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.

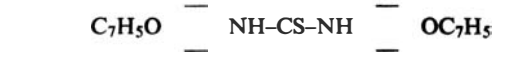
Anaemia: there was no marked anaemic effect resulting from the 5 years of sulphone therapy.

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.

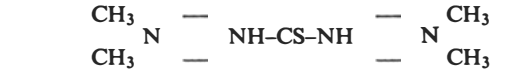
"Clinical trials of some new diphenylthiourea derivatives synthesized at the National Institute of Leprosy Research, Japan, are being carried out for such promine-resistant and non-treated patients, although these are small in number.

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."

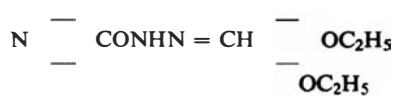
DR. CAP: "Nivaquine with us was not so wonderful but quite good, and had a prophylactic action."

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."