact has been traced with other family leprosy members in 40%. 60% cannot remember contact.

The earliest clinical sign is some skin patch with anaesthesia. In most cases almost 3 years were wasted before diagnosis: 70% of cases can work.

DR. BARBA RUBIO AND DR. G. PEREZ SUAREZ (Mexico):

The Anti-leprosy campaign in Mexico

The Dermatological Institute in Guadalajara is aided by private initiative (the Patronate). In Mexico we have opened up and modernised the campaign. We use 'ambulatory' and 'dermatology' and other general terms. We reject coercion and respect individual human liberty; nor is special legislation needed. Leprosaria should be called 'dermatological centres' and the clinics 'dermatological clinics'.

Prevention should be based on early diagnosis and treatment in out-patients departments. Children separated from leprosy patients should be cared for in general institutions.

DR. NUNEZ ANDRADE (Mexico):

Leprosy in Mexico in 1958

Mexico is a big country with 32 million inhabitants. On 13 July, 1955, we published an enlightened law on leprosy. A preliminary survey showed 1,460 cases of leprosy. In 1934, 2,449, and in 1958, 1,511 were found, bringing the total to 13,000. The various provinces have been assessed for incidence. The average is 41.29 per 100,000. The total estimated number of cases is over 60,000. The Pacific coast and the geographic centre of the country have the heaviest incidence. The State of Yucatan was infected from the east, from the Antilles. Most cases have bad economic conditions.

DR. M. H. GABRIEL (Queensland):

A Note Proposing Abolition of Strict Segregation for White Hansen's Disease Sufferers

Leprosy incidence is low in Australia. The white and aboriginal races have a far different social status. There is a low case rate in white staffs of leprosaria and in the white population generally, and we are thinking of relaxing the segregation rules for whites. "This Congress favours relaxation of segregation where the case rate is low and living standards high" is placed before the Congress for its opinion.

DR. P. BONNIOL (Madagascar):

The Anti-leprosy Campaign in Madagascar

We are applying the principles of epidemiology and control as in Dr. Doull's report. Out-patient and domiciliary patient treatment is carried on, and we now treat over 23,000 patients. The rate is 1 per 200 population, with 45,000 patients altogether. Patients come readily for treatment. We have fixed dispensaries and 5 mobile teams, which also cover other diseases: we hope to have 12 groups by 1959. The patients are carefully recorded from the beginning. There are also nine leprosaria in Madagascar. We use BCG in child contacts and have recently begun a trial of DDSO, which seems to do well for those with many reactions. We use the corticosteroids in reaction. We think that DDSO is slightly better than DDS.

DR. A. SALAZAR LEITE (Portugal):

Orientation for anti-leprosy campaign in Portuguese overseas territories

The initial leprosy campaign must be as complete as possible. A lot depends on roads and the existence of health centres. Angola has a moderate endemic, about 2,251 cases, and two types of campaign were chosen; (a) mobile units where roads are good and open all the year round; and (b) using more static health centres and dispensaries where the roads are bad and often closed in the rainy season. We use as the drug 'sulphone-retard'. Patients are found to attend well and ambulatory treatment is very popular. The mobile units are more effective than the static units.

Discussion

DR. MORGADO (Mozambique): "The work of Salazar Leite is interesting. I report on Mozambique, where we have a leprosy control service under the Public Health Department and dispensaries which cover leprosy treatment. There is a regional dispensary, 62 dispensaries and 123 treatment posts. Case-finding is done by mobile teams and by dispensary physicians. Good records are kept."

Paper

DR. E. AGRICOLA (Brazil):

Epidemiology and Control of Leprosy in Brazil

The control of leprosy in Brazil has proved a difficult task. The conclusion of previous Congresses have been studied and I recall them to you. In Brazil, in spite of a determined attack, we know we have not controlled the endemic. Now we propose to open up the campaign by integrating all doctors and health units, and by going to the patients as out-patients, using several mobile teams. We also retain the leprosaria and preventoria. The case-finding and registration of contacts should go together. The high lepromatous rate in Brazil is a difficult factor.

DR. A. R. PINTO (Portuguese Guinea):

Practical Application of Modern Methods to Leprosy Control

Modern therapy has given new hope of elimination. The drugs we have now are not the ideal, complete cure is slow and complications are fairly frequent. We found 25 per 1,000 incidence of leprosy in our country. We make surveys periodically, treatment is free and given in out-patient clinics. We use BCG. We have 9 physicians and hospital space for 1,500 patients. We have mobile teams and surveys for other diseases include a search for leprosy cases. Laboratory work is available at headquarters and in the field. Mobile teams use small Citroen cars or even scooters. The people co-operate actively and attendances are good. We bring the treatment to the home of the patient. We use DDS in injection and oral tablets. The latter are given once a week in the presence of the physician or nurse. This simple campaign has covered 80% of the total patients and we hope to break the back of the endemic. The cost is low.

Discussion

DR. P. J. CHANDY (India): "I feel there is an over-emphasis on taking treatment to the patient. There is a limit to mobile units and we should also have more institutions to keep up the standard of the general work. The age of onset in an endemic area drops upon any increase of the leprosy endemic."

DR. P. BRAND: "I agree that treatment should not be taken to the patient too much because outpatients walk too far even with deformities of the feet. This is from the surgeon's point of view."

Paper

DR. P. FASAL (U.S.A.):

A dermatologist's report on leprosy in California

In California only about 14 cases are found every year. The territorial origin of these cases is pretty wide-spread, but some counties show more. Most of the cases are of Mexican origin

although there were several in other races. All kinds of leprosy are seen. Many cases were first misdiagnosed and leprosy was missed. Some cases were wrongly given the diagnosis of leprosy.

Early diagnosis is most important for control of leprosy, from a dermatologist's point of view.

DR. M. ARIF (Indonesia):

The Leprosy Campaign in Indonesia

The population is 80 million: leprosy cases, 100,000. There are 182 out-patient clinics dealing with 20,000 patients and five leprosaria. The leprosy campaign is under the Ministry of Health. There is a laboratory and a research section and courses of lectures for doctors and students, nurses, propaganda officers, health officers, social services. There is a WHO consultant. There is a main central leprosarium of 450 beds which is being built: it will have all departments.

Rehabilitation is not forgotten, nor research in therapy and epidemiology. Preventive and curative surgery are available; and psychic and social rehabilitation are attended to. Treatment is by DDS by tablets or injections, and chaulmoogra. Segregation is arranged in a separate room or hut, or patients are admitted to the leprosarium or segregation villages. Social assistance is given. Children are removed at once after birth and cared for in other homes or orphanages or by social workers. Social rehabilitation is considered very important.

DR. G. L. FITE (U.S.A.):

Statement on the Principles of Work at Carville

Institutions grow old and get senile diseases and become somewhat useless in their old age. They need to be revitalised. Even Carville should take a new look at itself. The hospital becomes a focus for study of the disease, a museum of specimens. There are many causes in leprosy besides the bacterial agents. We must study the reaction of host and parasite in all directions. A cured patient is not cured until re-accepted by his family and community. Carville has to take note of these other factors: it will study all these interrelated components. The medical officer will study to bring Carville into its new inclusive role and bring in the changes without fear.

The Chairman: Dr. P. Brand: noted the social aspects side brought out in epidemiology and control and found the session fruitful as a whole.

Session closed at 4.30 p.m.

Dr. Brand explained the film. (A surgical film showing reconstructive operations was now shown.)

IMMUNOLOGY

18 NOVEMBER, 1958
9.00 A.M.

Chairman: DR. J. M. M. FERNANDEZ
Rapporteur: DR. K. YANAGISAWA

DR. FERNANDEZ gave his report of the committee on this subject.

1. *The lepromin reaction* is useful in prognosis and classification and its use is recommended. Lepromin should be made simple: there are various methods and modifications. The Mitsuda-Hayashi antigen is recommended as modified by Wade. As for bacillary extracts, further studies are needed (the name of 'leprolin' is recommended). Standardisation of lepromin is advised.

   Readings: Fernandez at 24 hrs, Mitsuda at 3 to 4 weeks: either can be read separately. The Fernandez means a hypersensitivity to the leprosy bacilli: a doubtful result is less than 5 mm. in diameter; a strong positive is 20 mm. or more in diameter.

   The Mitsuda may reach its peak in 3 weeks or after 4 weeks and should be observed up to 60 days. The doubtful reading is less than 3 mm. In strong positive there is ulceration. In all cases, record diameter in mm. The significance of the lepromin reaction is one of sensitivity, with or without previous contact with leprosy.
2. *BCG and lepromin reaction.* Conversion does occur but the evidence for change in resistance to leprosy is still inconclusive. A standard experiment applied in many countries is needed. Preliminary tuberculin testing may be given to one group and not to another. A reliable dried BCG is advisable (as Dr. Yanagisawa offers to supply.)

Paper

DR. K. YANAGISAWA (Japan):

Criteria of Reading the Lepromin Reaction

There is a great correspondence between the early and late reactions. No standard lepromin antigen is available at present. In Japan we make our lepromin in a central institute and try to standardise it before issue. We suggest the following standards for reading:

Using the Mitsuda antigen we suggest

0 to 4 mm.	negative
5 to 6 mm.	doubtful
larger than 7 mm.	positive

Using the Dharmendra antigen for the late reaction read at 15 days.

0 to 3 mm.	negative
4 to 5 mm.	doubtful
larger than 6 mm.	positive

For the early reaction at 48 hours with the *Mitsuda antigen*, 0 to 6 mm. is negative, 7 to 10 mm. doubtful, and larger than 11 mm. is

positive. With the *Dharmendra antigen*, 0 to 9 mm. is negative, 10 to 12 mm. is doubtful, larger than 13 mm. is negative.

There is a great deal of experimental and statistical analysis behind these figures.

DR. L. M. BECHELLI (Brazil):

The Influence of Repeated Lepromin Tests

We tried repeated injection of lepromin to convert negative lepromin reaction in children. The results were excellent, more than 70% of conversions or intensifications. Results were similar to that obtained with BCG. There were some variations in age groups. The lepromin acts as a sensitizing agent and may perhaps increase the resistance, though this is more uncertain. Most positivizations were in 5 to 14 years age groups.

DR. H. W. WADE (Philippines):

Nomenclature and Classification of Skin Test Antigens

We need to avoid confusion in the literature. Several lepromin antigens are now used and the name 'lepromin' can be applied to all of them. The term is taken to mean the Mitsuda-Hayashi type of antigen. 'Stefansky antigen' will be suitable for the *M. lepraemurium antigen*. The tissue elements lead to 'crude lepromin' and the removal of these leads to 'integral lepromin'. The extracted bacilli type could be 'purified bacillus suspension' or 'bacillary lepromin'.

The Dharmendra antigen is non-acidfast or defatted and the bacilli will not stain: it is not a lepromin: call it the 'Dharmendra antigen'. Special preparations to elicit the early reaction only may best be called 'leprolins'. The skin test antigen produces an early reaction (the Fernandez): the state produced is a hypersensitivity (in analogy with tuberculin sensitivity).

Discussion

DR. DHARMENDRA (India): "I have listened with great interest to the Report of the Committee on Immunology and to the papers of Dr. Yanagisawa and Dr. Wade.

"With reference to the antigen for the lepromin test prepared by the chloroform method and which has been associated with my name, I agree that the chloroform treatment will modify the bacilli in some respects. But the question is to what extent the antigenic activity of the bacilli is changed. When this antigen was first prepared, the results with it were compared in a large number of patients of various types and a very high degree of correlation was found between the results with this antigen and with the original Mitsuda-Hayashi antigen. I am glad to note that Dr. Yanagisawa in Japan has found the same results in a very large number of patients.

"A few years ago we compared the results of this antigen with that of Hayashi-Mitsuda lepromin prepared by Dr. Wade's modification. The same degree of high correlation in the results was seen.

"The one constant difference that has been observed is that the earlier reactions with this antigen are stronger and the late reactions weaker, giving rise to a nodule of smaller size and less frequent ulcerations than with the original

lepromin. This was considered a point in favour of this particular antigen. It is an antigen which can easily be prepared and gives conformable results with the original antigen."

DR. MONTESTRUC (France): "Concerning repeated lepromin injections to positivize the lepromin test, I point out that repeated tuberculin will positivize to that reaction. A certain number *of living* germs were needed."

DR. K. R. CHATTERJEE (India): "We have been trying to standardize lepromin. We found a saprophyte (Kedrowsky) which gave a good lepromin, the same as the Dharmendra. We tested it in India, and in Japan they found a very high correspondence of Kedrowsky to Dharmendra antigen. In Japan they made it themselves and got the same results. Repeated inoculations with Mitsuda antigen every 3 months we found to give a high rate of conversion and a high degree of protection from leprosy. Concerning nomenclature, how would Dr. Wade name this Kedrowsky one?"

DR. ROLLIER (Morocco): "I do not believe a figure of reading below 20 mm. is of any importance. In tuberculosis patients I did not find any relation between Fernández and early tuberculin reaction. This is against any inter-sensitivity. I saw 8 lepromatous cases where early pulmonary tuberculosis occurred."

DR. FROEHLICH (Taiwan): "Proteins become changed by physical measures (boiling, etc.). We should remember this in lepromin tests. Why not eliminate the human proteins in lepromin?"

DR. ESTRADA (Mexico): "Re Yanagisawa's paper, I was surprised he established Mitsuda positivity in lepromatous patients. We in Mexico believe in the complete lack of resistance in lepromatous patients. The measurements in mm are confusing and one can make mistakes. The reactions are useful however."

DR. AZULAY (Brazil) Re Dr. Wade's paper: "I have made Dharmendra antigen. Wade says the bacilli lose their acid-fastness. I find they become weaker in acid-fastness but do not necessarily lose it. We have tried Dharmendra against integral; we find it shows weaker late but stronger early reaction; this is sometimes reversed, perhaps by small variations in preparation. Re BCG: I agree much of the work lacks control, but my works had controls. Re Bechelli's remarks: it is difficult to control the variations. The youngest children are better controlled."

DR. G. L. FITE (U.S.A.): "Wade is right when he says we are still dealing with impure antigens. His idea of the names is sound. His purified antigen should be called bacillary antigen. I advise caution in borrowing from terms in tuberculosis. The tuberculin test is a late reaction (Fernandez is the early). Tuberculin and leprolin are two very different substances, and I do not like 'leprolin'."

DR. T. OGATA (Japan) showed a slide showing cross-reaction between sera from syphilis and leprosy, also from tuberculosis. He stated there was some kind of similarity in the antigens between leprosy and syphilis.

DR. H. W. WADE: "One point ought to be stressed. There is a big difference between young leprosy patients and normal individuals. In Japan tests on the young are difficult.

"Chloroform in antigen of Dharmendra also includes ether: the ether extracts the lipids. Acid-fastness does disappear. It is hard to find any acidfast material in the samples from Dharmendra or Japan.

"Tubercle bacilli can be made non-acidfast by growing with INH, and this removes their power to produce reactions. Even young children can be converted in lepromin reaction by repeated lepromin. Dr. Fite's remarks overwhelm me (re terminology) that the antigens are not pure. My purified antigen was tested in many countries and all reported its positivity, though the readings were lower."

(Intermission of 10 minutes at 10.45 a.m.)

Chairman: DR. R. G. COCHRANE

Rapporteur: DR. BUU-HOI

DRS. J. ALEIXO, J. STANCIOLI, J. MARIANO and A. SALOMAO, of Brazil.
(Read by DR. ALEIXO)

Mitsuda Test after Mass BCG

This was done in areas of severe leprosy prevalence where no previous immunological tests had been given. The Mitsuda not having been given, any possible converting by it was ruled out. That BCG was effective was known in Brazil from 1 and ¼ million previous BCG vaccinations. This paper reports the study of 1,889 inhabitants. The conversion was very satisfactory.

DRS. L. M. BECHELLI, RATH DE SOUZA, and R. QUAGLIATO, of Brazil.
(Read by DR. BECHELLI)

Correlation of Clinical and Histological Mitsuda Reaction

We reported this in 1953 on 159 biopsies. Now we report on 253 biopsies. In histology a clearly tuberculoid picture was necessary for us to read a positive. A negative showed only a general cell reaction of inflammatory nature.

There was an intermediate picture of 'tending to a positive', and this is found even in some doubtful reactions clinically, and even in some clinical negatives. The histology is almost similar in the 1 plus and 2 plus. With more work we propose the readings should be re-arranged.

DR. R. D. AZULAY (Brazil):

Lepromin Test in Guinea-pigs after Previous BCG and Dead M. Tuberculosis Vaccinations

We show the undoubted protection of guinea-pigs against rat leprosy. Effects vary with the dose of BCG (30 mg./kg. of guinea-pig body weight was the best). We tried larger doses of BCG for lepromin conversion and doses of killed *M. tuberculosis* (killed by irradiation). The positive results decreased with increased BCG, and no positive results with *M. tuberculosis*, but some doubtfuls. With ordinary doses of BCG the results are good. All doses were given by mouth. The optimum dose is similar to that for children.

DR. H. W. WADE and DR. R. E. GUINTO (Philippines):

Serial Dilutions of Lepromin in Normal Young Children

The tests were on healthy young children, 6–9 years. There were 5 groups of 100 children. Varying antigens were used and varying dilutions. In town children Dharmendra results were less than from the Mitsuda-Hayashi antigen. In country children, a full dose lepromin gave 91% of Mitsuda positives and lower dilutions were unsuitable for such children, though the reaction rate did not decrease in parallel with the dilutions. Early reactions were relatively few. There seemed in country children to be some conditioning factor, presumably environmental contact with non-pathogenic mycobacteria (this may operate also in tuberculin reactivity in rural areas in the tropics).

DRS. J. A. DOULL, R. S. GUINTO and M. MABALAY (Philippines):

Natural Reactivity to Lepromin: Association between Mitsuda and Tuberculin Reaction for Graded Doses of Tuberculin

The cause of natural reactivity to lepromin may be due to the effect of an antigen derived from another mycobacterium, e.g. *M. tuberculosis*, and this antigen may perhaps be present in some degree in other members of the group. As you increase the dose of tuberculin in our experiments you do not get increased correlation with lepromin. There is not any true explanation as yet for the greater part of Mitsuda reactivity.

DRS. T. OGATA and M. ABE (Japan):

Serological Agglutinations with Cardiolopin Lecithin Antigen in Leprosy Sera

I used Cardiolipin-lecithin antigen by a technique derived from my syphilis agglutination test. If there are equal parts of cardiolipin and lecithin, there will be a curve of highest end-titre which is in marked contrast with the syphilis one. This is characteristic enough to provide a lepro-agglutination test. The leprous antibodies are mostly in the beta-globulin of sera, and only to a less degree in the alpha-globulin. Lepromatous types give higher titres than in tuberculoid (and normal patients) so only high titres are useful. They are greater in L_3 than L_1, and in regressive leprosy.

DRS. T. FUJINAMI and H. HONDA (Japan):

Antigenicity of BCG Wax to Sera from Leprosy Tuberculosis

We studied the D-IV fraction of lipid and wax-P, and compared with brain lipid. Wax-IV obtained from BCG had the greatest antigenicity in the presence of mannose. The reaction against tuberculosis serum depends on the presence of mannose. This finding is of significance in explaining the Middlebrook reaction using tuberculin, and the specific and non-specific factors in leprosy. More experiments are planned.

DR. O. K. SKINSNES (Hong Kong):

The Defence Mechanism in Leprosy as Related to the Internal Lesion and Malnutrition

He showed diagrams of present concepts of immunity in leprosy. The inadequate defence mechanism is conspicuous in lepromatous leprosy. Leprosy is a systemic disease and one should not ignore the systemic aspects. There is a bacteriaemia and visceral lesions, and the endothelial and lymph systems are involved. There is propagation of the bacilli in visceral lesions.

The effect of severe protein deficiency on the progress of the infection in rats has been shown, and they lose ability to produce antibodies and even leucocytes. Depleted animals could not get rid of an infection, even when given penicillin. In leprosy patients we found a similar effect from protein malnutrition: the patients had high

morbidity and took long to respond to therapy. Hypoproteinaemia causes a severe type of leprosy which goes downhill and loses positive reactive power (Lazarine type of leprosy). It is not so much vitamin deficiency but a basic protein deficiency.

DR. J. M. M. FERNANDEZ (Argentina):

The Influence of the Factor of Tuberculosis on the Lepromin Reaction

He made an exhaustive study of all the work bearing on this subject by other authors and himself. Though some of the experiments have been technically imperfect and their conclusions debatable, he thinks there is a genuine para-specific influence on the lepromin reaction. Besides the specific factor of *M. leprae*, whether spontaneous in the leprosy infection, or provoked by the inoculation of lepromin, there is the para-specific factor of *M. tuberculosis* which also can be spontaneous in the shape of a tuberculous infection, or provoked by inoculation of BCG and suspensions of dead bacilli. Finally there is the non-specific factor represented by *M. lepraemurium* and other acidfast bacilli.

Session adjourned at 12.15 p.m.

SOCIAL ASPECTS

18 NOVEMBER, 1958
2.00 P.M.

Chairman: MR. T. H. JAGADISAN

Rapporteur: DR. HEMMERIJCKX
SISTER HILARY ROSS

MR. T. N. JAGADISAN gave the report of the Panel. This report is based on correspondence and discussion. There is a brightening in the outlook on leprosy. The sulphones have altered the outlook, and also physiotherapy and surgery have advanced. Rehabilitation therefore becomes urgent and important. In simpler communities rehabilitation is not a problem, but it is grave in the sophisticated communities. There are three kinds of patient (1) those recovered without marks of the disease: employment must be found for them and they should be reassured as to their non-infectiousness (2) those who recover but with deformities, who are a greater problem. Brand has shown that much could be prevented or repaired: centres should be formed for them. Education can prevent deformities and suitable work found and suitable tools made available, marketed from a central agency: (3) gravely crippled or blinded patients who should not be heartlessly discharged. Deformity can become a thing of the past but until then we have a large task. Psychic rehabilitation should not be left out. Large rehabilitation colonies are not desirable because they defeat the main purpose of rehabilitation, the return to normal life in society. We must give these patients hope and the training for return to useful life. A new spirit must be implanted in the patient and the community. Protection of children is also always paramount, as shown by Mrs. Weaver in Brazil. No other country has reached their scale of preventoria and educational orphanages. There are certain disadvantages, but they suit certain countries: most countries use other methods to protect and care for the children.

Propaganda remains important to help in the problem of infection of children. Some sort of health education is done in most countries but the effort in relation to the need is small. Education could be by teams who go among the people with advice and demonstrations.

Financial assistance to the family of the leprosy patient: in some countries social assistance is not done but the need is very great. The minimum constructive help should be given, either by private or state schemes.

There is very little enthusiasm for legislation in relation to leprosy. Abolition and amendment is often called for.

Some ask that more notice should be taken of the advice given in this Congress. Government and people often ignore the findings of the Congress. The very success of treatment may lead to ignoring the other spects of the problem. The wider picture must be kept before the younger doctors and the public. This Congress has used this wider vision.

MRS. E. WEAVER (Brazil):

Social Aspects of Leprosy Problems

We are happy to be in Japan and meet Dr. Mitsuda and see the fine work being done here.

A very comprehensive plan has been carried out in Brazil to perform our social duty to the patients and to their dependents. In countries where resources are less, social plans can at least be carried out by stages. Poverty and bad conditions afflict many of our patients and their families and we have tried to deal with them, even in the new period of expansion of the leprosy campaign in the last few years. Those who are put in preventoria are trained by it. But the people who take children as foster-parents to them are not always satisfactory. There is still too much social prejudice against leprosy-contact children, but some foster-homes are successful.

Still the preventoria remain the safest and best homes for separated children, and they go back well educated and normally stable and make good citizens. Political and religious sectarianism should be avoided in all social work for leprosy contacts. The educandaria are useful: they are like boarding-schools. We have 20,000 children in homes.

MONSIEUR R. FOLLEREAU (President of the Order of Charity):

Why I Have Established The "World Leprosy Patients' Day"

I established this day in 1954 to revive dignity and respect for leprosy patients. In many countries they are still treated shamefully. I try to appeal to the conscience and hearts of more and more people. All leprosy patients should be treated, respected and loved. It is we who have turned them into 'lepers'. Many countries have paid heed to this World Leprosy Patients' Day, and the practice spreads, and along with it there spreads friendship for leprosy patients and determination to treat them humanely. Love has conquered: the walls have fallen. All special legislation regarding leprosy should be abolished. Leprosy patients can marry freely and prejudice against their marriage should be removed. I will continue my travels and my protests against an unenlightened attitude towards leprosy patients. This century could become the century of victory over leprosy.

DR. F. CONTRERAS (Spain):

Social Assistance in Leprosy

I agree with Mrs. Weaver about the value of organized and complete social assistance. I congratulate the Japanese workers also. These Leprosy Congresses are of great value, but the amount of leprosy in the world is still huge. At the Rome Congress we saw the need of many teams and much co-operation. Social work must go hand in hand with the best possible treatment. We protect our patients. Entry into sanatoria must be voluntary, also discharge from them. Leprosaria are still of great value in many ways, as are the preventoria. We have dermatological hospitals also where leprosy patients are also admitted.

All patients receive a Social Security payment in Spain. We avoid special legislation for leprosy. All members of the family are protected, especially the children. There are various ways of overcoming any possible psychological damage to children put in preventoria or colleges: visits of relatives can be encouraged. We must be humble and respect the experience of all other workers.

DR. F. HEMMERIJCKX (India):

Pattern of Social Assistance in Countries of High Leprosy Prevalence

Such highly endemic countries usually have little money. Priority should be given to the medical and preventive side, but social problems must not be forgotten. The medical profession shows no interest in leprosy and avoids treating it. Medical workers in the leprosy teams, however, must take more interest in the conditions of the patients.

More workers must be trained, preferably in the medical colleges. Our own fault as leprologists is to keep leprosy too complex. Paramedical staff are very important: we must train many and train them carefully. Education should start in schools with the teachers: propaganda at the village level is essential. Propaganda must be repeated and made everywhere, and be very practical in answering the natural questions about leprosy. The real difficulty for the patient begins when we pull the patients out of their families: mass treatment has a great advantage in this. The patients themselves are very conscious of the advantages of treatment: they should get psychic and social understanding.

Discussion

DR. VENKATESWAR (India): "Remember socialized medicine will come in many countries. A proper course for undergraduates should be given in leprosy. Tackle the patients as a whole. All leprosy is infectious, more or less. All ages can catch the disease."

DR. RICHET (France): "Many physicians do not cooperate in dealing with leprosy. In underdeveloped countries the mobile treatment team is the best answer. I thank M. Follereau for his help in such campaigns. Attendance of the patient is helped by tax-exemption in reward for attendance."

DR. SUCH SANCHIZ and DR. F. CONTRERAS (Spain): "Social security extends over the world. We propose that all rehabilitation centres should coordinate their studies and agree on methods and incorporate their programmes into national programmes. The next Congress should include Rehabilitation for special consideration."

THE CHAIRMAN said this proposal was received with sympathy and would be handed to the secretariat of ILA for action.

DR. MURRAY (Korea): "I agree with most things said but am surprised at lack of mention of one point—that of family planning to prevent birth of children into such an environment."

Intermission of 10 minutes at 3.40 p.m.

Social Aspects

PROFFERED PAPERS

18 NOVEMBER, 1958
3.40 p.m.

Chairman: MR. A. SAITA

Rapporteur: SISTER HILARY ROSS

DR. M. C. ESTRADA:

Social Aspects of Leprosy in Mexico

The high contagion is a false idea which has done a lot of damage and we in Mexico are still fighting against it. The social and human side depends on eradicating this prejudice, and others. We study also history and social status and condition, and his state of mind. We talk with the patient in a friendly way. Obligatory segregation has been abolished in Mexico. There is only one leprosarium, and we have even changed the names to Dermatological Centres and Clinics. We never talk of 'lepers'.

We use all care to obtain a human and helpful approach to patients. I wish to describe one case who was first misdiagnosed as typhus. Leprosy was finally diagnosed. He tried to take his life by jumping under a train. We took him in and gave him an explanation, and finally clinical cure.

DR. R. OZAWA (Japan):

(Paper presented by Dr. K. Hamano on his behalf)

Social Activities at the Leprosarium in Japan

There are 14 leprosaria in Japan with 14,261 beds. We have about 15,000 patients in Japan. The Imperial family gave the impulse to the work, and various religious bodies have helped. The peak of the prevalence seems to have passed. There are many patients who have to be reached and given care, and to ensure this various social assistance measures are proposed. Their family financial troubles are relieved and the children and relatives are cared for, in special institutions if necessary. Education of children is provided. Elderly relatives who are deprived of support are given care in special homes. Vocational training and rehabilitation are given to patients in leprosaria. Funds are advanced to help their becoming settled in ordinary life. There are special social workers in each prefecture. It is very rare to have to enforce segregation. The families and the public are given education. The Japanese Leprosy Foundation was founded by the late Empress Teimei. It has done a lot of educational work and helped leprosy patients and their relatives, runs homes, provides scholarships. It has branch offices in 10 districts which promote the hospitalization of leprosy patients.

Discussion

DR. GIFFEN (U.S.A.): "As long as 'leper' is used, too little progress has been made. None can be called deformed but the unkind."

DR. HEMERIJCKX (India): "We need to protect patients against their employers sometimes. Special institutions are justified in many cases."

DR. SUCH SANCHIZ (Spain). A film show of his work on rehabilitation in Trillo was given with his explanations. He has built up at Trillo a carefully organized rehabilitation and training programme for leprosy patients approaching their return to civic life. Nothing is forgotten which will help them, whether training in a special skill, participation in cooperative farming and industry, or the infusion of courage and self-respect as citizens. The general public is also brought under training so as to receive them naturally. Due regard is given to the prevention and correction of deformities.

VII International Congress

FINAL PLENARY SESSION

19 NOVEMBER, 1958
10.20 a.m.

President: DR. KITAMURA

Vice-President: DR. WADE

The President thanked all members of the Congress for their hard work and assiduous attendance.

"*The Report on Classification* is in your hands. Do you wish to have it read?" *Accepted* that it be considered without reading (by show of hands). "Is it accepted or rejected?" *Accepted* (by show of hands).

"*Report on Therapy* is in your hands." Voted by the assembly not be read. Dr. T. F. Davey read the few suggested changes. The assembly now voted to accept the Report.

Report on Bacteriology and Pathology. Dr. Muir suggested it should be accepted. Dr. Hanks read some corrections in punctuation and some other corrections. The assembly now voted to accept the Report.

Report on Immunology had already been read in the symposium. The assembly voted to accept the Report.

Report on Epidemiology and Control. Dr. Doull read out some changes and additions.

Dr. Azulay complained of the lack of time to consider the report, and pointed out on page 11 the remarks at bottom of page 11 were not in agreement with the summary in No. 6 on p. 14: also on page 1, in the 2nd para., he wanted 'the dispensary' replaced by 'out-patient'. These changes were accepted.

The assembly voted to accept the Report.

Report on Social Aspects. This was read in the symposium and there was no need to read it now.

DR. SUCH SANCHIZ proposed an addition on social rehabilitation and that the next Congress should have a special committee on rehabilitation.

Mr. Jagadisan said it was more a matter for the Council of ILA and of future Congresses, and the secretariat of I.L.A. would take note of it.

The Report on Social Aspects was accepted by vote of the Assembly.

DR. WADE said there would have to be an editorial committee to edit the Reports which are now acts of the Congress on their acceptance. 'The Congress recommends' will now replace 'The Committee recommends'.

DR. MUIR reported a cable from Mr. Perry Burgess "We send heartfelt greetings to all: 7th Congress will be outstandingly successful".

DR. MUIR proposed a return telegram, which was approved by acclamation of the Congress.

MR. A. DONALD MILLER spoke as follows:

"Mr. President, as we come to the end of this memorable Congress I am sure that every delegate is deeply conscious of the debt we owe to those who have made these days together so happy and so significant.

We have met in your beautiful and ancient land where the graces of courtesy and culture still shine amid the stresses and ardours of technical progress. We are grateful for the abundant hospitality we have received, and as we scatter to many parts of the world we shall take fragrant memories of you, our true friends.

The Congress has been notable in many ways. To those of us who remember earlier ones the progressive advances in hopefulness and authority have been evident. And this Congress, I believe, will be remembered for its clarity of thinking, its unity of spirit, and its humanity of outlook.

There are those, Mr. President, to whom, on behalf of the members of the Congress, it is my privilege to express our thanks, though there are many who have earned our gratitude who cannot be mentioned personally.

First, we express our deep appreciation of the gracious and active part taken by THEIR IMPERIAL HIGHNESSES PRINCE AND PRINCESS TAKAMATSU. Their help has been a visible confirmation of that Imperial concern which has been so marked in the past.

And then we are grateful to:

THE MINISTER OF HEALTH AND WELFARE,
THE MINISTER OF FOREIGN AFFAIRS,
THE GOVERNOR OF THE METROPOLIS OF TOKYO, and
THE PRESIDENT OF THE NATIONAL COUNCIL OF SCIENCE

for the various and valuable parts they have played in facilitating the gathering and operation of this Congress with such easy efficiency.

We are greatly indebted to the TOFU KYOKAI and its PRESIDENT MR. SHIBUSAWA, and to the Japanese Leprosy Association which has been associated with the Tofu Kyokai in sponsoring all arrangements for our reception.

Especially must I make reference to the ORGANIZING COMMITTEE members, under the honorary chairmanship of DR. MITSUDA. It has been one of our greatest honours to meet this veteran and distinguished doctor who for over sixty years has rendered such yeoman service in Leprosy work.

We are grateful also for the acting chairmanship of DR. KITAMURA; and it is difficult to express adequately our thanks for the self-effacing, arduous, and skilful work of the Executive Secretary, our good friend DR. HAMANO.

A member of the Committee who has rendered invaluable help in more ways than we can realise is the CHIEF LIAISON OFFICER, INTERNATIONAL AFFAIRS, MINISTRY OF HEALTH AND WELFARE, our familiar guide and counseller MR. SAITA.

To those and the MEMBERS OF STAFF of Tofu Kyokai and the many VOLUNTARY HELPERS we offer our warm gratitude.

The visits that have been made by delegates to the NATIONAL LEPROSY RESEARCH INSTITUTE and TAMA ZENSHO-EN were greatly

appreciated and we are grateful to DR. KOBAYASHI and DR. HAYASHI and their staffs.

The LADIES COMMITTEE has rendered a splendid service in gracious helpfulness and imaginative planning for the happiness of the wives of delegates. We are grateful to these, and for all the other arrangements made for our social entertainment.

Our most sincere thanks also goes to the INTERNATIONAL LEPROSY ASSOCIATION and its distinguished officers. The Association has been co-sponsor of the Congress and of indispensable help. I am sure I voice the feeling of us all when I pay tribute to the gallant and devoted service rendered for so many years by DR. WADE, its President. In between two Congresses the Journal which he edits with meticulous care holds us all together and conserves what would otherwise become ephemeral. And to DR. MUIR, the Secretary-Treasurer, we pay our homage for the selfless and dynamic work he has engaged in, not only for this Congress but in blazing a trail of new and natural life. The Deputy Secretary, DR. ROSS INNES, has quietly carried all the exacting burden of detailed minute-to-minute work, and our gratitude to him is very real.

I must now mention very summarily other bodies or people to whom we are grateful:

THE WORLD HEALTH ORGANISATION, represented by DR. FANG, Director of the Western Pacific Region in Manila, and DR. GAY PRIETO, recently appointed Head of the newly-created leprosy section of WHO in Geneva.

THE INTERPRETERS, led by MR. SIMHA of the Geneva headquarters and MR. SCHELLENBERG of the Western Pacific Region office, and helped by their friends in Tokyo.

The simultaneous translation has been of a very high order; and many of us have listened and watched with fascination Mr. Simha translating technical papers with consummate ease and literary grace.

And then MISS MCGREGOR of the Manila office who flooded with manuscripts and requests, has with imperturbable charm dealt, together with her office staff, with the oceans of typing and duplication.

To all these we are most grateful.

THE COUNCIL OF THE INTERNATIONAL ORGANIZATION OF MEDICAL SCIENCE has materially assisted by a grant to ILA in its preparatory work and by help to enable research workers in nearby countries to attend.

We are all most grateful also to DR. DHARMENDRA, on whose shoulders fell a great deal of preparatory work of a most important character when it was expected the Congress would be held in India. The Organizing Committee greatly benefited by his work, enabling it to prepare for the Congress in Japan at such short notice.

The beautiful flowers sent by PATIENTS have kept us in constant remembrance of those whom we endeavour to serve in many lands. Our greetings go to them, and the assurance of our loving concern.

MR. PRESIDENT, I request you to accept this inadequate recital of our thanks, and I would ask delegates assembled here to express their endorsement of them by standing, and by applause.

VII International Congress

CLOSING CEREMONY

MR. A. SAITA, *presided*

DR. HAMANO, *supporting*

DR. HANKS spoke on some outstanding features of the Congress.

"Mr. Chairman, members and sponsors of the VII Congress I count it an unusual privilege to have been invited to say a few words in recognition of the accomplishments of the VII Congress. On all sides, there has been praise for the organization, the program and the hospitality.

The symposia were illuminating and helpful. These and other papers have helped us to appreciate the progress in general areas of knowledge and in specific investigations. To mention but a few of the highlights (I am sure I do not do justice):

It seems possible that a way has been opened to the study of leprosy infections in experimental animals.

We have seen evidence that rat leprosy bacilli have been induced to grow in cell cultures *in vitro*.

We have been shown repeatedly that histologic studies of sites of the lepromin test may demonstrate response of lymphocytes and epithelioid cells, even when Mitsuda reactions are doubtful or mild.

It is gratifying to learn that the physiologic basis of physical incapacities and deformities has been more adequately defined; also that the simplest of preventive measures often suffice.

In immunology we have seen clearer analyses of the varied causes of the positive Mitsuda reaction, and the way in which this state can be established.

Work in serology has shown a new specificity of reactions.

The subject of classification has been examined more critically and wisely than ever before.

It seems possible that differences of opinion arise from several causes:

1. The difficulty of compressing into a few words both a snap-shot of the more stable polar types and a moving picture of the evolutionary and transitional stages of the disease.
2. If a suggestion from the side lines is permissible, I would emphasise that biological phenomena tend to form a well known distribution curve.

   Extremes or polar types occur least often, while intermediate stages occur most frequently.

   Recognition of the extreme differences between L and T leprosy historically should attract first attention.

   We have now progressed to a point where study and patience will be required to work through this middle ground and to designate the evolutionary and transitional phases of leprosy.

   This goal might be accomplished by constant communication within a standing committee and if its members take opportunity to examine patients wherever Leprologists may meet in every country where a Congress may be held."

"I could not close these remarks without paying tribute to all who worked and sacrificed to make this meeting possible. We are indebted especially to our Japanese colleagues for their untiring sacrifices and for the wonderful way in which they have collaborated with us."

MR. SAITA translated a special message from their Imperial Highnesses Prince and Princess Takamatsu, likewise the Minister of Health and Welfare (of good wishes and farewell). These were received by acclamation.

DR. T. F. DAVEY reviewed Therapy, Epidemiology and Control, and Social Work, and said:

"Mr. Chairman, in reviewing those aspects of this Congress which have dealt with therapy, epidemiology, control, and social work, it is well to remind ourselves that the 6th International Congress was held too early in the suphone age for the full implications of the new era to be understood. During the intervening years, and now at this Congress we have come to realise that we are in fact living through a revolution in the history of leprosy, the extent of which is only penetrating into all those human relationships where leprosy all too often brought fear, hopelessness and degradation. This Congress has illumined the fundamental changes which are going on and are affecting us all in our approach to this disease.

The leprosy worker has now new equipment of great value. He has a cheap, simple, and relatively effective basic treatment, capable of the widest application. Alternatives are available when needed, and more may safely be predicted. We have a new understanding of deformity and a new responsibility in its prevention. We are no longer a small group working in almost a state of professional isolation. We now have the inestimable benefit of the experience and knowledge of colleagues in other fields, for example tuberculosis and immunology, to reinforce our efforts, and powerful organisations like WHO and UNICEF to advise us and give practical assistance in our work.

For the patient, an entirely new situation has arisen. Because his sickness is for practical purposes curable, and knowledge of it is spreading, it need no longer bring loss of dignity. He now knows he is a man like anyone else. He may be able to lead a normal life while taking treatment and continue in his employment.

If a period in a leprosarium is called for, it is but for a time, and can profitably be spent in learning useful occupations and gaining physical, mental, and spiritual adjustment. For him the advances of medicine and surgery can bring ease in reactive episodes and abolish established deformity, and when the time comes for him to leave, we acknowledge a continuing responsibility for him.

Among the general public prejudice dies hard, but here too fundamental change is occuring. Mass treatment campaigns are not only exposing the extent to which leprosy has penetrated in many localities, but by rendering less infective the many, rather than rendering non-infective the few, they are striking a powerful blow at *M. leprae* in its natural environment.

This shift in emphasis from the settlement to the local dispensary is one of the focal points in our thinking at this Congress. We have been reminded that the only sound basis for leprosy control is know-

ledge, for with the discovery that leprosy is both preventable and curable, the disease is robbed of its peculiar aura and becomes but one disease among many.

Leprosy education is thus another focal point in our responsibility to the public. From it alone can develop the normal and humane attitude which will minimise the social trauma caused by the disease to the patient and his family, and gain their co-operation in such public health measures as may be necessary. Only then can we expect the early diagnosis and treatment which is fundamental to leprosy control, and the easy rehabilitation which is the right of every patient.

We have in addition been guided in the technique of sound epidemiological observation, and heard the call for more integration between leprosy work and other health and social services.

As Mr. Jagadisan put it, the outlook on leprosy is brightening, and we who have shared in this Congress have witnessed that at first hand, for there has been a new unity among us. Enthusiasts we may be, but in pooling our experience and our problems we have both become wiser and gained in humility. If science can be married to sentiment, Mr. Follereau's motto may yet be realised, love may indeed conquer, the walls may indeed fall.

DR. HAMANO expressed his pleasure and that of his colleagues of the kind words of appreciation.

He was grateful for the help of Dr. Wade, Dr. Muir and Dr. Ross Innes, also the simultaneous translators and especially for the help of Mr. Saita and all his colleagues in Japan. "I give you a greeting from all the patients in Japan who wish for an early eradication of leprosy in the world".

At 11.40 a.m. Mr. Saita declared the Congress closed.

DIETHYL DITHIOL*ISO*PHTHALATE IN THE TREATMENT OF LEPROSY. (ETIP or 'Etisul'); A PROGRESS REPORT

T. F. DAVEY, O.B.E., M.D., M.Sc., and
L. M. HOGERZEIL, MED. DRS. (Leyden)
Leprosy Service Research Unit, Uzuakoli, E. Nigeria.

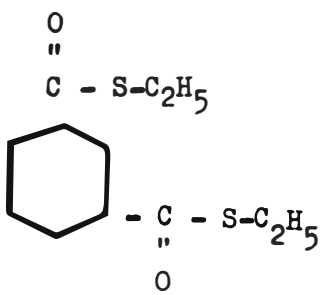
Introduction

In 1950 Del Pianto stated that a mixture of certain thiol compounds prevented the development of tuberculosis in infected guinea-pigs. Although his original statement had later to be modified, it attracted the attention of other workers to the thiol compounds as a possible source of anti-tuberculous substances, and some interesting facts soon emerged. Davies, Driver, Hoggarth, Martin, Paige, Rose and Wilson (1956) traced the active principle to ethyl mercaptan and compounds capable of breakdown or metabolism to it, and found that this property was limited to the ethyl homologue only. Furthermore, it was evident only *in vivo*, the mercaptan having only a slight action *in vitro*, and it was concluded that a metabolite of ethyl mercaptan was the ultimate active agent. They suggested thiol esters as the most promising group of compounds for the treatment of human disease.

After examining many such compounds, Davies and Driver (1957) ultimately chose diethyl dithiol*iso*phthalate as the most promising for therapeutic use. They found this substance to have an anti-tuberculous effect in mice comparable to that of isoniazid and streptomycin, effective when given in single doses, and against isoniazid resistant strains. It was most effective when injected subcutaneously or applied to the skin. Drug resistance was demonstrated. The effects of this and other thiol esters were antagonised by their methyl homologues. Its toxic qualities were of a very low order. These findings prompted the trial of this substance both in tuberculosis and in leprosy.

Notes on Physical and Chemical Qualities

Diethyl dithiol*iso*phthalate is the ester formed from isophthalic acid and ethyl mercaptan. For convenience we shall call it ETIP in this paper. It is also known as Etisul. Its chemical structure is as follows.



The mercaptans or thiolalcohols are mostly colourless volatile liquids with disagreeable smells. Chemically they resemble alcohols in many ways, but differ in their behaviour towards oxidising agents.

Esters formed from them are aesthetically much more pleasant than the corresponding thiol alcohols. ETIP is a bland pale yellow oily liquid with a smell suggestive of garlic, and very similar to the smell of decaying neem fruits. Although decidely less unpleasant than that of ethyl mercaptan, and indeed quite tolerable when first encountered, its odour is persistent, and we have found that tolerance to it tends to diminish with increasing acquaintance. When given by injection, the odour of ethyl mercaptan can be detected in the breath within fifteen minutes.

Clinical Trial in Leprosy

Italian workers have continued to study sodium ethyl-thiosulphate, one of the two thiol compounds used by Del Pianto in the work referred to above. Bertaccini (1957) described a trial of this substance in a total of thirty-one leprosy patients, to whom it was given orally in a dose rising from 0.8g daily to 1.6g daily. All the patients were classified as lepromatous, but twenty-six had had previous sulphone treatment, and only fourteen were stated to present overt and active lepromatous lesions. They were treated for periods up to nine months. It was considered that sodium ethyl-thiosulphate had a chemotherapeutic action not inferior to that of other drugs, and deserved further study. Reference was made to a lack of toxicity, and to the smell of garlic in the breath. (See also in this issue a report of the contribution of Del Pianto, page 22).

This substance was one of those examined by Davies, Driver, and their colleagues, but as has already been mentioned, their choice for a drug of greatest practical usefulness finally fell on ETIP. This compound has now been subjected to clinical trial both in tuberculosis and leprosy. We here describe a pilot trial in leprosy, which has so far covered sixty-five patients, all with their disease in an active condition, and nearly all of them without previous chemotherapy. They have received treatment with ETIP at various times during the past eighteen months, mostly for short periods.

Standards

Although clinical appearances, photography and histology have all contributed to our judgment in estimating the progress of patients in this trial, reliance has been placed primarily on changes in the numbers and morphology of *M. leprae* as observed in routine smears. The Bacterial Index with a maximum reading of 4.0, based on the average of findings at multiple sites, has been used as a register of quantity, and its variation during the course of treatment has provided a measure of progress which experience has shown to be the least subject to criticism, while detailed records of the condition of the bacilli at all sites tested have given much useful additional information.

The practice, formerly routine, of selecting individual controls in drug trials, has been superseded at this unit by the use of a standard graph showing average decline in Bacterial Index during DDS treatment. This has gradually been built up during the past five years and represents the average decline in Bacterial Index of 150 patients who have had DDS treatment alone and continuously for four years. It is considered that this yields a more reliable standard

than can be provided by individual controls. It offers a means of comparing one new drug with another, and enables the progress of individual patients or of groups of patients to be compared with the average for the unit. This standard is used in this trial.

Toxicity

Very frequent examinations of blood and urine were undertaken as routine on all patients receiving ETIP. In the dosages used it has been impossible to demonstrate any significant toxic action of any kind.

Progress of the Trial

The nature of ETIP, the manner of its administration, and its effects have introduced unusual features into this trial and necessitated its development in four stages. These will be described in turn.

First Group

The original trial group of patients consisted of nine lepromatous and nine tuberculoid cases, all unselected apart from the criteria of good general health, active leprosy, and no previous chemotherapy. It so happened that the lepromatous cases were all relatively recent infections, the majority representing a degeneration from a previous borderline form of the disease. In them all the disease was active and progressing, the high proportion of normal bacilli in routine smears confirming the lack of previous chemotherapy.

At that time the ETIP preparation consisted of a 70% cream lacking a perfume strong enough to mask the smell of ETIP. This cream was administered by inunction in a dose of 3 cc. weekly, with vigorous massage over a wide area of the body surface.

The trial soon proved self-limiting. After a few weeks patients found the persistent odour of ETIP (and ethyl mercaptan in their breath) increasingly offensive both to themselves and their neighbours. Although all did their best to persevere, gradually one by one they asked to stop the treatment, until by the fourth month it became necessary to abandon the trial for the time being, and patients with two exceptions were transferred to standard oral treatment with DDS, DPT, or DDSO. The arrival of a second preparation more strongly perfumed than the first failed to affect the outcome, but did enable four patients to take combined treatment for a further three months. The two exceptions did continue with the treatment, and more is said of them later.

Results. (a) Lepromatous cases

Even in the short period of trial some surprising results were obtained. Without exception all lepromatous cases showed a marked change in the state of their bacilli within eight weeks, with diminution in numbers and a considerable increase in the proportion of degenerate forms, not only locally at the site of inunction, but generally at all sites tested. In some of them change was evident in the first month. Later, progress tended to slow down, and at the conclusion of the experiment had become erratic.

There was here a reversal of the usual sequence in the chemotherapy of leprosy, for bacteriological progress preceded clinical progress instead of following it, and patients themselves, although feeling well, did not appreciate from the appearance of their lesions the change that had occurred. Clinical improvement became obvious later, in most cases after oral treatment with DDS or CIBA 1906 had been instituted, and with the passage of time it became evident that clinical and bacteriological improvement was continuing at a rate decidely above average. This was not an individual finding but was common to the group as a whole, as is evident from Figure 1, in which the average progress of the Bacterial Index of the group is compared with the DDS standard. The two exceptions who continued ETIP treatment after the others are excluded.

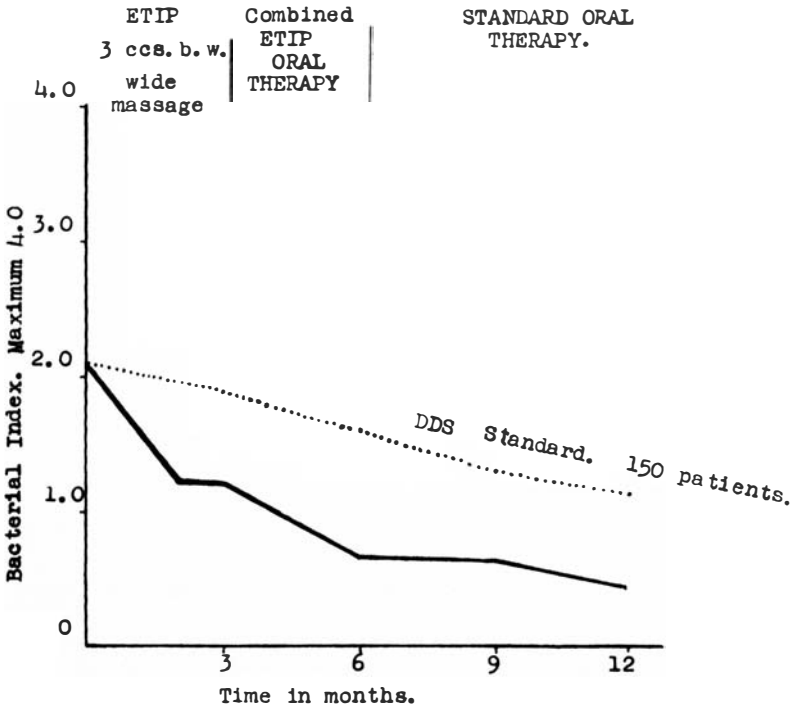


FIGURE 1
Variation in Bacterial Index in patients receiving ETIP followed by standard oral chemotherapy.

The following case notes on three of the patients in this group illustrate the general trend.

1. Ref. No. 9815. Male aged 14. Early but very active diffuse, nodular and macular leproma of two years duration. No previous chemotherapy. Bacterial Index 2.6 on admission, with bacilli almost all in normal form. ETIP was given in a dose of 3 ccs. twice weekly for ten weeks. During the first month the B.I. fell from 2.6 to 1.6, with the development of degenerative changes in a large majority of bacilli. This progress was not maintained, and at the tenth week the B.I. was tending to rise. DDS treatment was then instituted, when progress was resumed. Six months later the B.I. had fallen to 0.9 with all bacilli in a degenerate condition. Clinically and bacteriologically the improvement shown by this patient in nine months was well above the average shown by patients on DDS alone.

2. Ref. No. 1160. Male aged 28. An early infection with symptoms of five months duration. Borderline leprosy now rapidly degenerating to leproma with severe nerve involvement. Bacterial Index 2.5 with 100% bacilli in normal form. ETIP was administered in a dose of 3 ccs. twice weekly for ten weeks. Six weeks after treatment had started the Bacterial Index had fallen to 1.5 with a majority of bacilli now degenerate. Four weeks later it was still 1.5, though at some sites further degeneration of bacilli had taken place. Treatment was now changed to DDS, and progress continued. Six months later the B.I. had fallen to 0.8 with all bacilli degenerate and the condition of the patient excellent. In this patient an unusual decline in Bacterial Index in the first weeks of treatment was succeeded by improvement during DDS treatment which continued to be above average.

3. Ref. No. 865. Male aged 28. Very active nodular, diffuse and macular lepromatous leprosy of only two months duration, a relapse four years after discharge in a previously indeterminate case who had had hydnocarpus and sulphone treatment. Bacterial Index 3.3 with bacilli almost all in normal form. ETIP was given for seven weeks in a dose of 3 ccs. weekly. At the end of this time the B.I. had fallen to 2.7. At this point DDSO 100 mg. daily was given in addition to the ETIP for a further three months. During this period the B.I. remained steady, but the proportion of degenerate bacilli continued to rise. Thereafter treatment continued with DDSO only. Six months later the B.I. had fallen to 1.1, with all bacilli in a granular condition. Clinical improvement was also excellent. After one year progress was definitely better than would have been expected with either DDS, DPT, or DDSO alone.

(b) Tuberculoid cases

During the period of trial, three of the nine cases showed rapid clinical improvement, the others exhibiting nothing outstanding. Subsequently on oral treatment all have made very good progress.

Comment

Here was a drug of obvious interest. All the lepromatous cases appear to have received in the first weeks of treatment an impetus to recovery which later stood them in good stead, so that by the end of a year their progress was at least six months ahead of that expected with standard oral treatment. It was impossible to explain this and the rapid change in the condition of bacilli in the first weeks of treatment on any other grounds than chemotherapy. Unfortunately in the presentations then available ETIP had no future. Our patients possess in high degree, a willingness to co-operate which would go far to overcome their squeamishness where an odoriferous compound was concerned. If they reached the limits of their tolerance after a few weeks it seemed most unlikely that others would find the drug more tolerable. The manufacturers were advised accordingly.

Second Group

Three months later a fresh preparation of the drug was received, this time much more effectively perfumed. In order to make it still more acceptable to patients the suggestion was offered that it should be applied to a limited area of the body only, avoiding hairy parts, and at a site not normally covered with clothing if possible.

A fresh group of twenty-two patients volunteered for trial with this preparation. They consisted of fourteen lepromatous and eight tuberculoid cases. Some of the lepromatous cases were severe, and the whole group represented a heavier level of infection than obtained in the first group. In addition two of the first group volunteered to join the second and were allowed to do so.

These patients received a dose of 6 ccs. ETIP twice weekly, i.e., double the dose administered to the first group. It was rubbed into the legs from above the knees downwards, an area of the body usually kept free from clothing. It quickly became apparent that although this third preparation was aesthetically a considerable advance on the first, the perfume in it effectively masking the ETIP when first applied to the skin, it was still by no means perfect, as the perfume tended to disperse before the smell of ETIP disappeared. With some difficulty patients were persuaded to continue with this preparation for periods up to five months. The lepromatous cases were divided into two sub-groups, one of which received INH orally in addition to their ETIP, as it had been suggested that this might be beneficial. In actual fact the INH appears to have had no perceptible effect on the outcome, and can be ignored.

Results. (a) Lepromatous cases

Progress with this group was in distinct contrast to that observed with group 1. During the first two months of treatment bacteriological improvement comparable with that observed in group 1 was witnessed in only four out of the fourteen cases. Three others showed some progress, but the remaining seven showed little if any change apart from some diminution in the proportion of normal bacilli in routine smears. During the third month failure to improve became almost general, except in two cases in whom some change in leprosy type was developing. From the fourth month onwards the reappearance of normal bacilli in increasing numbers in the ears and nose was noted in six patients, followed by a rise in Bacterial Index and heightened clinical activity of the disease. Here was evidence that *drug resistance* had begun to develop, and this was strengthened by the fact that both the group 1 patients who continued taking ETIP exhibited exacerbation of their disease with considerable increases in Bacterial Index after six months treatment with ETIP. The following notes on one of these may be of interest.

> Ref. No. 5660. Male aged 33. Two years history of leprosy, evidently borderline, now becoming frankly lepromatous. B.I. 2.0 with strongly positive smears in ears and face, and macules on the body with varying bacillary concentration. ETIP was first given in doses of 3 ccs. twice weekly for four months, then raised to 6 ccs. twice weekly. Six weeks after the onset of treatment the B.I. had fallen to 1.0, with a majority of bacilli degenerate. Subsequently the B.I. rose again, the proportion of normal bacilli increased, until in spite of increased dosage the B.I. at the end of seven months was 3.2 with 100% normal bacilli in the nose, and the clinical condition of the patient obviously degenerating. Treatment was then changed to DDS, with subsequent rapid clinical and bacteriological improvement. The movement of the Bacterial Index in this patient is compared with the DDS standard in Figure 2.

(b) Tuberculoid cases

Irregularity of resolution was also witnessed among the group of eight tuberculoid cases. One made very good progress, five made progress that was not outstanding, one remained stationary, and after some resolution the eighth showed fresh spread of the disease.

When transferred to standard oral chemotherapy, all these patients made very satisfactory progress within three months.

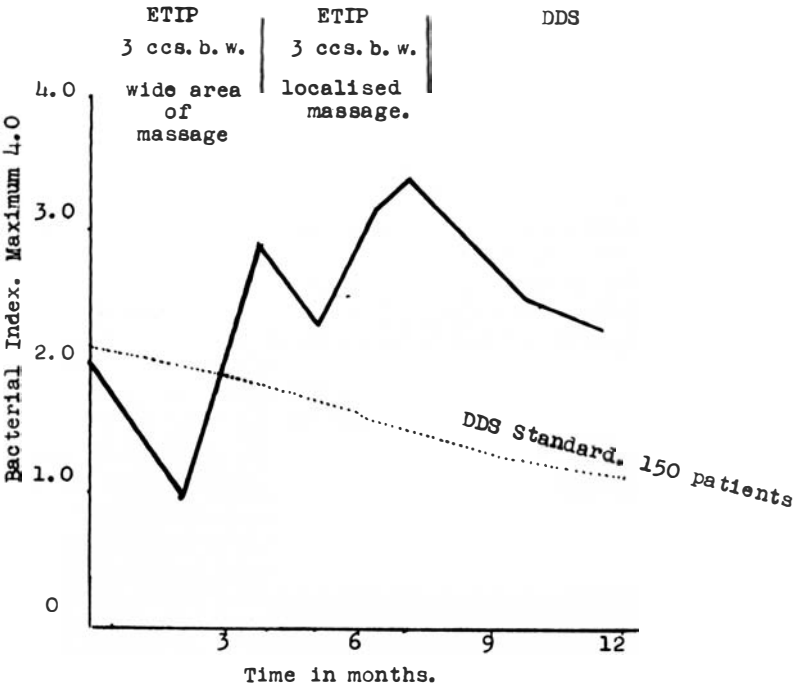


FIGURE 2
Variation of Bacterial Index in a patient developing drug resistance to ETIP.

Comment

Thus in spite of an increase in dose ETIP appeared on the whole to have had considerably less therapeutic effect in this group than in the first group of patients, with strong evidence of drug resistance developing if treatment was continued for more than four months.

When considering possible causes for the discrepancy between the findings in Groups 1 and 2, attention was directed first to *the method of inunction.* Close observation of the patients soon made it highly probable that absorption of the cream from the limited area of the body to which it was applied by Group 2 was defective. Patients quickly tired of rubbing just one area of the body, and it seemed likely that any virtue there may have been in increased dosage was more than counterbalanced by inadequate absorption from a relatively small area of skin, and that one not the best, adapted for the purpose.

It became necessary therefore, to test the drug once again in a third group, in whom the larger dose would be combined with inunction over a wide surface of the body.

Third Group

This group consisted of ten lepromatous and five non-lepromatous cases. The lepromatous cases were a very representative selection of this type of the disease. One was a very serious reactivation after TB_1 treatment. The others with one exception had had no previous chemotherapy.

These all received a dose of 6 ccs. ETIP administered twice weekly by inunction over a wide area of the body. All were submitted to very close observation, several being biopsied, with routine smears being taken at intervals of two or three weeks in all cases. The course of treatment was deliberately limited to eight to twelve weeks, after which standard chemotherapy was initiated.

Results

Improvement was general in these patients during the period of trial, the pattern observed in group 1 being resumed. During the first eight weeks in eight out of ten lepromatous cases a decline in Bacterial Index was seen, varying from 0.3 to 1.5 and averaging 0.8. It was accompanied in all cases by a marked diminution in the proportion of normal bacilli, strangely enough least evident in the nose. A considerable change in the state of the bacilli was also seen in the two patients in whom the Bacterial Index remained steady, and these subsequently made good progress.

During the third month progress once again became variable, five showing continued progress, the other five remaining stationary. By the end of this month ETIP was either joined or replaced by DDS in all the patients. Their progress during the period of trial is well illustrated by the following case notes on two patients, both heavy infections of unquestioned lepromatous leprosy, both previously untreated.

1. Ref. No. 5692. Male aged 30. Very severe diffuse, nodular and macular leproma, diffuse on face and ears, nodular elsewhere, particularly involving buttocks, arms and legs. Two years history. No previous chemotherapy. B.I. 3.2. ETIP 6 ccs. twice weekly. Eight weeks after starting treatment the B.I. had fallen to 2.9 with a diminution in the proportion of normal bacilli from 70% to 25%. At the eleventh week DDS was added. By the thirteenth week the patient was well and happy. Clinically there was by now an obvious change in his condition, with infiltration of the face much less, and increased localisation and diminution in size of nodules generally. B.I. still 2.9 but now only 15% normal.

2. Ref. No. 5697. Male aged 23. Early but widespread nodular leproma, with six months history of symptoms but only two months history of eruption. Now presenting innumerable nodules on all parts of the body, relatively well localised. B.I. 3.7. ETIP given, 6 ccs. twice weekly. During the first month the B.I. remained steady, but during the second month it declined to 3.0. By the tenth week clinical improvement was evident and the patient very well. Biopsy of this patient at the third week showed a typical and quite extensive foamy leproma on histological section. Biopsy at the twelfth week from a site adjacent to the first indicated a considerable reduction in the area of leproma, most marked in the more superficial layers, but evident throughout the corium.

Comment

It is impossible to envisage changes of this nature, occurring so quickly in patients of this type, apart from effective chemotherapy.

Reviewing the three series of patients up to this point, two interesting facts emerged. The first was the advantageous course taken by the patient when ETIP was associated in some way with DDS. Reference has already been made to the excellent progress of those who received DDS after their course of ETIP. In Group 3 the greatest progress of all was made by the one patient who had had some previous chemotherapy, namely five months of DDS treatment.

He was a patient with quite severe diffuse lepromatous leprosy. During the first *eight weeks* of the trial his Bacterial Index fell from 3.0 to 1.5, a fact that speaks for itself. In a patient of his type such a change would have been incredible on DDS treatment alone. The second observation made was that progress was also good in patients in whom there was a macular element in their clinical picture.

The first of these observations prompted the trial of ETIP in conjunction with DDS in a fourth group of patients. This trial is still in progress and will be reported more fully later. Here it can be said that in the ten lepromatous and borderline cases at present included in it, obvious bacteriological improvement has taken place within six weeks of starting the combined treatment.

Discussion

From the facts elicited so far it may be said that ETIP is a drug of considerable interest to the leprosy worker. The possibility that drug resistance may develop quite quickly if the drug is used alone is itself sufficient to remove ETIP from the select group of basic leprosy remedies, but it already appears to have a place as an adjunct to oral chemotherapy, and if drug resistance can be delayed by combination with other drugs, its future influence in leprosy treatment may be considerable. It has not been an easy drug to study. This report is only a beginning, for many points of interest arise in connection with it which as yet are not clear. The following call for further comment.

Speed of action

The main action of ETIP appears to be concentrated in the first two or three months of therapy, and during this time the speed with which it may influence leprosy bacilli is something new in our experience. Although some borderline cases and the occasional lepromatous case do respond very quickly to oral chemotherapy, the effects of DDS are usually more evident in the second three months than in the first. CIBA 1906 (DPT) approaches most closely to ETIP in its influence during the first three months, but with it a fall of Bacterial Index by 1.0 in this period would be exceptional, whereas with ETIP it was by no means rare.

Administration by inunction

The method of administration by inunction is a novelty, but one that is psychologically sound. Provided the preparation is aesthetically acceptable to patients there is every thing to be said for supplementing oral treatment with skin massage, particularly if thereby a further therapeutic effect can be obtained. In our patients the cream itself has had a useful effect in improving the general condition of the skin. It remains to be seen whether the perfumed preparation now in use will prove generally acceptable.

The technique of inunction is obviously important. The similarity of findings in groups 1 and 3 and their difference from those in group 2 are sufficient to demonstrate this. The cream needs to be rubbed in until it is no longer visible as such. We have found the following general method of treatment the most acceptable to our patients.

Loose garments, the minimum necessary, need to be reserved for the period of treatment. On arrival the patient changes into these, and inunction is then undertaken, avoiding hairy parts, other patients assisting as necessary in applying the cream to the back. The inunction is given with good massage, the treatment occupying about fifteen to twenty minutes for a 6 ccs. dose. The patient thereafter rests for three hours, keeping the inuncted area exposed to the air as far as is possible, and then takes a warm bath using scented soap, after which normal clothes are resumed.

Irregularity of results

One of the curious findings in the trial has been *the difference in effect produced by ETIP as between one patient and another.* Whereas one patient may show a phenomenal change in the state of his bacilli in a few weeks, another of apparently identical type shows nothing comparable. The cause of this is obscure. It does not appear to be directly related to the vigour with which inunction is undertaken. Within the limited range studied, dosage is not the factor responsible. Duration of the disease and the state of nutrition may be involved.

Mode of action

Known peculiarities in the mode of action of ETIP are of interest here. The difference found by Davies and Driver between its activity *in vitro* and *in vivo* strongly suggest that the action of ethyl mercaptan is not directly on *M. tuberculosis*, but is mediated through physiological processes in the body of the host. The same authors (1958) have recently shown that ethyl mercaptan exerts its action intracellularly on tubercle bacilli in tissue cultures of both human and guinea-pig monocytes, and it is evident that no product of metabolism formed elsewhere in the body is required. Rose (1958) suggests that the effect of ethyl mercaptan in the tuberculous animal is to stimulate its natural defences perhaps by inducing a measure of anti-bacterial activity in the macrophages.

If this applies also in the case of leprosy, the effects of ETIP could be expected to be most pronounced in those patients in whom there was already some degree of tissue resistance. It is of interest that a tendency to increased localisation of nodules has been common in our patients, and that macular lesions have tended in several patients to become better defined and closer to tuberculoid in appearance. In these patients there does appear to have developed a heightened immune response, but in all of them a decline in Bacterial Index took place before any clinical change of this nature was evident. It remains to be seen whether these findings were fortuitous or not.

Drug resistance

ETIP is the fourth drug in our experience with which signs highly suggestive of drug resistance have arisen. In all cases the first signs of this have shown themselves by the reappearance of normal bacilli at sites, particularly the nose and ears, at which bacilli had become granular. In succeeding smears the numbers of normal bacilli increased rapidly and soon there was clinical evidence of increased activity of the disease. With ETIP treatment these signs, appearing in some patients after four months, were encountered more quickly

than with any other of the drugs concerned. We may note the slow effect of the drug on bacilli in the nasal septum in this connection. It remains to be seen whether drug resistance can be averted or delayed by combined treatment.

It is of interest that in spite of the similarity in chemical structure between ETIP and the thioureas, CIBA 1906 has proved an effective continuing treatment for patients exhibiting signs of drug resistance to ETIP.

Future work

There is immediate need for the study of this drug in combination with basic oral chemotherapy with DDS or CIBA 1906. One of the most promising features of ETIP is indeed the ease with which it can be combined with DDS. If later observation confirms the results obtained hitherto, we may have here a valuable adjunct to DDS, particularly in mass treatment, in which the cheapness and lack of toxicity of ETIP are important virtues.

The possibility may now be entertained that suitably combined with DDS, or DPT, ETIP may lead to a material shortening in the period of treatment now needed. The most serious disadvantage of ETIP is its odour, not yet completely masked. Related compounds deserve study both from the standpoint of activity and also this important aspect of acceptability to patients. In conclusion it is not without significance that for the first time since trials of ETIP began, patients are now coming forward on their own initiative and asking for it.

Summary

A pilot trial of diethyl dithiol*iso*phthalate (ETIP or Etisul) in the treatment of leprosy is described. Administered by inunction in a dose of 3-6 ccs. twice weekly to sixty-five patients with active leprosy, divided into four groups, the drug, provided inunction is adequate, has been found to exert a chemotherapeutic action in the first two to three months of treatment which is variable but in some patients is very marked indeed. When continued for more than four months signs suggestive of drug resistance appeared in several patients, but when after a course of ETIP lasting eight to twelve weeks, standard oral chemotherapy with DDS, CIBA 1906, or DDSO was instituted, progress continued to be better than average, and all those concerned appear to have received an impetus to recovery during the first few weeks the effect of which continued, so that after one year their progress was at least six months ahead of that expected with oral treatment alone. This led to the trial of ETIP in combination with DDS which is still in progress.

No signs of toxicity have as yet appeared. The only disadvantage of ETIP is its rather unpleasant odour not yet perfectly masked by perfume, but the effects of this can be minimised by a suitable inunction technique.

The safety with which it may be used and its low price commend ETIP for use in mass treatment as an adjunct to DDS, with some hope that combined treatment may lead to a shortening in the period of treatment needed.

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