CURRENT LITERATURE

ABSTRACTS OF CONGRESS PAPERS

This section of The Journal *carries abstracts of papers presented at the Rio Congress, as printed for its participants in a large volume, entitled "Abstracts of Papers," which was prepared under the auspices of the Organizing Committee and distributed to those in attendance at the time of the meeting. That volume included, in addition, abstracts of some papers, originally offered for presentation, which, as it turned out, could not be presented personally. The abstracts, in Portuguese, Spanish, English and French, of 171 scheduled papers, were arranged by topics corresponding to the individual sessions in the scientific program.*

In addition to these abstracts about 30 more were furnished to the Organizing Committee after the volume was completed, but prior to the opening of the Congress. Most of these were printed, in the language of the presenting participant, in a supplement to the main volume. These also are here reproduced. A number of the translations from the Spanish and Portuguese in the latter group were furnished to the Editor by the Secretary-Treasurer of the International Leprosy Association, Dr. J. Ross Innes.

Although it is anticipated that the bulk of this material will be made available to participants in the Congress in its forthcoming Transactions, *it has appeared desirable, for the benefit of a wider audience, to carry the abstracts in extenso, in* The Journal *also. In order to make this financially feasible, the abstracts have been incorporated verbatim in these pages through the use of a duplicating procedure that proved economical in space and cost. Inevitably certain minor defects, including some typographic errors, have been carried along in the process. These, while regrettable, are not believed to interfere significantly with the value or the use of the abstracts.*

ROUND TABLE ON PATHOLOGY AND EXPERIMENTAL TRANSMISSION

1

Histopathology in early leprosy

C. M. HASSELMANN

Correct diagnosis of Leprosy at the earliest possible moment is essential in order both to institute adequate treatment when such promises the greatest effect, and for epidemiological reasons to control and prevent contact and transmission, respectively, to susceptible contacts, especially infants.

Even at a very early stage when no acid-fast bacilli are yet demonstrable, a pronounced *narrowing of the stratum spinosum of the Epidermis proper* to no more than 3 or 4 cell-layers is sometimes encountered with consecutive *flattening of the rete-pegs*. The concomitant changes in the mesodermal corium and the upper cutis may be only perivascular round-cell infiltrations, but are rather often still without any so-called "tuberculoid" histopathological architecture.

Based on observation in leprosy patients from, and seen in, the Philippines, Indonesia, India, China, Japan and Africa during the last 40 years, this typical histopathological feature of succinct *epidermal atrophy* has occasionally greatly enhanced our efforts to arrive at the correct diagnosis already during the earliest stages of leprosy.

2

Cerebrospinal fluid proteins in leprosy (I)

W. BROTTO — A. SPINA-FRANÇA

This paper is based on the observation of 45 patients with lepromatous leprosy, in all of whom the Mitsuda test was negative. Alcohol- and acid-fast bacilli were found to be present in 6 cases in cutaneous lesions and/or in the nasal cavity.

In every case the CSF proteins were the object of a study comprising determination of the total protein content analysis of the protein fractions, the latter being examined by paper strip electrophoresis. One sample of CSF from each patient was studied. This was collected from the cisterna magna and presented no changes in aspect, color or cell count. The complement fixation tests for syphilis and for cysticercosis were negative in all samples.

For comparison purposes, other data were studied at the same time, viz.: 1. The total protein content of the blood serum and its protein fractions, the latter also being studied by paper strip electrophoresis. 2. The age of the patients and probable time of the disease. 3. The degree of neurological impairment, evaluated in a semiquantitative way, under criteria presented in Table 1. Results are given in Table II.

The total concentration of CSF proteins was normal in 42 patients. It was slightly greater in 3 cases. Changes in the electrophoretic pattern of the CSF proteins were found at times, the most frequent being an increase in the gamma-globulin fraction, observed in 14 cases. Its occurrence in this form of the disease has been related in a former paper and is confirmed by present data.

The data discussed in this paper show that the increase in the CSF gamma-globulin is probably related to changes in the protein pattern of the blood serum. It seems to be secondary to the increase of the gamma-globulin fraction in the latter.

⁘ In some cases printing considerations have made it necessary to condense the title.

3

Cerobrospinal fluid proteins in leprosy (II)

A. Spina-França — W. Brotto

The protein pattern of the cerebrospinal fluid in 25 leprosy patients was studied and the results correlated with the clinical progress of the disease, clinical form and Mitsuda reaction.

The protein pattern was found to be altered in 11 cases, of which 6 showed an increase in the albumin fraction, 3 in the gamma-globulin fraction, and 2 in the beta-globulin fraction. The ratio of the cerebrospinal fluid proteins to the serum proteins was likewise changed, being higher as regards albumin and beta-globulin and lower as regards alpha-globulin.

The increase in the albumin fraction of the cerebrospinal fluid was observed in patients with undifferentiated forms of leprosy, and with greater frequency in cases of short evolution.

The increase in the beta-globulin fraction of the cerebrospinal fluid was observed in tuberculoid forms of the disease; this increase was seen to occur together with a positive Mitsuda reaction, but statistical analysis showed no significant correlation therein.

The increase in the gamma-globulin fraction was found in cases of lepromatous leprosy, and may be secondary to an increase of this fraction in the serum. Occurrence of an increase in this fraction with a negative Mitsuda test was observed, and here statistical analysis showed significant correlation.

4

Some examples of hepatic involvement in leprosy

A. P. Oliveira — N. Oliveira — L. S. Prigenzi — G. Vorobow

Hepatic involvement in leprosy has long been an intriguing field of enquiry.

The purpose of the research described in this paper was to ascertain whether involvement is consequent to the disease and whether or not it is aggravated by the antileprotic drugs employed. To this end, a group of patients was chosen that had never previously been given specific treatment. At the outset of the trial, these patients were subjected to a dermatological, general clinical and laboratory examination, with particular reference to the hepatic function, confirmed by punch biopsy. After administration of antileprotic drugs for a varying length of time, the examination was repeated in order to assess the therapeutic results obtained.

5

Content of non-proteinic nitrogen compounds and serum proteins in the blood of lepromatous patients

M. P. Azevedo — P. H. Mello — C. E. Rudge — A. C. Marques — E. A. L. Wanderley — T. Kliemann

In the blood of 150 patients suffering from lepromatous leprosy, a group that was being treated with Ciba 1906, determinations were made as follows: urea, uric acid, creatinin, the mucoproteins, C-reaction protein, whole proteins and the serum proteinogram. The laboratory tests were repeated every 2 months over an observation period of 14 months. The normal control values used were obtained from healthy adult inmates of the São Paulo State penitentiary.

The authors ascertained that the various non-proteinic nitrogen fractions were distinctly higher in the group as a whole. These results are examined in the light of the internal pathology of lepromatous leprosy. They likewise noted a significant increase in the mucoprotein content and high frequency of positivity in the C-reaction protein. Finally, the proteinic spectrum of the serum was found to be subject to constant qualititative alterations. Inversion of the albumin-globulin ratio occurred, the increase in the latter element being due mainly to a rise in the gamma-globulin content, followed in importance by additions to the alpha-2 fraction. These results are discussed with special emphasis on the possible correlationship between the increase of the alpha-2

fraction and of the reactional flares and/or occurrence of kidney disorders. The authors proceed to an attempt at analysis of the observed variation in the light of the evolution of the cases throughout the 14 months of specific treatment.

6

Contribution to the diagnosis of renal lesions in lepromatous leprosy patients by means of radioactive tracers

N. Carvalho — M. P. Azevedo — C. E. Rudge — A. C. Marques —

With the intention of interpreting the working conditions of the kidneys in sufferers from lepromatous leprosy by using contrast media tagged with radioisotopes, the authors took a nephrograph of the patients with radiohippuran and studied the track made by the tracer element passing through the vessels, tubules and collecting tubes of the kidneys. They also determined the renal depuration by means of radiohippuran and finally proceeded in some cases to map the kidneys by recording the concentration of neohydrin tagged with mercury^{203} in the renal parenchyma.

It is their belief that the 3 tests made simultaneously are calculated to provide valuable information about the working condition of the kidneys and topographic diagnostic of the lesion, i.e. which kidney is damaged and to what extent. Such tests being harmless, non-traumatic and yielding immediate, reliable results, they would seem to be indicated whenever it is desired to secure data on the functioning of each kidney separately, in any evolutionary stage of the aliment.

7

Fibrocytic histiocytes as host cells for cultivation of Mycobacterium leprae

Y. Yoshie

Before attempting to propagate *Mycobacterium leprae* in cultivated tissue cells, it is indispensable to search for and establish a cell line adapted to the growth of *M. leprae*. Hence, the author has succeeded in establishing cell lines of fibrocytic histiocytes, LH strains capable of yielding continuously transplantable growth, from the clinically lepromatous-type patients.

The behavior of *M. leprae* implanted *in vitro* in the fibrocytic histiocytes of of 5th to 10th subcultures of strains LH 7 and LH 8 was observed, in culture flasks specially designed by the author, over a period of 60 to 80 days at intervals of 15 days. In 4 out of 5 similar experiments, evident elongation of the bacilli (9 to 10.6 microns) was noted in the cultures of 15 to 30 days or more, and the bacterial count per cell was also seen to have increased 1.8 to 3.8 times.

There is a marked difference between these findings and those recorded when the bacilli are similarly cultivated in fibrocytic histiocytes isolated from healthy individuals and tuberculoid-type patients. It is assumed, therefore, that the characters of the lepromatous tissue material, though undergoing changes in successive subcultures, are preserved for a certain period of time even after isolation.

Within the limit of the author's experience, at least, these LH strains may be considered to be the most suitable of host cell lines for studies involving cultures of *M. leprae*.

8

Studies in vivo of the metabolic aspects of M. lepraemurium

T. Nakayama — T. Ozawa

When lepromas became palpable 3 months after inoculation, radioactive substances, viz.:

$CH_3 . C^{14}CONa$ and $C^{14}H_3 . COONa$

were given intraperitoneally in doses of 6 μc (0.2 ml. of physiological saline solution) repeated 13 times at intervals of 1-2 days. On completion of the series of injections, the animals were killed

and the lepromas and various organs made into emulsions diluted 10 times in distilled water. Test materials were prepared by drying 1 ml. of each emulsion under an infrared lamp, and a 2π gasflow-counter of the windowless type was used to compare their radioactivities.

The radioactivity of the nodule in the $C^{14}H_3.COONa$ group was 4 times as high as in the $CH_3.C^{14}OONa$ group. Radioactivity of a single bacillus, moreover, was 5 times as much in the former case as in the latter. The number of C^{14} atoms taken into a single bacterial cell were roughly estimated at 10^4 in the former and 2×10^3 in the latter case. These figures correspond to $1.5/10^{11}$ and $0.3/10^{11}$ respectively of the total number or C^{14} atoms administered per mouse.

Similar experiments were made with Glycine-2-C^{14}, Sodium acetate-2-C^{14}, Glycine-1-C^{14}, d-Glucose-C^{14} and Succinic acid-1,4^{14}, and the amount of C^{14} atoms fixed in the bacilli diminished in the order in which these chemicals are listed.

9

Experimental transmission of the leprosy bacillus to the black mouse

SHINJI NISHIMURA

The most important problem in the successful transmission of the leprosy bacillus to animals is to find a sensitive animal. The black mouse was selected for the present experiment.

Materials and Methods: Inoculum: Fresh lepromata of 3 untreated leprosy patients were excised aseptically, frozen and stored for 1 to 3 months, emulsified in YLH solution, centrifuged, sterile india ink added to the bacterial supernatant and this solution was used as the inoculum.

Experimental Animals: Mice, 2 to 7 days old, were inoculated subcutaneously, sacrificed after 10 to 14 months and studied microscopically. The site of inoculation, lymph nodes and organs were examined.

Results: Of a total of 711 animals inoculated with living bacillis, 14 (2%) showed proliferation of acid-fast bacilli. No proliferation was found in any of the 111 controls inoculated with killed bacillus. There was no significant relationship between the mouse strain and inoculum in the animals showing proliferation.

Identification Tests: The majority of the proliferating organisms showed the following properties. 1) The organisms proliferated in the mouse and rat but did not grow in the guinea pig. 2) There was no growth on Löwenstein or Ogawa medium. 3) The morphology of the organisms and the pathological changes in the mouse were similar to those in murine leprosy. 4) There was no specific reaction with the human leprosy bacillus by agar-diffusion technique using rabbit immune serum with whole cell as the antigen. 5) A positive lepromin reaction was found in most of the lepromatous type patients using the isolated organisms as the antigen. 6) The amidase activities gave results similar to the murine leprosy bacillus. 7) The response to chemoterapeutic agents was similar to that of the murine leprosy bacillus.

From the results, it was believed that the isolated organism was of the same strain as the murine leprosy bacillus.

10

Studies on the acid-fast bacillus isolated from healthy mice

Y. KAWAGUCHI—S. NISHIMURA
K. KOSAKA

The unexpected isolation of an organism similar to the murine leprosy bacillus from animals inoculated with the leprosy bacillus has been reported previously. The two following experiments were conducted in an attempt to clarify the origin of this organism. In the first experiment, quartz sand was injected subcutaneously in healthy animals to see if a lesion could be induced and in the second, a large number of healthy animals were examined for the presence of acid-fast bacillus.

Of a total of 66 animals inoculated with quartz sand, not a single animal showed a lesion after 7 months. In one animal, however, a clump of the bacilli was found in the subcutaneous connective tissue.

Examination of spread preparation from the subcutaneous connective tissue of the back, and of stab smear from lymphnodes and organs of healthy animals revealed acid-fast bacilli in 2 of 97 animals bred and reared for 1.5—6 months, in 8 of 109 animals reared for 8—12 months in our laboratory, in 5 of 40 animals reared for 4—12 months in the T laboratory, in 18 of 77 animals reared in the N animal farm for more than 12 months and in 22 of 73 animals reared for more than 12 months in the G district.

Cultivation and serial passage to mice are still in progress. Three strains of the detected organisms have been successfully passed to mice and show a picture similar to that of murine leprosy. Tubercle bacillus was isolated by cultivation from one animal in the T laboratory.

The results suggest that even in healthy animals, the older the animal, the greater the count of acid-fast bacilli, and the murine leprosy bacillus may be be present in the form of an unapparent infection.

Acid-fast bacilli have also been isolated from several apparently healthy hamsters.

It is believed that the above findings are factors which must be considered in the experimental infection of mice, and hamsters with the leprosy bacillus.

11

Contribution to the study of reflex motoricity in leprosy

C. F. Jordy — S. Manzolli — J. L. Alonso-Nieto

In this paper an assessment is made of the results of systematic research on reflex motoricity in 100 patients at the Rehabilitation Service of the Leprosy Prophylaxis Department of São Paulo, and the findings of this study are correlated with other data supplied by the neurological examination.

12

First results of electromyographic studies in leprosy

J. L. Alonso-Nieto — C. F. Jordy S. Manzolli — J. E. Faggin — W. Belda — E. Cruz — N. G. Almeida L. E. Reginato

The authors record the electromyographic potentials obtained in fifty patients suffering from leprotic neuritis, comparing their findings with the electromyographic pictures of other diseases affecting the peripheral motor neuron, and seek to correlate the electromyographic alterations observed with the clinical-neurological picture, the stage of evolution of the disease and the data obtained by electrodiagnosis.

13

Inoculation of the golden hamster with human leprosy bacilli

J. S. F. Niven — M. F. R. Waters

Forty-eight golden hamsters, inoculated in the left ear and testis with living suspensions of *Mycobacterium leprae* and in the right ear and testis with heat killed suspensions, were followed from 5 to 22 months. Four of the 15 left ears examined histologically 18 to 22 months after inoculation showed small granulomatous lesions containing acid-fast bacilli, and in two of these nerves were involved. No granulomatous lesions were found in 27 pairs of testes examined, although acid-fast bacilli were recovered from suspensions prepared from 9 testes.

Passage was attempted to 19 hamsters. After 18 months, 5 of 8 ears examined histologically showed unequivocal intracellular mycobacteria in small cellular foci and mycobacteria were also

seen in cells of the perichondrium of the ear cartilage, and in 3, nerves were involved. Homogenates from 9 other ears contained acid-fast bacilli, suggesting multiplication, and counts on 4 confirmed a tenfold increase. It has not proved possible to cultivate the mycobacteria. It is of interest that while the lesions resemble those reported by Shepard in the mouse foot-pad, nerve involvement was also noted in our material and intracellular mycobacteria were most readily found in cells of the perichondrium.

14

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

K. R. Chatterjee — R. J. W. Rees

Transmission studies using the hydrid strain of mouse have been continued since 1960 at the National Institute for Médical Research, London. The mice were inoculated usually subcutaneously or intraperitoneally with approximately 10^5 freshly isolated *M. leprae* and a progressive infection was established eventually in a proportion of the animals by repeatedly passaging the infected mouse tissues. To date the infections have been established with 7 out of 20 samples of bacilli from different patients with untreated lepromatous leprosy. Two of the strains have been passaged five times, 4 four times and 1 twice. Although the infection once initiated is generalized, involving the liver, spleen, lymph nodes and skin, there is also nerve involvement. From 234 mice examined bacilli have been found in 81% of stained smears prepared from the sciatic or brachial nerve. The bacilli recovered from the patients or from the animals failed to grow in bacteriological media. The generation time for this organism in animals was approximately 18 days; limited multiplication has also been obtained in tissue culture where the mean generation time was 12 days. Immunological and serological studies are being undertaken to compare the antigenic components of this organism with other mycobacteria, including *M. leprae* and *lepraemurium*. The results of these studies will be discussed.

15

Transmission of human leprosy to animals under special dietetic conditions

Meny Bergel

A study is made of *Mycobacterium leprae* inoculated into mice and black rats by various ways—foot-pad of rat, mouse testicle, rat testicle, etc.—the animals being fed as follows: complete standard diet with tap water; pro-oxidant diet with linseed oil and cod-liver oil; with pure fatty acids: esters of linoleic and linolenic acid; with the addition of silver nitrate, ferrous gluconate and potassium iodide to the drinking water; and with injection of homologous animal blood homolizates. The results are checked by means of bacillary recounts Hilson & Elek and Hanks methods) and by histopathological examinations. Conditions of pro-oxidation are shown to be favorable to the growth of *M. leprae*.

16

The value of hepatic punch biopsy in leprosy in West Africa

R. Camain — A. Basset — M. Basset

Two investigations have been made in West Africa to ascertain the value of hepatic biopsy in leprosy: one at the Marchoux Institute of Bamako (Mali) in 1957, and the other at the Dermatological Clinic of the Faculty of Medicine of Daker (Senegal). The results of the two investigations are very similar and agree with the findings of other authors.

In lepromatous leprosy, the hepatic lesions are characterized by a Virchow transformation of the Küpfer cells and the Kiernan's space histocytes. These

lesions are paralleled by the cutaneous lesions, except for the fact that they can be found in patients suffering from the nervous form of leprosy, where skin lesions are absent but nerves lepromatously involved. Indeterminate and tuberculoid leprosy, hepatic involvement is erratic and occurs in about 25% of patients, nearly all of them suffering from the severe tuberculoid form of the disease.

Repeated leprous reactions are often accompanied by hepatic amylosis, the severity of which may readily be ascertained by punch biopsy. In leprosy contacts, punch biopsy has not been instrumental in detecting early hepatic changes. The use of hepatic punch biopsy enables the extent of leprotic invasion to be ascertained and, like nerve biopsy, helps to determine the exact nature of certain forms of leprosy.

17

Experiences with mouse inoculatien of leprosy bacili originating from the Congo

P. G. JANSSENS — S. R. PATTYN

During the past three years we inoculated a total of 11 suspensions of acid-fast bacilli obtained from cutaneous biopsies of leprosy patients in Leopoldville, in the Republic of Congo. Inoculations into foot-pads of mice and quantitative evaluations were done as described by C. C. SHEPARD. Three strains were thus established *in vivo* and are in their 4th and 2nd passage respectively. Insufficient time has elapsed since the inoculation of the last 5 biopsies to draw any conclusions as to their success.

Quantitative data permit the calculation of the generation time. Multiple inoculations on bacteriological media did not produce any growth *in vitro*. Comparative studies were made with foot-pad inoculations of *M. leprae, M. lepraemurium, M. balnei, M. ulcerans, M. fortuitum,* and showed that *M. leprae* behaved differently in the mouse footpad, quantitatively, clinically and histologically. Limited spreading of the bacilli from the hind feet to the front feet was observed.

The microscopical aspect observed ofter Ziehl-Neelsen staining in relation to the probable viability of the bacilli as described by REES *et al.* was found to be reliable.

Data are given on the preservation of *M. leprae* during transportation. A strain was isolated from a patient under treatment with Ciba 1906 since two months.

18

Inoculation of Mycobacterium leprae in plants

E. SANTABAYA — F. WILKINSON
P. R. DE CHIERI — J. GAGO

In view of the difficulty of successfully inoculating animals with *Mycobacterium leprae,* an attempt has been made at plant inoculation. This required the choice of a plant that can be grown in a test tube under aseptic conditions. To add water and allow the rootlets of the plant and the water it is growing in to be examined, Roux tubes were used with the addition of a lateral branch. The plant chosen was the common string bean, *Phaseolus vulgaris,* of which two varieties were used. The inoculum free from cellular débris was injected into the radicle when it started to grow. One control was inoculated with killed bacilli (lepromin) and another with physiological salt solution, while a third was not inoculated at all.

Thirteen days after inoculation, the water in the tubes seeded with living bacilli clouded, and germs were found to have developed, some of them anaerobic and others cyanophilus. Still others were found similar in appearance to the spores of *Bacillus proptermariam.* All these germs were examined bacteriologically. Cloudiness was also observed in the control tubes with lepromin, but not in those inoculated with physiological salt solution or not inoculated at all. Staining of samples taken from the sediments in the water of the tubes showed: in the lepromin tubes, elliptical

bodies similar to those found in the tubes inoculated with living bacilli (?); in one or another of the remaining control tubes, fine cyanophilous germs in very small numbers.

The authors have perfected the method, and consider it promising for the study of germs that prove refractory to animal inoculation.

19

The transmission of M. leprae to animals: nerve lesions in the golden hamster

C. H. Binford — R. M. Madison

The authors report on the results of transmission experiments in which suspensions of *M. leprae* obtained from skin lesions of lepromatous leprosy were inoculated into the golden hamster (*Cricetus auratus*).

The evaluation of the results was accomplished by histopathologic examination of the inoculation sites. Microscopic lesions consisting of histiocytes containing mycobacteria were seen in the ears and footpads of many animals but specially significant were the nerve lesions observed in the ears of some animals. The nerve involvement by *M. leprae* was quite comparable to that seen histopathologically in the dermal nerves of patients with indeterminate or early lepromatous leprosy.

Nerve lesions developed very slowly and generally were not apparent until the 2nd year after inoculation. The evaluation of 20 human to hamster experiments in which the inoculated animals were followed until death occurred spontaneously, resulted in the detection of microscopic nerve lesions in the ears of approximately 30% of the hamsters. In none of the experiments were mycobacteria cultivated from the suspensions of human skin used as inoculum nor in suspensions prepared from the ears of inoculated hamsters. No lesions developed in control animals that had been inoculated with heat-killed suspensions of *M. Leprae*.

20

Determinants of tissular susceptibility to development of lepromatous infiltrations

S. González del Cerro

The work described in this paper forms part of a plan of investigation that the author is engaged upon with the aid of a fellowship grant from the Argentine National Council of Scientific and Technical Investigations. The object was, by submitting lepromatous patients to a strictly comparative clinical, bacteriological, histopathological and immunological survey of the skin areas supposed to be refractory or susceptible to *M. leprae*, to endeavor to determine the cause of the difference, if any, in the behavior of said areas.

1. *Clinical study*: An examination of 100 lepromatous patients confirmed the existence of areas generally exempt and others generally attacked by the bacillus. Original data are believed to have been contributed to the topographical study of skin lesions in lepromatous patients and it is hoped they will help to diagnose the lepromatous type of leprosy. Furthermore, new concepts have been evolved to establish the relative importance that should be attached to the factors; cold, circulatory stasis, solar radiation and repeated traumatisms, as localizing agents of the lepromatous lesions.

2. *Bacteriological study*: A comparative bacteriological study was carried out upon fifteen lepromatous patients with reference to the areas observed clinically to be generally exempt or attacked, and it was confirmed that the former are often baciloscopically positive.

3. *Histopathological study*: In 8 lepromatous cases of severity L3 and L2, a comparative histopathological examination was made of the skin areas clinically found to be habitually exempt or attacked. In the clinically unaffected area chosen, viz, the antecubital fossa, the findings were as follows: *a*. Histopathological diagnosis indicating leprosy of the indeterminate prelepromatous type in all 8 cases.

b. Perineuritis in 6 of the 8 cases.
c. Ziehl-Nielssen stainings of sections from all of the 8 patients positive. The abundance of bacilli present in an area that was nevertheless clinically unaffected was strikingly apparent in 6 of the cases.

4. *Immunological study:* A comparative immunological study of the areas clinically observed to be habitually exempt or attacked was extended to cover 5 lepromatous, 5 tuberculoid and 5 non-leprotic control patients, using integral lepromin of the Mitsuda Hayashi type. In none of the three groups was any substantial difference detected between the clinically unaffected and clinically affected areas.

21

Factors affecting the growth of Mycobacterium lepraemurium in cultures of mouse peritoneal macrophages

Y. T. Chang

Efforts have been made in the past 8 years to grow *Mycobacterium lepraemurium* in cultures of mouse peritoneal macrophages. With horse serum and balanced salt solution as the basal medium, the effect of various supplements was studied: chick embryo extract, beef embryo extract (BEE), homogenates made of spleen and liver of the mice, glycerin, Eagle's basal medium and the chemically defined, protein-free medium, NCTC 109. The best medium for growth of the host cells (macrophages) consisted of 40% horse serum, 50% NCTC 109 and 10% of a 1:5 dilution of BEE. Elongation of multiplication of *M. leproemurium* was observed in cultures grown in various media. Glycerin enhanced the elogation, and the homogenates of spleen and liver accelerated the multiplication of the bacilli. Growth of *M. lepraemurium* was studied in cultures of different media for a period of 40 days. With a medium composed of 90% horse serum and 10% of a 1:5 dilution of BEE, moderate growth was observed in only 10% of the experiments. With a medium composed of 40% serum, 50% NCTC 109 and 10% of a 1:5 dilution of BEE, moderate growth was observed in 17% of the experiments, marked growth in 7%. Supplementing the latter medium with 10% liver homogenate, moderate growth was observed in 30% of the experiments, marked growth in 41% and maximal growth in 29%. In cultures of maximal growth, all macrophages were studded with the acid-fast bacilli. The generation time of *M. lepraemurium* was about 10 days (6.2 to 17.2 days), approaching the growth rate of the bacilli in mice.

22

Extremity deformity in leprosy: a morphologic inquiry

T. I. Akino — O. K. Skinsnes

An inquiry into the histopathology of the leprous deformities in the extremities, here presented as a preliminary report, has been conducted. The use of the "large section" method in the study of a group of amputated extremities from patients of the Hay Ling Chau Leprosarium in Hong Kong has been found a useful approach. The method, without sacrifice of histologic detail, provides entire sections of hands, feet or digits in which all structures are kept in continuity; vessels, nerves, muscles and bones can be studied as a unit. Serial radiographs of the lesions are available to provide useful correlation. The majority of the specimens are from patients having tuberculoid leprosy and all but one of the specimens are from the lower extremity. In this material, so-called "metatarsophalangeal osteoarthritis" has been the most frequent lesion. Granulomatous lesions have been found in the marrow space in four patients, two of them tuberculoid. Arterial sesions are impressive in some specimens.

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Studies on the pathology and experimental transmission of leprosy

W. A. Hadler

The lesions induced by inoculation of *Myco. leprae* and *Myco. lepraemurium* in guinea-pigs and rabbits are tuberculoid in structure, whereas in rats and mice they are lepromatous. Histophysiological and histochemical investigation of these two types reveal differences in the functional and chemical activity of the macrophages, determining the appearance of physiologically different cells, epithelioid in the tuberculoid structure and leprous in the lepromatous structure.

In the guinea-pig and the rabbit, the macrophage (an argyrophil cell) has lytic properties (lysing the phagocytized mycobacteria), coincident with inphophatases; it rapidly metabolizes lipids (including the phospholipids), present in the cytoplasm, and exerts a strong lipolytic action; it has numerous mitochondria and discrete ribonucleic basophilia. It turns into an epithelioid non-argyrophil cell, with no bacilli and possessing a small amount of sudanophilous substance; this cell has an acid and alkaline phosphatasic action; it shows no phagocytic activity, but is capable of metabolizing such stains as may possibly be present in the cytoplasm.

In the rat and mouse, the macrophage (argyrophil cell) does not lyse the mycobacteria engulfed and has only a slight alcaline phosphatasic activity and no acid phophatasic activity at all; it metabolizes the lipids contained in the cytoplasm very slowly, its lipasic activity being histochemically null; it possesses numerous mitochondrias and very discrete ribonucleic basophilia. It gives rise to the leprous cell, partially argyrophil, with numerous bacilli and a great number of lipid droplets in the cytoplasm; it exerts a phagocytic activity, but shows no tendency to metabolize the stain phagocytized.

As regards human lesions the findings are very similar; thus, the cells of tuberculoid lesions resemble those of the guinea-pig and the rabbit; the lepromatous lesions are like those encountered in the rat and the mouse.

The difference in behavior between the cells of the two types of lesion seems to depend on the biosynthesis of enzymes, some of which are mycobacteriolytic. This hypothesis was tested: (*a*) by stimulating the cells of the lepromatous lesions by means of electronegative particles; (*b*) by depressing the cells of the tuberculoid lesions.

The results obtained are favorable to the hypothesis advanced, and reveal, furthermore, parallelism between the lytic activity of the cells. This parallelism suggests a connection betyeen the lytic activity and acid phosphatic of the cells. This parallelism suggests a connection betyeen the lytic activity and the presence and concentration of the lysosomes.

These findings are correlated with the pathology and experimental transmission of leprosy.

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Experimental transmission of human leprosy to rabbits and mice

N. Hirano — K. Sushida

White adult rabbits were used in the experiment. In the epididymis inoculated with human lepromatous material a thickening appeared about 20 days after the inoculation. After 50 days this thickening was removed, but the epididymis did not show any definite sign of infection nor the presence of many acid-fast bacilli. 65 days after the inoculation the other testicle was removed: in the epididymis of this testicle many acid-fast bacilli were found. Two rabbits were inoculated with the epididymis emulsion. In one animal it was injected into the epididymis and in the other a small piece of the infected epididymis tissue was inserted between the skin and tunica vaginalis. The inserted tissue disappeared after a few days and then thickenings appeared at

the inoculation site. The thickenings were transmitted to the next normal rabbits. After 2 months thickenings were recognized, but transmission to the next generation failed. In contrast, the same leprous material was inoculated into the testicles of mice. One of the ten mice died after about one year and abundant acid-fast bacilli were found. This bacillus was transmitted to the next generation mice successively, but this disease was very similar to murine leprosy.

25

Mast-cell response in murine leprosy and as influenced by antileprosy drugs

L. KATO — B. GOZSY

In and around the subcutaneous murine leprosy granuloma the number of mast cells rapidly increases, reaching a peak 40 days after infection. With progression of the lesion the number of intact mast calls suddenly falls far below normal and mast cell disruption occurs to a very great extent so that within 58-80 days after transmission the mast cells will have become fewer and fewer. On the 80th day there is seldom a mast cell to be found in and around the granuloma. Intravenously injected India-ink accumulates intensely at the site of infection at the time when mast cell disruption is maximal, thus suggesting that the natural defense mechanism is working efficiently and is maintained by mediators of mast cell origin: histamine and serotonine. It is suggested that mast cell response is advantageous to the host rather than to the parasite. When the mast cells disappear from the local lesion the disease advances to the fatal outcome. Drugs with established antileprosy effect retarded the granuloma formation and an intense mast cell response was maintained long after these cells disappeared from the infected nontreated rats. Results were obtained by the authors' "transparent skin techniques", permitting the simultanous visualization of capillary, mast cell and connective tissue response to the granuloma formation, and as influenced by drugs.

26

Iatrotopic phenomenon in leprosy

R. N. MIRANDA

The "iatrotopic phenomenon" is an expression used by the author to denote the regression or cure of skin lesions after biopsies have been taken from them. This phenomenon has been observed by others in granuloma annulare and by the author in cases of verruca, erythema, lichen planus, etc.

Tuberculoid leprosy is no exception, and this paper records various cases of this type of leprosy in which the skin lesions, at varying lengths of time after biopsies, began to show regression or cure without treatment.

27

Treatment of leprosy with retard action sulfas (sulfamethoxypyridizin)

A. R. MERCAU — R. CULASSO — E. DEPAOLI — P. M. PRIETO

A trial of sulfamethoxypyridizin was made on fourteen patients, thirteen of them without prior treatment, the form of the disease was lepromatous in 12 cases and indeterminate in 2. The drug was administered by mouth in doses of half a gram every 12 hours.

In nine patients the sulfonamidermia was controlled by the Bratton and Marshall method. Two years of observation enabled the following conclusious to be drawn; 1. Sulfamethoxypyridizin is active in any clinical form of leprosy and remarkable clinical improvement was noted. Homogenous bacilli mutate to broken and granulated forms; the indeterminate cases turn negative. Infiltrates and vacuoles diminish with the appearance of giant cells for each foreign body under histopathologig examination. 2. The therapeutical activity is slower than that observed with the sulfones and their derivatives. 3. The tolerance is excellent and better than

in the case of the other antileprotic drugs; there are no gastric, hepatic, renal, cutaneous or hepatic disorders of any importance. 4. Leprotic reaction recurs with the same frequency and severity observed in the usual treatments. 5. The highest therapeutical efficiency is reached from the sixth to the twelfth month, after which the initial drive seems to slacken. 6. It is consequently a drug that can be classified as one of the few tools available for leprosy control, and one that is really useful in eases of intolerance or resistance to the established treatments or when it is desired to adopt an alternating schedule.

28

The clinical forms of leprosy

J. M. M. Fernández—A. R. Mercau—E. A. Carboni—E. Depaoli—R. Culasso—P. M. Prieto

Leprosy is considered as one disease, with distinct clinical manifestations differing with the physiological medium in which the bacillus multiplies. Two extreme or polar eventualities stand, one at either end of the scale, viz. the environment is particularly suitable for the germ to develop in and it grows with the utmost facility, invading the host, which offers no resistance; or else the medium is extremely unfavorable and the germ develops with difficulty. Between these two extremes or poles there stretches a varying combination of media and germs, which represents the successive resultants of more or less *bacillary agressivity* and less or more *host resistance*. If the extreme or pole where the environment is conducive to the development of the bacillus and offers no resistance to it, be given the name of polar lepromatous leprosy, we shall have two polar forms of leprosy about which there can be little discussion. These concepts will be made clearer by the diagram on page 13.

As may be seen, between the two extremes there are many variations of the attack/defence ratio which will necessarily condition distinctive clinical aspects. When the chronic evolution of leprosy is interrupted in a given patient by an acute episode, this episode will also be attended by distinct clinical manifestations, and this is indicated on the right side of the diagram, the left side being reserved for the chronic forms. This leaves us with what may be termed limiting forms, of which the tuberculoid is best represented by the tuberculoid leprosy reaction of Nelson de Souza Campos and the lepromatous by Wade's borderline type, which figures as dimorphous in the present classification. In the middle of this section lies the indeterminate reaction with its well-established clinical manifestations. All of these clinical aspects, whether chronic or reactional, should be termed interpolar — "interpolar type" in the quiescent state and "interpolar reaction during the acute episodes.

29

Correlationship between the clinical and histopathological aspects of hypochromic and erythemato-hypochromic maculae in leprosy

L. Cezar de Andrade

The divergence that has arisen in some leprological centers with regard to the international classification of the clinical forms of leprosy has led the author to proceed to a review of the material in the files of the Pathological Anatomy Laboratory at the Leprology Instituto of the Brazilian National Leprosy Service, with a view to establishing the correlationship between the clinical aspect of the lesions and the corresponding histological structure.

For a start, the hypochromic and erythemato-hypochromic maculae were chosen for study, as these lesions are more closely connected with the anesthetic macula group proposed by the Hindus, which is the main stumbling-block.

The sampling on which this study is based comprises 750 cards relating to hypochromic or erythemato-hypochromic lesions biopsied in patients that had been given specific treatment prior to examination. The skin samples had been sent in to the Laboratory by doctors from various units of the Federation to obtain confirmation of

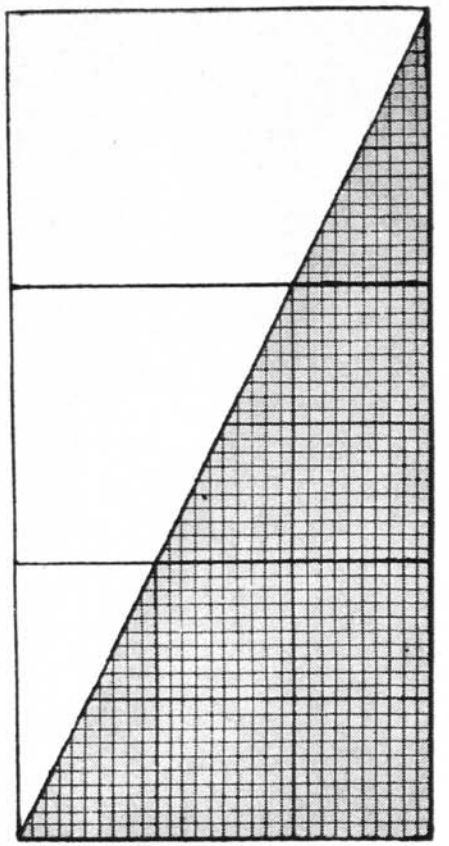
DIAGRAM OF BACILLARY AGGRESSIVITY AND HOST RESISTANCE

CHRONIC STATES

Tuberculoid leprosy

Indeterminate or interpolar leprosy

Lepromatous leprosy



ACUTE STATES

Tuberculoid reaction

Limiting tuberculoid form

Tuberculoid leprosy reaction of Souza Campos

Indeterminate reaction

Wade borderline or dimorphous type

Limiting lepromatous form

Lepromatous reaction

Interpolar reactions

their diagnosis of the clinical forms involved.

It is not the author's intention to draw conclusions, but merely to bring forth elements available to her for comparison with those from other sources, in an endeavor to broaden the field of information that may lead, in the near future, to the establishment of a uniform criterium that will fit in with the international viewpoints.

30

Use of new species of small mammals in experimental leprosy research

W. H. FELDMAN

Until means are perfected whereby growth of *M. leprae* can be achieved by *in vitro* methods, multiplication of these reluctant bacteria must be sought by *in vivo* procedures. This has been attempted since the time of HANSEN. Reportedly successful results have not always been confirmed by others. Striking and impressive though the results of recent experimentation are, they do not imply that the problems of experimental pathogenesis of leprosy have been solved. Instead, as a consequence of the progress reported, the situation has become more urgent and exciting than ever. Future efforts must be directed towards the discovery of an animal, or several animals, that will provide for rapid and vigorous pathogenesis of *M. leprae*. The pathogenesis should be characterized by a distinctive, consistent cellular response, with the production of myriads of *M. leprae*, capable of serial passage to other animals of the same species.

To accomplish this objective may require the screening of many species of small mammals not heretofore utilized in experimental leprosy research. A wide diversity of such mammals exist in a wild state throughout most of the temperate zone, and many species are probably indigenous to tropical and subtropical regions. Whether the animals could be otained in sufficient supply for *in vivo* studies of *M. leprae* would depend upon the imagination, enthusiasm and persistence of the investigator. The task is a challenge; not an impossibility. Other materials pertinent to the panel discussion will be presented.

31

Electrodiagnostic studies in Hansen's disease

A. MAGORA — F. SAGHER — E. ADLER

Preliminary results are presented covering: Faradic-Galvanic test, Chronaximetry, Time-Intensity curve and Electromyography, in a study of 46 patients all of whom had thorough dermatological and neurological examinations and had undergone complete histological, bacteriological, immunological and serological investigations. In each patient the same 4 muscles (opponens pollicis and abductor digiti V bilaterally) were chosen for examination for the following reasons: 1. They were found to be most frequently damaged from the point of view of muscle power loss. 2. In most patients, even if other muscles were weak, at least two of the examined muscles were also damaged. 3. Need for a uniform method of examination. 4. Easy technical approach and localization.

The results are summarized in tabular form, comparing all the neurological findings (muscle power loss, atrophy, sensory loss, positive Tinel sign and thickened nerve) with the time-intensity curve and electromyography, and may be outlined as follows: 1. Electromyographic finding of a myopathic pattern in 25 out of 184 examined muscles seems to indicate primary damage to the muscle. 2. A high number of pathological time-intensity curves (65) and electromyographic records (38) were obtained from clinically normal muscles. 3. The faradie-galvanic and chronaximetric tests were found to be not so trustworthy as the time-intensity curve and electromyography. It is therefore considered that, as in other conditions, electromyography may prove a reliable tool for the diagnosis of early muscle damage (neurogenic or myogenic) and that repeated time-intensity curves, because of their high sensitivity, may turn out to be adequate for evaluation and prognosis of the muscle status.

The future aims of this project, which is supported by an international research grant from the U. S. Dept. of Health, Education and Welfare, are two-fold: 1. To further investigate the electromyographic observation of primary muscle damage in leprosy, and the time-intensity and electromyographic findings of early nerve and/or muscle damage clinically still undetected. 2. To assess and compare the reliability for all the electrodiagnostic methods and to determine their diagnostic and prognostic value in leprosy.

32

The swollen lower leg in leprosy

E. W. Price

The swollen lower leg and foot is a common complication of leprosy; if persistent, it is a considerable disability to the patient. The common causes of this condition in leprosy are reviewed — generalized lepromatous condition of leg, disuse edema, local infection, lymphangitis leading to elephantiasis, and thrombophlebitis of the deep veins of foot and lower leg.

Attention is drawn to the frequency of thrombophlebitis of the deep veins in the syndrome of swollen lower leg, and to the prolonged disability that results if the condition is unrecognized and untreated.

The clinical course is illustrated, and the cause of the swelling is discussed in detail. The importance of early treatment is stressed. Satisfactory methods of controlling swelling of longer duration are available, and both medical and surgical procedures give satisfactory results. In all cases, treatment should be undertaken before the irreversible condition of chronic fibrosis and solid edema make the condition uncurable.

33

Influence of the thioureas, pyrazinamides and sulfonamides on the average survival of mice inoculated with *M. lepraemurium*

A. C. Mauri—C. E. Corbett

With a view to evaluating the chemotherapeutical action of certain drugs on the infection produced by *M. lepraemurium*, 10 lots of mice (with 30 animals in each lot and a mean individual weight of 20 grams) were inoculated intraperitoneally with 0.5 c.c. of a suspension of Stefansky bacilli. Seven days later, the trial drugs (see table) were administerered to each lot with daily the ration, except for lots 2 and 5, for which the drug was suspended for 10 and 14 days respectively, owing to the appearance of toxic symptoms. Lot 1 was given no drugs at all and served as a control. The dates when the mice died having been noted, it was possible to calculate the survival average for each lot (see table).

AVERAGE SURVIVAL OF MICE INOCULATED WITH *M. LEPRAEMURIUM*

Lot	Drug	Daily dose mg/kg	Average survival in days
1	Control (no drug)	——	106.8
2	4-4'-diaminidiphenylsulfone	200	158.1
3	Pyrazinamide	125	100.6
4	Morpholinomethylpyrazinamide	200	145.5
5	Butoxythiocarbanilide	50	90.8
6	Isoamyloxythiocarbanilide	50	103.9
7	3-sulfanilamido-6-methoxypyridazine	400	129.3
8	4-sulfanilamido-2-6-dimethoxypyrimidine	400	118.1
9	3-sulfanilamido-2-phenylpyrazol	400	133.3
10	2-sulfanilamido-5-methylpyridine	400	123,8

With pyrazinamide, butoxythiocarbanilide and isoamyloxythiocarbanilide, the average survival was near and even lower than that of the control group. Favorable results as regards the average survival of the animals were observed with the other lots, the most outstanding being those corresponding to treatment with 4-4'-diaminodiphenylsulfone and morpholinomethylpyrazinamide, and then, by decreasing order, with 3-sulfanilamido-2-phenylpyrazol, 3-sulfanilamido-6-methoxypyridazine, 2-sulfanilamido-5-methylpyrimidine and 4-sulfanilamido-2-6-dimethoxypyrimidine.

In the experiments, at least the drugs that appreciably lengthened the average surival, viz.: diaminodiphenylsulseem to intervene in the evolution process of the infection. These findings may enable an index to be established for the chemotherapeutical action these drugs have on murine leprosy in mice, confirming the activity of DDS already determined in rat infection.

34

Electromyographic findings in leprosy

A. Baccaredda-Boy — C Mastropaoli — P. Pastorino — G. Sacco — G. Farris

An electromyographic study was carried out on 45 leprosy, patients, 42 of whom were cases of lepromatous leprosy, either active (30) or stabilized (12), while 2 were cases of tuberculoid and 1 of dimophous leprosy.

From the neurological standpoint, various altogether typical disturbances of sensation were present in all cases. Clnical signs of motor involvement of the peripheral nerves were present in 39 cases. Motor deficits in the territory of the radial nerve were present in 7 cases, being bilateral in 5. The ulnar nerve was involved in 34 cases, in 27 cases bilaterally. Signs of involvement of the median nerve could be observed in 16 cases, bilaterally in 8. The lateral popliteal nerve was involved in 18 cases, bilaterally in 11, while weakness in the muscles innervated by the facial nerve was observed in 16 cases, in 2 of which it was bilaterally evident. Typically, muscular wasting was prominent in the distal muscles of the limbs, prevailing in the intrinsic muscles of the hands and feet.

The electrical muscular activity was recorded by concentric unipolar electrodes connected to a tro-channel DISA electromyograph. The EMG pattern at maximum effort, mean action potential duration, incidence of polyphase potential and of synchronization between the different leads were evaluated according to the technique described by Buchtal.

In all, 98 muscles were sampled electromyographically; out of them, 38 exhibited various degrees of alterations which can be summarized as follows. 1. Frequent presence of silent areas, up to complete electrical silence in all the examined points of the muscle, in cases of total muscular wasting (6 muscles, in which both spontaneous and voluntary activity was lacking). 2. Presence of spontaneous activity, consisting of positive denervation and fibrillation potentials, with lack of motor unit potentials, in highly fibrous muscles (8 muscles). 3. No spontaneous activity, scanty voluntary activity represented by broken-up and polyphase motor unit potentials, in severely wasted muscles 15 muscles). 4. Single mixed-oscillation pattern at maximum effort, with presence of positive denervation and fibrillation potentials, no significant increases in mean action potential duration, slight increase in polyphase short-spike potentials (11 muscles). 5. Single mixed-oscillation pattern at maximum effort, with or without denervation potentials, significant increases in mean action potential duration, slight increase in polyphase short-spike potentials (8 muscles).

Fasciculation potentials could be recorded in 2 muscles in 2 different cases. No increase in incidence of synchronization was ever found. The EMG findings, therefore, pointed typically to a peripheral neurogenic type of affection, sometimes of long standing, without any sign of involvement of the anterior horn cells of the spinal cord. EMG

alterations always occurred in muscles with clinical signs of involvement, being thus more frequent in the distal muscles of the limbs. A complete correspondence between EMG and clinical data could therefore be established.

ROUND TABLE ON BORDERLINE AND INDETERMINATE LEPROSY

35

Evolution of cases in the indeterminate group treated at the dispensary of Nova Iguacu from 1949 to 1960

A. Rabello Neto — R. S. Castro de Andrade — L. M. Cezar de Andrade — R. G. Neves — N. C. Silva

The authors report their observations in 17 cases of the Indeterminate Group (I) treated with sulfones and thiosemicarbazone in the period 1949 to 1960. Clinically, all of them were suffering from skin lesions (maculae). These cases were documented bacilloscopically and histopathologically and given a lepromin test, before, during and at the end of the period of observation, which averaged 83 months in duration. Of the 75 cases under observation, 45 healed (60%), 22 showed some improvement 2 worsened (2.6%) and only 2 (2.6%) exhibited a tendancy to change into the tuberculous form. No case evolved toward the lepromatous form, and the cases with only one lesion healed more rapidly.

The authors comment on the cases where the treatment was irregular and others which, for various reasons were not included in this investigation.

The Mitsuda reaction was found to be unstable in 40.0% of the cases, viz.: 30.7% negative to positive; 4% positive to negative; 1.3% negative to doubtful; 1.3% doubtful to negative. The reaction remained negative in 2.7% of the cases. In the authors' opinion, instability, variation in intensity and inversion of the Mitsuda reaction are peculiar to the immunobiological lability of this Group, and failed to have any influence on the favorable effects of the treatment or prevent the improvement or cure of the patients.

The conclusion is reached that the treatment of I cases with sulfones is a prophylactic measure of great value, for it heals the lesions and soon halts the development of the disease, preventing it from evolving into the lepromatous form. Nothing cound be concluded about the effect of thiosemicarbazone (TB1).

36

Borderline leprosy from the viewpoint of electron microscopy

T. Imaeda

Borderline leprosy lesions, diagnosed clinically and histopathologically, were examined with the electron microscope. The lesions are mainly composed of cells characterized by abundant distribution of cytoplasmic organelles and also by complex cell membranes, which are very similar to epithelioid cells in tuberculoid lesions. The features of these cells suggest that the cellular reactivity always exists in some degree. The bacilli are distributed as single individuals or in small groups in these cells. It is noted that electron transparent substance, which can always be seen in large clumps of bacilli—called "globi"—in lepromas, in this case does not surround the bacilli even when they form groups. Thus, the bacterial environment of bacilli in borderline leprosy lesions is different from that of lepromatous lesions. The majority of bacilli show their characteristic details in borderline leprosy, such as the bacterial surface, the plasma membrane, the intracytoplasmic membrane system, the cytoplasmic bodies, the nuclear apparatus, etc. These bacterial features persist for a relatively long time, different from those of bacilli in lepromas which

display the intact features only in the initial stage of leproma formation, suggesting that the bacilli soon degenerate as a result of rapid intracellular growth. They are also distinguishable from reactional tuberculoid cases in which bacilli degenerate very rapidly, owing to the strong cellular reaction.

On the basis of these observations, it is concluded that the bacterial activity and the cellular reactivity are balanced for some time in borderline leprosy and consequently the bacilli multiply very slowly under the slightly reacting conditions of the host cells.

37

Dimorphous reactions

G. L. FITE

A study of dimorphous leprosy attempted to discover what might be learned during and following reactive periods in 20 cases. Two of the cases illustrated a vasculitis of the Schwarzmann-reaction type, but most of the reactions were: (1) development of epithelioid elements in dominantly lepromatous cases, or (2) appearance of bacilli in essentially tuberculoid cases. Inflammatory changes were most inconsistently present, and both good and bad clinical results followed reactions. The results of dimorphous reactions are most unpredictable, and probably result from alterations in the immune status. The wisdom of classification of cases of leprosy as being of a dimorphous "type" appears debatable. During quiescent periods biopsy may be confusing. Most seem to be cases of lepromatous leprosy that have undergone material improvement, with degeneration of bacilli into products which stimulate epithelioid cell production. Others are cases of tuber- under treatment, or in which the relatively immune responses of the tuberculoid type are ineffective. Only a few "dimorphous" cases maintain the same state continuously. Dimorphism occurs in leprosy sometimes as a result of treatment. Many histologic changes, unusual in leprosy, but nevertheless repeating themselves frequently enough, are not adequate for the establishment of an additional type of disease.

38

Clinical, histological and immunological aspects of dimorphous leprosy

E. D. L. JONQUIERES

As much from a doctrinarian viewpoint as from a clinical, histological and immunological angle, the dimorphous group should be maintained as a division in the classification of leprosy. This opinion by no means conflicts with the concept of polarity, but tends rather to reaffirm it. The incidence of the group is not negligeable, as may be seen by the fact that it accounts for 8% of the cases recorded since 1948 at the Central Dispensary of Dermatology (Leprology) of Buenos Aires. The author has investigated 115 dimorphous cases in the course of 15 years of experience in leprology. There is an early dimorphous picture, with maculae and infiltrations, where the histological structure and bacilloscopic and immunological characters suggest the lepromatous form (*Lepra perilepromatosa*, ROTHBERG), in spite of which it is readily recognizable clinically to the trained eye. The most characteristic sympton is that of "acute infiltration" (TAJIRI) or "tuberculoid pseudoexacerbation of lepromatous patients under sulfone treatment" (SOUZA LIMA and RATH DE SOUZA). This phenomenon, which may also be occasioned by the slow sulfas and methimazole, occurred in 35% of the author's cases. It is identifiable with the "borderline" aspect described by WADE and RODRIGUEZ. It would seem, therefore, that "borderline" leprosy is a particular, reactional aspect of dimorphus leprosy. In other words, it is the "dimorphous reaction". "Dimorphous" and "borderline" are not, therefore, synonymous. During this "borderline" stage, dimorphous leprosy tends, clinically and histologically, towards the reactional tuberculoid form. *It is not accompanied by erythema nodosum*, even though it is, at times, by dissemination of the lesions (particularly the face, nucha, etc.)

This picture, controlable by ACTH and corticoids, is very often recurrent. Fluctuating or "ping-pong" immunity is observed in the course of the evolution of dimorphous leprosy. Bacilioscopy may be positive for a long time in the skin, but not in the nasal mucus. The sulfone treatment inclines dimorphous leprosy towards the tuberculoid extreme. Clearly defined lepromatous lesions are observed to develop, however, through insufficiency of the treatment. There are dimorphous cases that are cured without taking a definite turn to one form or the other or ever reaching the reactional "borderline" status. The wisdom of stopping the treatment should be accepted with the utmost caution, except in the case of a repeatedly strongly positive Mitsuda reaction. In some patients, the author has tried out immunological reinforcement with BCG, but the results are still uncertain.

Finally, it is affirmed that the dimorphous group, owing to its unstability and ambiguity, can be diagnosed by experienced clinicians so long as they observe and follow up the cases dynamically. The adoption of a static, or purely histopathological, criterion is what has given rise to the Byzantine discussions that revolve about this form of leprosy.

39

Borderline and indeterminate leprosy

K. KITAMURA

Both clinically and histologically, imunologically and bacteriologically, borderline cases can also be converted to tuberculoid by treatment. Likewise, the clinical features and other findings in purely lepromatous cases may undergo a transformation to the tuberculoid form after treatment. Tuberculoid, borderline and lepromatous are terms applicable to phases of the disease transmutable one into another. The indeterminate group comprises cases either with erythematous lesions (a form that may be called "simple-macular") or with well-defined depigmentations ("maculo-anesthetic"), or else depigmentations not so sharply demarcated. All erythematous and depigmented lesions show histologically nonspecific lymphocytic infiltration. After the disappearance of the erythematous lesions, simple-macular cases may well develop changes that are sometimes tuberculoid and sometimes lepromatous. As much from an imunological point of view as from a bacteriological angle, maculo-anesthetic cases are of a nonlepromatous nature while those with less sharply demarcated white patches are likely to be lepromatous. Essentially, leprosy should be divided into two forms: lepromatous and nonlepromatous. The lepromatous form has been regarded as a more or less stable polar type of the disease. However, conversion from lepromatous to nonlepromatous and vice versa should be accepted more readily than it generally has been hitherto.

40

Borderline and indeterminate leprosy

F. SAGHER

An exact definition of borderline leprosy or dimorphous leprosy should be accepted in order to have a common ground for discussion. So far, borderline cases have been described as displaying clinical features of lepromatous leprosy, but behaving immunologically and in their prognosis more like those of the tuberculoid type. The indeterminate type with its characteristic clinical picture may remain unchanged all through life or else develop either into the lepromatous or into the tuberculoid type. The question should be raised as to whether the terms "borderline leprosy" or "dimorphous leprosy" could be applied to any such combinations as: features of both lepromatous and tuberculoid leprosy occurring together; lepromatous cases with features of indeterminate leprosy; and tuberculoid cases with features of indeterminate leprosy. This would enlarge the present concept,

but the term "dimorphous type" would seem to be more suitable.

41

Cases of dimorphous leprosy in regressive lepromatous patients

A. C. PEREIRA — C. A. C. PEREIRA

The first cases of dimorphous or borderline leprosy that came to the notice of the authors were observed in their department in connection with patients suffering from the lepromatous form of the disease, treated with sulfones. These cases were mentioned in a survey presented by author Antonio Carlos Pereira as rapporteur to the "Symposium of Dimorphous Leprosy", promoted by the Brazilian Leprology Association, and published in *Arquivos Mineiros de Leprologia*, number III, of July 1960.

Of the 18 dimorphous cases presented, four were patients in transition from the lepromatous (L) to the tuberculoid (T) form, classified as dimorphous, a type which was first described in T to L patients, prior to the use of sulfones in the treatment of leprosy. The first case of L to T mutation was detected at the Dispensary in a patient who had left the Leper Colony to continue the treatment after mucus and leproma smears had proved negative. Routine clinical and histopathological check-ups were made on all of these patients, and in the case of one of them, Antonio A., sent to the Colony more than 5 years ago and registered as being in an advanced stage of lepromatous leprosy, the histopathological examination revealed the presence of both forms, subsequently verified clinically. This case aroused the authors' attention, and in the course of the treatment of lepromatous patients at the Dispensary after sulfones had been introduced, they observed a similar mutation in three more cases, viz. João J., Walter N. and Nelcy A. Observation of these four instances showed that the borderline type described by WADE, WADE & RODRIGUEZ, and later by SCHUJMAN, ALONSO & AZULAY, PEREIRA and others, originates in patients suffering from the T form in evolution, the cases described by PEREIRA in 1960 occurring among patients under treatment, with regression of the disease, a fact that was never observed prior to the use of sulfones.

42

Some aspects of secondary diffuse leprosy

J. H. FRENKEN

Though scarcely mentioned in the literature, secondary diffuse leprosy occurs much more often than the primary diffuse form which is gradually disappearing, even in Mexico. As regards diffuse infiltration, leprosy reaction, absence of nodules, vessel disorders, histopathology, etc. the syndrome is exactly the same in both primary and secondary diffuse leprosy, but there are certain characteristic differences, such as a slower evolution covering a period of over 8 years (even extending to 15 or more). Secondary diffuse leprosy is always preceded by a stage of indeterminate leprosy. The widespread alteration in sensation and the histamine reaction follows a special pattern in which a triangular zone on the upper thorax always remains unaffected, even in advanced cases. Diffuse infiltration is sometimes so slight that it is scarcely or not at all perceptible. Even madarosis may be absent. Diagnosis thus presents special problems.

The progressive pattern of distribution enables three stages to be clearly distinguished at least in this form of leprosy. The first is the indeterminate leprosy stage, probably localized around the area of infection; in the second, the lepra bacteria multiply in the blood, but are retained in the acra, e. g. toes, fingertips and ears, while in the third stage they slowly invade the skin from distal to proximal.

PANEL ON REACTIONS

43

A new treatment of the leprotic reaction applied at the Dermatological Center of Bogotá

F. LONDOÑO G. — J. ARENAS R. — F. MUVDI CHAHIN

The etiopathogenic mechanism of the leprotic reaction being unknown and at the same time one of the great therapeutic problems of the present day, we decided to go ahead with an investigation of the properties of cyproheptadine, an antihistaminic and antiserotoninic drug, with a view to the possible allergic nature of the leprotic reaction.

18 cases were treated, all of them under control at the Dermatological Center of Bogotá, preference being given to those who had received antireactional treatment without favorable results. All the cases were photographed at the start and the following determinations were made: blood picture, erythrocyte sedimentation, partial urine analysis and bacilloscopy, with periodical controls throughout the investigation. The initial dose was 16 to 20 mg. *per diem* of cyproheptadine without sulfones until the disappearance of the reactional elements (lesions), after which the dose was immediately lowered to a minimum of 8 mg. daily and a start made with sulfones in small doses (20 mg. *per diem*).

In all the cases studied, in a few weeks (from 2 to 12) the elements of the reaction characterized by erythema nodosum had entirely disappeared. In some cases new lesions appeared during the treatment, but they were characterized by a more superficial localization, smaller size and greater sensitivity to the therapy under investigation. A notable diminution in the speed of sedimentation was observed in all the cases treated. The sulfones were found to be better tolerated and in a high percentage of cases no reactional episodes reoccurred with daily doses of 40 mg. of cyproheptadine. In some cases, at the outset of the investigation, slight depression and transitory apathy were noted. Seeing that all the cases were strikingly benefitted by this new therapy, the range of experience should be enlarged to arrive at definitive conclusions.

The paper is illustrated with copious figures in color of all the cases before and during the therapeutic investigation.

44

Procedure to be followed with regard to the reactive of forms of leprosy

N. P. BUU HOÏ — A. BASSET

Reaction fevers complicate 30% of the lepromatous forms treated with sulfones. Reactive tuberculoid forms are fairly frequent in Africa. The Dakar Dermatology Service has to keep six beds for permanent occupancy by patients in these various reactive conditions. Among the causes of such accidents, emphasis must be laid upon: 1. Therapeutic errors: faulty rate of increase in administration of the drugs; irregularity of treatment. 2. Associated ailments: parasitoses, paludism, tuberculosis. 3. Vaccination: anti-smallpox, BCG, *B. marianum*.

These reactive states are an obstacle to the continuance of treatment, and their repetition tends to induce visceral amylosis. In general, they can only be controlled by corticotherapy. To avoid recidivation, it is indispensable to select an anti-leprosy therapeutic that is well tolerated. The choice depends on the individual patient. All antileprotic drugs are liable to set up reactions. Nevertheless, experience shows that the frequency of these accidents varies with the product used. By decreasing order, the following classification can be established: Sulfones, sufonamide derivatives, antibiotics (Kanamycetin, Viomycin), thioureas (1906 Ciba, Dialide, Isoxyl). The thioureas seem to be best indicated for reactive forms. They are the only drugs that can be used in the complex forms of visceral amylosis.

45

The purpuric syndrome in the leprosy reaction

A. J. Melamed

Capillaritis, arteriolitis and phlebitis as part of the leprosy reaction display clinical pictures in which the pathology and causative agents coincide with those of Schönlein's purpura. The selectivity of the vascular phenomena mentioned, at the leproma level, is justified by the alteration that determines the penetration of the leproma into the vascular wall. Thus a *locus minor resistentiae* is set up in the altered vessels of the leproma, which in turn are converted into an allergic "shock organ" for the bacillary antigens of the leproma and their corresponding antibodies circulating in the bloodstream.

The exogenous and endogenous factors liable to cause toxic or allergic vascular alterations are likewise capable of aggravating the damage to the though these phenomena may alone be instrumental in provoking necrobiosis and hemorrhage at that level. Although these phenomena may alone be instumental in provoking necrobiosis and suppuration in the leproma, in cases of more severe inflammation (allergic vasculitis) there would seem to be evidence of a phenomenon of Arthus in the peri-, juxta- and intravascular leproma. Very likely this allergic phenomenon is facilitated by hemorrhage and the irruption of wandering antibodies into the antigenetic zone of the leproma.

The etiological treatment consists in suppressing all toxins and allergens (drugs, foods, septic foci, stress factors) liable to cause vascular impairment.

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Relapsing lepromatous nodular hypodermitis

J. Ramos e Silva

The author is of the opinion that the socalled erythema nodosum leprorum should not be considered a "reaction", but rather be raised to a non-exceptional evolutive sub-type of the lepromatous form of leprosy. In reality, it may arise as the first clinical manifestation of the disease and recur at greater or lésser intervals. These relapses, with regard to Hansen's bacillus, probably depend on the immuno-allergic potential of the patient and supervene irrespectively of therapeutical interventions or other occasional circumstances of a banal nature (apart from their possible purely provocative effect) as would seem to be implicit in the term "reaction".

In an earlier paper the author took pains to show that the right name for the frequent clinical subtype of lepromatous leprosy known as "erythema nodosum leprorum" was *relapsing lepromatous nodular hypodermitis*, inasmuch as this term sums up the main features of seat of the disease (hypodermitis), morphology (nodule in the dermatological acceptation of the term), etiology (directly leprous) and clinical evolution (tendency to relapse).

It stands to reason that it is a mistake to assimilate this phenomenon with the classic erythema nodosum, for the similitude is purely morphological. On the contrary, the evolution is totally different, for (1) e.n. is acute or subacute and usually not relapsing, whereas r.l.n.h. is chronic and hopelessly relapsing, and (2) e.n. is resolvent, generally not leaving permanent aftereffects, while, on the contrary, r.l.n.h. may go so far as to produce colliquation of the central part of the larger nodules and nearly always leads to more or less intense fibrosis of the invaded tissues, which gradually take on a characteristic aspect and consistency. Likewise from a histopathological point of view, the mere contiguity of the lepromatous infiltrate, showing the usual Virchow cells, with a polymorphous infiltrate of lymphocytes, plasmocytes, some histocytes and fibrocytes, together with some polynuclear and even giant foreign body cells, draws attention at once to the etiopathogenic significance of the tissular alteration. Another point worth noticing is the perivascular localization of this cellular infiltrate,

an occurrence that is, moreover, frequent in various nodular lesions of the hypodermis and especially in the so-called allergic forms of vasculitis. The question of Miescher's radiate granuloma, stated to be specific to erythema nodosum strictly so called, is gradually losing importance, on the one hand because this feature is not constant, even in classic erythema nodosum, and on the other because most histopathologists deny its presence in r.l.n.h. P. H. MELLO for instance did not succeed in finding it in 150 cases of r.l.n.h. or even when he reexamined 58 of them with the specific purpose of looking for it. Prior thereto, a similarly negative conclusion had been reached by WADE; PEPLER, KOOIJ & MARSHALL; PAULO RATH DE SOUZA; and HELVIG.

This seems, therefore, to strengthen the position that r.l.n.h. is directly linked to infection by Hansen's bacillus and characterized by spontaneous recidivation, i. e. not depending in most cases on extrinsic factors, and justifiably to be considered a special evolutive subtype of lepromatous leprosy.

47

A clinical and histological account of severe necrotizing reactions in lepromatous leprosy

D. S. RIDLEY — M. F. R. WATERS

The VIth International Congress of Leprology divided reactions in lepromatous leprosy into "lepra reaction" and erythema nodosum leprosum, leaving the status of the Lucio phenomenon undecided. By following the criteria of WOLCOTT and of JOPLING little difficulty is experienced in classifying the milder reactions, but severe ones, especially those showing pustulation and necrosis, remain a cause of uncertainty and disagreement. A clinical and histological account is therefore given of six patients—four lepromatous, and two lepromatous with slight borderline features—who developed severe reactions, five with pustulation and ulceration. All six required treatment with corticosteroids. Specific anti-leprosy therapy was continued, with good results in five patients although the sixth is thought to have developed amyloid disease. Four patients have been successfully weaned from steroid therapy, the two borderline lepromatous patients showing a change in histological classification towards tuberculoid as their reactions subsided. The classification, treatment and prognosis of the reactions is discussed, and the importance of accurate histological assessment is emphasized.

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Conception of the pathogenesis and treatment of leprosy reactions

J. T. DE LAS AGUAS

The leprosy reaction may well be the greatest obstacle to the cure of the patient, retarding it in the most favorable cases and often bringing about the death of the sufferer after successive reactions over a period of years have culminated in visceral lesions. In the author's opinion the phenomena involved are allergic by nature and due to the balance between the bacillus and the host organism being upset by the administration of sulfones and by hormonal action and associated pathological circumstances.

The three classical stages in the evolution of the disease from the moment the treatment is begun are described, viz: an initial stage of improvement without reactions; followed by a second setage which is reactional, starting after 1 month to 2 years of treatment and lasting several years; and finally a third stage in which either the patient becomes negative and is cured, or else on the contrary the lepromas gain ground, visceral lesions appear and death supervenes. The two major factors of the reaction, then, are the bacillus and the sulfones, but if the latter are withheld, the disease advances and a vicious circle is established that it is hard to break. The author is therefore in favor of not interrupting the treatment except in exceptional cases.

He goes on to a discussion of the list of drugs considered useful, headed by the corticosteroids and ACTH, the most rapid and efficacious; the pros and cons of the latter are set forth, the most serious disadvantages being the frequent relapses and the necessity of gradually increasing the dose. He finds that dexamethazone and prednisone are the two best remedies, but among others that have displayed undeniable qualities, he cites adenochrome monosemicarbazide, the chloroquines, dimethylisopropylazulene, hematoplasmatherapy and in some cases the antibiotics.

The idea is put forward that, in the absence of any etiological treatment, the only course to be followed is to seek to avoid the reactions and bring the patient to a negative condition as soon as possible, for with the disappearance of the bacilli, the reactions will likewise disappear.

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Erythema nodosum leprosum — a clinicopathological study

C. K. Job

36 cases of erythema nodosum leprosum admitted to the S. L. R. sanatorium Karigiri, South India, and willing to undergo biopsy studies were analysed.

32 were males, and 4 females. The duration of the disease was 3 years in 1, between 5 and 10 in 17, and above 10 years in 6. The bacterial index determined according to WADE's technique showed 3 cases below index 1, 11 between 1 and 2, 18 between indices 2 and 3, and 4 above index 3. 29 cases were receiving treatment with diaminodiphenylsulphone, 5 had other antileprosy drugs, and 2 cases had no specific antileprosy drugs.

32 out of the 36 cases had fever. 17 had joint pain, 6 neuritis, 5 edema of the extremities, 3 swelling of the breasts, 2 orchitis, and 2 iritis. Histopathological examination of the nodules showed macrophages collected in varying numbers in the dermis and/or in the subcutaneous tissue in all cases. Polymorphonuclear leucocytes were also present in varying numbers in every case. They were distributed both in the dermis and in the subcutaneous tissue. In 12 cases abscess formation was noticed in the dermis and in 4 casse abscesses were present in the subcutaneous tissue. These abscesses contained mostly polymorphonuclear leucocytes. 12 cases showed vasculitis. Out of these 12, 6 showed abscess formation also in the dermis and/or in the subcutaneous tissue. The prognosis of the cases with vasculitis was found to be poor in comparison with others. 9 out of 12 developed repeated reactions and progressed to the chronic phase.

Erythema nodosum leprosum is an allergic inflammatory reaction with polymorphonuclear leucocytes including eosinophilis infiltrating the skin which has a granuloma composed of macrophages. Together with tissue edema and vascular proliferation a nodule is formed. Most of these cases resolve spontaneously and completely. However some progress to the chronic phase. Those with abscess formation and vasculitis are more prone to go on to the chronic phase.

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Lepra reaction: an immunologic investigation

O. K. Skinsnes — D. T. S. Tsang

A formulation of lepra reactions in terms of anaphylactic and delayed type hypersensitivity is presented as a hypothetical immunological explanation of such reactions.

A series of pilot experiments on cell and serum transfer of lepromin reactivity in humans is summarized. These suggest that lepromin reactivity is cell mediated and transferable with the transferred cells, but also indicate that such transfer does not alter the tissue hypersensitivity of the recipient host. These, and related observations, while not proving the validity of the thesis advanced in explanation of lepra reactions, nevertheless lend support to the concept insofar as they are compatible with the results that might be expected if the concept is valid.

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Trecator in the treatment of erythema nodosum

O. Borges de Macedo

Trecator (1314 TH, ethionamide or thiomide of ethyl-2-isonicotinic acid or ethyl-2-thiocarbamoil-4-pyridine), when used in the acute eruption phase with leprosy patients, has proved to be a very efficient drug for controlling the disease.

The paper describes the administration of the drug to a number of patients. In the first one, fever remained for several days, ceasing only after the disappearance of the cutaneous nodules; in the second a rapid involution of concomitant adenitis was observed; in the third, the disease reappeared when the treatment was interrupted, which shows the efficiency of the drug; in the fourth, at the dose of 4 tablets a day for 4 days, the drug produced quick regression of the nodules. In the other patients a similar regression was noted. Response was evident, with specific action on the nodules, which disappeared after a few days. It is true that acute eruptions were observed even during the treatment, fresh nodules emerging among the old ones in involution, but they were less numerous than before, viz. 1/4 to 1/6 of the earlier ones, and diminished progressively up to complete cessation of the erythema nodosum.

On the basis of these trials, we believe that, amongst all the drugs hitherto used to treat the leprosy reaction, Trecator alone has a direct action on the nodules.

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Titration of antistreptolysin "O" in leprosy patients with or without leprosy reaction

N. C. Almeida — C. Silva

Antistreptolysin "O" was titrated in the serum of T and L leprosy patients during the outbursts of leprotic reaction and in the quiescent stage. The purpose of this research was to enquire into a possible influence of streptococci on the leprotic reaction, as has been suggested by various leprologists. The technique adopted was of Hantz and Randall, with modifications, according to which titers of less than 200 Todd units are considered normal.

In the sample examined, made up of patients from the Frei Antonio hospital (Rio de Janeiro), no correlationship was found between the antistreptolytic power of the serum and the leprotic reaction, either in lepromatous or in tuberculoid patients, inasmuch as the incidence of titers above 200 streptolytic units was pratically the same among all patients, whether with or without a reaction, in both groups. It should be pointed out that the percentage with titers of more than 200 units is much higher among these patients than is normally encountered in a healthy community, some excessively high titers having been recorded even in the absence of clinical signs of rheumatism, an occurrence for which no reasonable explanation could be found. No significant fluctuation was observed in the titers, when the antistreptolytic determination was made in the same individuals before, during and after the reactional flare.

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Leprous reaction

E. Depaoli—A. R. Merceau—
R. Culasso—P. M. Prieto

The so-called leprous reaction is an acute episode that may occur in the chronic evolution of the disease and is probably caused by the presence of the bacilli in the blood, though the pathogeny differs with the location and clinical form involved. In the tuberculoid form, the bacillemia develops in an organism sensitized to the bacillus and prepared to struggle against it, so that the organism mobilizes specific mechanisms such as the epithelioid cells in its defence. In the lepromatous form, there is no sensitization and consequently no

specific defence mechanism, with the result that the organism falls back on the ordinary means of protection against any infectious agent and this leads to fever, leucocytosis, greater rapidity of erythro-sedimentation, etc. In the interpolar forms of leprosy, there would seem to operate a combination of these mechanisms to a varying extent.

It should be noted that in the lepromatous forms bacillemia is more frequent than the acute episodes. Why, then, does not bacillemia always produce a state of reaction? Perhaps this may be explained by the presence of autoimmunization features and therefore the existence of agglutinins that act on the Virchow cells and their metabolites and on the host cells, the leprosy bacilli, and their metabolites, as OLMOS CASTRO and ARGURI have suggested. When for some reason the antigen-antibody balance is upset, the acute reaction sets in as a fever or flare.

This disturbance of the antigen-antibody balance may be produced in two ways: either by a sharp rise in antigens, such as might occur with the sudden death of the Virchow cells owing to intensity of the treatment, anemia, intermittant fever, etc., or by diminution of the antibodies, in this case the agglutinins, brought about by a very severe infectious process, e. g. angina, influenza, erysipelas, otitis, sinusitis, gastroenteritis, emotional stress, etc.

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The Rubino reaction in leprosy

E. A. CARBONI—A. R. MERCAU—E. DEPAOLI — R. CULASSO — P. M. PRIETO

As has been established by RUBINO and the other researchers working with this reaction, it is due to the presence of agglutinins in the leper serum and takes place when this serum is brought into contact with formalinized sheep erythrocytes. With a view to checking OLMOS CASTRO and ARGURI's interpretation of the test as an explanation of the acute episodes in lepromatous leprosy, itl was decided to follow a small number of patients, giving them a Rubino test before, during and after the reaction.

According to this interpretation, when agglutinins are present in sufficient quantity, the Rubino test is positive, and the agglutination is quite conclusive; on the other hand, when there are not enough agglutinins, the Rubino reaction is negative and the patient is liable to a recrudescence of the leprotic reaction. The results obtained so far are not numerically significant, but they seem to confirm this explanation. The authors hope shortly to be able to throw more light on the matter.

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Acute reactions in leprosy

J. C. TOLENTINO

There are seven recognizable types of lepra reaction, namely:

In the lepromatous form of leprosy: (1) the acute lepromatous infiltration characterized by acutely inflamed lepromatous infiltration and new lepromatous nodules; (2) the classical erythema nodosum leprosum (ENL) characterized by painful red nodules which is recognized by some as the only true lepra reaction; (3) the Lucio phenomenon, or erythema necrotisans, characterized by necrotizing vasculitis.

In the tuberculoid form of leprosy: (4) the tuberculoid reaction, characterized by large inflamed tuberculoid lesions; (5) the reactional tuberculoid, flare-up, or *aicuter Schub*, characterized by numerous tuberculoid papules and nodules, together with an inflamed primary tuberculoid lesion.

In the borderline form of leprosy: (6) the borderline (dimorphous) leprosy reaction, characterized by the appearance of new borderline lesions; (7) the reversal phenomenon of Wade, or the pseudo-exacerbation of de Souza Lima, or the acute infiltration of Tajiri, characterized by the appearance of tuberculoid or tuberculoid-like lesions in a lepromaous case.

56

A tentative interpretation of erythema nodosum leprosum

R. Rollier — M. Orusco

Resulting as it does from an allergic condition, E.N.L. requires the conjunction of three elements: suitable milieu, irritant factors and an allergen (in this case: *Mycobacterium leprae*). The milieu can scarcely be changed. As to *M. leprae*, its destruction leads to healing or at least dealbation of the lesions, thus avoiding any possibility of E.N.L. developing. The irritant factors are of many kinds: *a*) *M. leprae* itself which promotes Lucio's phenomenon, i.e. a leprous necrotis capillaritis that is a true Sanarelli-Schwartzmann reaction. *b*) Concomitant infections that may promote attacks of E.N.L. curable by treating the causative infection, e. g. tuberculosis, BCG vaccine, parasitic colitis, hepatitis, hepatosplenomegaly. *c*) Malnutrition: avitaminosis and multiple deficiencies (pellagra). *d*) Drugs: overdosage is more often to be held responsible than lack of tolerance; this is evident with the sulfones, but it is often true of other drugs, including the general anesthetics. *e*) Hormonal disturbances, e. g. puberty, pregnancy, menopause. *f*) Emotional stress; in some cases E.N.L. may be induced by hysteria.

Prognosis is bad when E.N.L. begins by frequent attacks. As a rule, the affection becomes cyclic between the second and fourth year of treatment, and tends either to cure or amylosis. The humoral condition agrees with the clinical one, a low serum-globulin quotient being the main element of the dàsproteinemia.

There is a wide range of therapy: chloroquine, the antihistamines, histaglobulin and the like (useful in eye affections), the gamma globulins (efficient, but by no means harmless and phenyl butazone all give inconsistent results; greater reliance can be placed on anthomaline, emetine, homologous plasmas and whole blood; ACTH, though useful, may give rise to shock; the corticoids are the most suitable drugs for treatment, but as time goes by, they may induce amylosis and encourage its development. It must be borne in mind, however, that the only effective way of controlling E. N. L. is to be found in etiological treatment of the irritant factors.

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Reading schedule for Mitsuda whole lepromin test on healthy individuals

S. Nakamura—L. M. Bechelli—G. G. Duarte—R. Quagliato

The investigation was performed on children, adults and old people, without any knowr previous exposure to *M. leprae*. The readings of the reaction were taken at the end of 48 and 72 hours and 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, 84 and 91 days, as recommended at the VII Congress of Leprology (Tokyo, 1958).

1. In non-contacts, the lepromin positivity—zero on the 7th day and only very slight on the 14th (1.9% + and 2.1% + +)—began to be really evident in the readings for the 21st day, viz.: 29.2% +, 17.2% + + and 4.87% + + +. The average duration was 2.22, 2.12 and 3.0 weeks respectively for +, + +, and + + +, which shows that the reactions already positive on the 21st day lasted until the 35th. Modal calculations also show that the most frequent duration value was 2 weeks, 36.6% of the total doubtful reactions (±) being observed on the 21st day; the average duration worked out at 0.875 weeks and therefore failed to last until the 28th day.

2. The reading on the 35th day showed all the reactions that turned positive on the 21st, 28th and 35th day to be included: 80.35% of the +, 89.22% of the + + and 85.35% of the + + +.

3. There was no need to take a reading on the 42nd day, inasmuch as the reactions on this day lasted until the 49th day, when they were up to 91.23% +, 96.75 + + 92.65 + + +.

4. A study of the curve of evolution of the lepromin reactions according to sex and the 1-20-year and 60-80-year

age groups revealed no significant difference in the behavior of the Mitsuda reaction.

5. The mean duration or persistance of the doubtful reactions (±) was low, a week at the most, and this was equally true of the mode. Every week there were significant reactions, on the whole, and a reading taken on a given date, the 21st day, for instance, would not be the same a week later—the 28th day. The sample, however, was too small to enable an accurate deduction to be made, for it represented no more than 5% of the total sampling.

6. Should the data be confirmed, readings of the Mitsuda reaction in non-contacts on the 35th day should make for a higher percentage of positivity (about 85% for +, ++ and +++ reactions) with a better indication of the degree of intensity (+, ++ or +++). In scientific investigations, it is interesting to take another reading on the 49th day, so as to reach 90% positivity or more. If it is desired to study the doubtful reactions, various weekly readings should be made from the 21st day to the 49th.

PANEL ON THERAPY

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Treatment of leprotic amyotrophies with Vitamin E and Steranabol

O. Mattos — A. Mello

The authors have treated the amyotrophies of leprosy patients with Vitamin E and Steranabol.

The vitamin used was Ephynal Roche, which is DL-alphatocopherol acetate in aqueous colloidal solution, in 2-c.c. 100 mg. ampules. The dose prescribed was 100 mg. injected weekly into the affected muscles. 20 patients were treated, 8 of which ceased the treatment after the first applications and 12 were regularly treated. In the latter case, the results were very good. The muscles returned to their normal size and the patients developed greater muscular strength. The number of injections required for the best results to be obtained varied from 14 to 25. When the medication was suspended, the authors observed that the results were maintained for the first 6 months; from the seventh month on, the amyotrophies began to develop anew and the treatment had to be resumed. The tolerance was perfect, execept for one patient who complained of ulnar neuralgia and asked to have the treatment stopped. As to the tendinous retractions, there was no alteration. The muscles regained their normal appearance, but the retractions remained unchanged.

For the treatment with Steranabol, a synthetic steroid with the structure 4-chlorotestosterone acetate, the authors selected 12 patients. They were likewise given injections into the atrophied muscles, beginning with 1 c.c. and increasing the dose to 2 c.c. weekly. The applications varied from 10 to 27, with exception of the patients who stopped the treatment of their own accord. The results were null. Only in 2 cases was there a false appearance of recovery which vanished 30 and 40 days, respectively, after cessation of treatment. The tolerance was perfect and the injections painless.

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Results obtained with the use of alphachymotrypsin in leprotic neuralgia

A. Mello — R. G. Neves — J. G. Azevedo — N. D. Silva

The authors have used alpha-chymotrypsin locally, perineurally, and intraneurally, to treat leprosy patients suffering from acute neuritis.

Alpha-chymotrypsin is an enzymatic substance obtained in the pure form from the pancreatic enzyme of mammals, chiefly cattle. Its lytic properties which enable it to remove exudates, necrotic residues and fibrin are widely made use of in various branches of

medicine, ophthalmology for instance. The patients under observation all belonged to the lepromatous form and the majority were suffering from cubital neuralgia. The alpha-chymotrypsin was used by itself or associated with xylocain (lidocaina). Some of the patients required more than one application at weekly intervals. Beneficial results, in the form of gradual disappearance of the local swelling, mitigation of the erythema and suppression of pain, were noted in nearly all the individuals tested.

It seems that the association with xylocain, besides rendering the infiltration painless, strengthens the enzymatic action. No manifestations of intolerance or local or general hypersensibility were observed. The authors believe that this enzyme represents a valuable therapeutical weapon that should be essayed principally in cases of recurrent neuralgia that prove refractory to the usual treatments.

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Tests of the therapeutic value of Ciba 1906 in the treatment of leprosy

A. M. Alonso

The author has been testing the Ciba product SU 1906 orally since 1955 and intramuscularly since 1961. All observations have been made under strict clinical, bacilloscopic, histopathological and immunobiological control.

When given orally, the medicine was administered in the form of 0.50 gm. tablets and doses of 3 gm. and, exceptionally, 2 gm. per diem. The following results were observed in the group of 43 patients treated (25 of them lepromatous, 6 tuberculoid, 4 reactionally tuberculoid, 4 indeterminate and 4 dimorphous):

In lepromatous cases, fading of the erythematous patches was observed in the course of the first six months, sometimes with flattening of the nodules; blanching within one year of treatment was clearly marked in no less than 4 cases (16%); in 11 cases (44%) bacterioscopic observations gave negative results after 12 to 20 months; in the remainder, the tests continued to be positive, though there was a diminution in the degree of positivity, with disappearance of the nodules; 3 cases (12%) remained positive in mucus and skin despite 40 months of treatment; histologically, there has been a reduction in the exudates, disappearance of the nodules, and diminution and granular degeneration of the bacilli; in 5 cases the disease converted to the "lepromatous regressive" stage, and in 1 of them this happened in no more than 8 months; however, in two cases and only two the structure became "nonspecific chronic inflammatory", one in thirty and the other in thirty-six months.

In the other clinical forms, the results observed from the same clinical, bacterioscopic and histopathological angles turned out to be obviously superior.

Intramuscular injection: Test begun 18 months ago with 5 c.c. per week, containing 1 gm. of active substance. A group of 30 patients is being given this treament—22 lepromatous, 4 indeterminate, 3 tuberculoid and 1 dimorphous. Only two abscesses are recorded as having developed in the gluteal region. Though observation has not covered a very long period, the results obtained do not seem to be better than those secured by oral administration.

Tolerance is excellent whether the drug be given orally or intramuscularly, and no toxic accidents or disagreeable after-effects have been recorded.

The author is thus of the opinion that Ciba 1906 is comparable to DDS.

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Treatment of leprosy with urea and a high protein diet

C. G. Pereira

Urea is mainly a product of protein metabolism, animal protein being the most actively concerned in uropoiesis. Synthesized by the liver and by the mammary gland in activity, it is diuretic, highly diffusible and bacteriostatic or bactericidal, depending on the concentration.

Where animal protein is scarce, leprosy is endemic. In the Middle Agas,

hunger and leprosy existed side by side in Europe. On the Andine plateau, the mesologic conditions are such that leprosy is sporadic. Sufferers from chronic uremia remain negative to leprosy. The rare patients who spontaneously follow a high protein diet are cured, not by the sulphones but by the diet, recovering sensitivity to touch and to heat. The association of urea with the high protein diet makes it more efficacious.

C. D. 24 years old, Brazilian, white, seminarian: 15.7.62. Form: Lepromatous. Lepromatous infiltration, rare lepromas. Mucus +. Lesion ++. Promin: 1 amp. I.V. every 48 h. 24.12.62. Mucus —. Lesion +. Ulnar neuritis, left. Hypothenar atrophy, left, with tactile and thermic sensibility destroyed. Urea: 20 Gm. every 12 h. Promin: stopped. Uric acid: 0.05 Gm., 3 times a day. High protein diet. 24.1.63. Mucus —. Lesion —. Improved. 2 patches, e. nodosum. Neuritis arrested. Urea: 20 Gm. every 8 h. Uric acid: stopped. 24.2.63. Mucus —. Lesion —. E. nodosum, 2 patches. Improved. Urea: 20 Gm. every 12 h. 24.4.63. Mucus —. Lesion —. Greatly improved. Sample —. Nasal curettage —. Biopsy —. Reappearance of body hair. Gradual recovery of tactile sensibility. Left hand, muscular contraction improved.

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Dexametazone and epineurectomy in the treatment of leprotic neuritis

J. M. Rosas Netto—N. Oliveira

Seeing that the results of the various therapeutical methods, both clinical and surgical, used in the treatment of the painful afflictions and motor disorders arising from the specific inflammatory processes of the ulnar and median nerves frequently occurring in leprosy, are controversial and not always satisfactory, the authors resolved to investigate the effects of a corticoid derivative (dexametazone) and of epineurectomy of the ulnar and median nerves on a group of in-patients at the Pirapitingui Sanatorium.

To this end, the patients were divided into three groups: *a*) Patients given medical treatment with dexametazone. *b*) Patients treated surgically with epineurectomy of the ulnar and median nerves. c) Combined medical and surgical treatment (dexametazone and epineurectomy).

A description is given of the therapeutic schedule adopted and the surgical techniques used, with particular attention to the choice of access to the nerve involved. The cases were numerous enough to allow conclusions to be drawn with regard to the various methods and therapeutic norms to be established on the basis of the long-range results achieved.

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Tentative treatment of lepromatous leprosy with a combination of three drugs

J. G. Aguiar Filho—G. Vorobow — D. V. A. Opromolla

Pursuant to concomitant studies on resistance to sulfones made at the Aimorés and Pirapitingui sanatoriums, the authors proposed a trial of certain three-fold combinations of drugs of known antileprotic value when used separately, to be carried out under the guidance of the doctors who had made the studies aforesaid. The objects of the trial were to avoid the development of resistance which occurred when the drugs were used separately, with particular attention to the sulfones, and also to observe how far it was possible to promote more rapid regression of the symptoms of lepromatous leprosy with the use of a combination of three such drugs.

The tentative treatment was administered to three groups of patients, varying the combination of drugs for two of them, with a fourth as control group; the minimum duration of the treatment was 6 months, as follows: *1st group:* 14 cases without previous specific treatment were given daily doses of: 100 mg. 4-4'-diaminodiphenylsulfone + 500 mg. diphenylthiourea + 500 mg. sulfamethoxypyridizin. *2nd group:* 36 cases with-

out previous sulfone therapy but treated with other drugs separately, e.g. D-4-amino-3-isoxazolidinone, 3-sulfamido-2-phenylpyrazol, 2,4-dimethoxy-6-sulfanilamido-1,3-diazine, were given daily doses of: 100 mg. 4-4'-diaminodiphenylsulfone + 500 mg. diphenylthiourea + 500 mg. 2,4-dimethoxy-6-sulfanilamido-1,3-diazine. *3rd group:* For comparison of the therapeutic results a third group of 4 patients, presumably sulfone-resistant, were given the same 3-fold combination of drugs as the first group. The sulfone was deliberately included to see whether there would be any change in the clinical picture. *4th group:* The overall therapeutic results obtained with the first three groups were compared with a control consisting of 10 patients without previous specific treatment who only received the 4-4'-diaminodiphenylsulfone in daily doses of 100 mg. throughout the same period.

Conclusions: The results gained with the 1st and 2nd groups were found by the authors to be distinctly better than when one drug was used separately. In the 3rd group the results were satisfactory, the three-drug combination causing regression of the lesions observed at the start of the treatment.

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Resistance of the Hansen bacillus to chemotherapy

L. S. Lima — F. R. Arantes

The authors examine the limiitations of chemotherapeutics, emphasizing the importance of the problem of "relapses" in lepromatous cases treated with sulfones. A study of the literature, both Brazilian and foreign, and observation of 127 cases of their own, lead them to a three-fold classification: 1. Relapse of lepromatous patients with "lesions healed and bacilloscopy negative", after treament has been stopped; 2. Relapse of lepromatous cases with "lesions healed and bacilloscopy negative", in spite of continuation of the treament; 3. Exacerbation of the condition of lepromatous patients, with clinical and bacilloscopical deterioration, while under treatment. The sampling covered treatment with sulfones and diphenylthiourea.

The facts recorded under headings 2 and 3 are attributed to the development of the phenomenon of bacterial resistance to the therapeutic chemical, for which clinical, bacilloscopic and histopathological evidence is adduced, and emphasis is laid on the far-reaching importance of the matter in view of the influence it may have on prophylactic orientation, now based on treatment with sulfone drugs and threatened with the possibility of a new generation arising infected with strains that have become sulfono-resistant, nullifying to a very large extent the effort laid out in mass campaigns. The authors go into the possibility of resistance to diphenylthiourea and review all the literature on sulfone resistance, finally proposing a new therapeutical orientation for lepromatous cases, based on the association of three of the leading drugs now used in the treatment of leprosy: for hitherto untreated cases, diaminodiphenylsulfone + 4.4-butoxyldiphenylthiourea + sulfadimethoxin; for cases already treated for a long time with sulfones, choose between the various possible associations of diphenylthiourea, oxydiazolone, sulfadimethoxin, sulfamethoxypyridazine, semithiocarbazone and the antibiotics (Rifamycin, Streptomycin, Cyclozerine, etc.). The results obtained with various types of association will be reported by other workers.

The authors propose a scale of drugs arranged according to their therapeutical value in the treatment of leprosy, to be used as a guide in the choice of triple medication.

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Ophthalmological findings in the treatment of leprosy with diphenylthiourea

J. C. M. Araújo

The author sums up the ophthalmological results observed in connection with the treatment of patients with diphenylthiourea. The examinations were systematized under the following headings: *a.* External examination: eye-

brows, eyelashes, eyelids, conjunctivas, sclerotic, cornea, iris and anterior chamber. *b*. Visual acuity. *c*. Fundus of the eye. *d*. Biomicroscopy.

98 patients were examined initially, but only 71 took the two twice-yearly check-ups. Considering these 71 patients only in relation to the initial examination, 39 showed no change of any kind at the first check-up, nor did 47 patients at the second check-up. At the first check-up, 25 patients presented modifications and at the second, 16 patients. Of these alterations, the most numerous came under heading *b*: visual acuity. They are not, however, worth taking into consideration, because the modifications are only slight and the great majority are likely to have arisen from the fact that the examination was subjective and consequently open to error. Next came the alterations covered by heading *a*, such as: lepromas, cysts, edemas, etc. Numerically, the third place was occupied by those ascertained by means of biomicroscopy: degeneration of the iris, infiltration of the cornea, etc. As to heading *c* only two cases were encountered with modifications of the fundus.

Among the changes for the better, the author records eleven cases under heading *a* and three under heading *d*. Among the cases which got worse or where new lesions appeared, ten belong under heading *a* and three under heading *d*.

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Alterations in the blood counts of lepromatous patients treated with diphenylthiourea

P. Peres Filho

Leprosy being a disease that depletes the hematic reserves of the individual, an attempt has been made to ascertain whether dyphenylthiourea administered over a long period increases this debilitating tendency. Every two months, the hemoglobin count was made (photographic method) and the hematocritic volume determined (Wintrobe's method) in a sampling of 108 lepromatous patients (77 men and 31 women). 46 patients completed the whole series of determinations (7), while a mere 13 patients, for various reasons, failed to reach the 4th determination. As regards the hemoglobin count, it was observed that in 58 cases there was a slight diminution, in 26 cases a slight increase, and in 11 cases no change at all, simply considering the content before and at the end of the treatment (first and last determinations). In no case was there any continuity in the increase or decrease, which eliminated the possibility of drawing up statistics. The hematocritical alterations were of the same nature, preventing the establishment of any criterion for purposes of systematization. Diphenylthiourea cannot be held responsible for the changes that occurred.

In view of its evident value, erythrosedimentatior was used to supply auxiliary data for the study of the therapeutical action of diphenylthiourea on lepromatous patients. For various reasons, the method chosen was that of Wintrobe and Landsberg, which corrects the sedimentation of the hematids in function of the concentration of the formed elements of the blood. In the sample of 108 patients (77 men and 31 women) the speed of sedimentation of the red blood corpuscles was determined regularly every two months. There was no case in which the successive determinations showed that this speed of sedimentation of the red blood corpuscles was determined regularly every two months. There was no case in which the successive determinations showed that this speed of sedimentation provided a reliable indication of the clinical evolution of the disease. All the 108 cases showed increases in the speed of sedimentation of the hematids in some of the determinations, but this was neither indicative nor followed a logical system of variation. Before the treatment was started, in 5 cases only were normal values recorded. After the treatment, normal values were found in only 6 cases. In the course of the successive determinations 28 cases presented normal values once or twice. Speed of sedimentation of the erythrocytes can not therefore be considered a utilizable datum for prognostics.

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Clinico-bacilloscopic results with Ciba SU-1906

A. C. R. Marques — G. Vorobow

The authors kept 133 leprosy patients in treatment with the Ciba preparation SU-1906 under controlled observation for the period of one year. This work was carried out in accordance with the policy framed by the Study Group Commission of the Prophylaxis Department of the State of São Paulo. The patients, selected from the Sanatoriums of Pirapitingui and Santo Angelo and from dispensaries in the state capital, were all lepromatous to a severe degree; 108 of them, though having suffered from 15 to 35 years and taken the sulfone treatment for at least 10, were still in a thoroughly active stage of the disease, while the remaining 25 had taken no specific treatment before. The drug was administered according to the usual schedules, and at no time were any symptoms of toxicity or intolerance observed to justify any change in the therapeutic orientation.

A clinical check-up at the end of 6 months showed that only 32 patients had improved, while 6 were even worse than before. In contrast with the discrete clinical results, a strong diminution in the positivity of the mucus was observed at the end of 6 months, while in the skin the decrease was discrete. Clinical evaluation at the end of 1 year stood at 45 patients improved and 5 worse. From a bacilloscopic point of view, it was observed that the bacilloscopic index of the nasal mucus had risen again, while the decrease in the skin was less marked. Apart from the alteration in the numbers of the bacilli, a change of form was also observed, but on examining them again after a year of treatment, the bacilli were found to have resumed their normal appearance.

Under the conditions in which this work was pursued, it must be concluded that exclusive treatment with Ciba 1906 does not furnish a way of overcoming the therapeutical impasse arising out of the reactivation of the disease in patients previously treated with sulfones; in such cases the results obtained are scarcely encouraging. Emphasis must, however be laid on the highly unfavorable condition of our cases, in which, even so, the action of Ciba 1906 was undeniable. It would seem, therefore, that the drug should be associated with other medicines, as will be seen from the evidence in other papers written by workers in the same sanitoriums.

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Histopathological assessment of the antileprotic activity of Ciba 1906

J. Stecca—P. Homem de Mello

The authors examined 752 preparations corresponding to 376 skin biopsies obtained from 154 lepromatous patients treated with Ciba 1906. A series of three biopsies was taken from each subject: immediately prior to treatment (initial biopsy), 5 to 8 months later (first assessment) and 12 to 18 months later (final assessment), staining in each case with hematoxylin-eosin and Ziehl-Neelson carbol-fuchsin (Faraco's method).

There was ample evidence of the antibacterial activity of Ciba 1906. The morphological and tinctorial modifications of *M. leprae* did not differ from those observed with sulfone therapy. In the authors' opinion, the quantitative modifications were neither so intense nor so stable. In a group of 88 patients, a comparison between the initial biopsy and the first assessment showed that in 8% of the cases there was an apparent increase in the number of germs, in 35% the count stayed the same and in 57% it decreased. Between the first and final assessments, the corresponding percentages were: 33—37—30%. The therapeutic results observed in the second stage seem to be clearly less encouraging and it should be noted that, at the end of the test, lesions rich in typical bacilli and globi were often encountered. However, a comparison between the initial and final biopsies (16—33—51% respectively) in-

dicates that the group as a whole got some benefit out of the treatment.

The degradation of the lepromatous structures offered like aspects to those seen in lepromatous patients receiving a sulfone treatment. In some cases, mutation to the reactional tuberculoid form was also observed. In a group of 82 patients where the initial biopsy revealed 82% typical lesions and 18% lesions regressive in appearance, the following figures were obtained for the two successive assessments: 19%—81% and 28%—72%. This was further evidence of the antileprotic activity of Ciba 1960 with better results in the first period of treatment.

In the authors' opinion, the histological and bacilloscopic aspects are not characterized by the same progressive, stable regression as that observed in sulfone therapy. Early reactivation of the foci seems to take place in the course of the treatment, particularly after the first six months. In this stage, lesions are most frequently found with aspects of regression and reactivation co-existing, either mingled or side by side, which very often make it difficult to define the actual condition of the lesions observed.

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Therapeutic assessment of leprostatic drugs, especially slow elimination sulfonamides, B 663 and mixed treatments

R. Bréchet

Accurate assessment of new leprostatics demands the use of fresh cases, hitherto untreated. It should be insisted that assessment be limited to idiopathically lepromatous cases, which, alone deprived of tissular resistance, are capable o f displaying objectively the true effect of the product in question. Biopsies and photographs taken every six months are sent to a center with the necessary facilities for making a serious investigation, based moreover on bacterial counts made every three months and plotted in the form of individual *bacteriological graphs*. The latter not only show the effect of the product tested, but enable the physician to visualize the long-term evolution of the disease, the way the patient reacts, and often to forecast the building-up of resistance.

The pilot experiments made in connection with the drugs referred to in the title of this paper were carried out on 49 patients and are summed up in a table, the gist of which is as follows: 1. Slow elimination sulfonamides (*Bidizole, Orisul*) had an undeniably leprostatic action, but one that was not strong enough for severe cases of lepromatous leprosy. 2. *B 663* was not so interesting and had more disadvantages. 3. Certain *leprostatic associations* were disappointing, but others had a stronger effect than when given separately, e.g. Vadrine + Suphétrone. 4. The use of *DDS* produced several irreducible "permanent positives", but *DPT* gave better results (at least in the first two years). The bacteriological graphs, plotted over a period of years, also reveal that, despite our optimistic expectations, DDS does not always prove satisfactory in lepromatous cases.

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A new way of using diaminodiphenylsulfone (DDS)

V. M. Marini — M. L. Marini — J. A K. Yankah

The authors have succeeded in proving DDS is absorbed through the skin of leprosy patients in the course of a clinical trial in which this drug alone was used. After 9 months the clinical and bacteriological results are very promising.

It is thought that further study of percutaneous DDS will be interesting on the grounds that: *a*. Progress may

be made in understanding the mechanism of the action of DDS and other leprotic drugs. *b.* Percutaneous DDS may be a third alternative for mass treatment and prophylaxis of leprosy.

The vehicle for the ointment was prepared in the leprosarium, since pharmaceutical firms alleged that previous research demonstrated conclusively that DDS was not absorbed through the skin.

Preliminary clinical trials have also been started using other drugs percutaneously, and the impression is that a common feature of all these experiments is a rapid change in the morphology of *Mycobacterium leprae*.

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Evaluation of the effects of sulfone treatment on indeterminate leprosy patients, covering 14 years of observation

J. M. Barros — R. Quagliato — R. G. Nobrega

The authors have studied 112 cases of indeterminate leprosy submitted to the action of sulfones in the course of what was considered to be regular treatment. The cases were followed annually up till 1963, 14 years being the maximum period of observation and 5 years the minimum. The lepromin reaction was initially negative in all cases. Statistical methods were used to calculate the probabilities of the lesions healing, improving or worsening, or even remaining stationary. For purposes of observation, the patients were divided into 2 groups, viz.: those who, at the start of the treatment, had shown signs of the disease for less than 1 year, and those who, at that time, had shown signs of the disease for more than 1 year. With a view to comparison, a sample group of indeterminate leprosy patients, initially lepromin-negative, but treated irregularly with sulfones, is also presented.

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Treatment of leprosy with sulfamethoxypyridizin

J. C. Gatti — J. E. Cardama — L. M. Baliña — F. F. Wilkinson — J. J. Avila

From a study of 46 leprosy patients treated with sulfamethoxypyridizin (in some cases for two and a half years) it may be affirmed that: *a.* It is a useful drug for application in the various forms of leprosy. *b.* The benefits obtained are first clinical (improvement from the first months), then bacilloscopic, and in many cases histopathological improvement is also observed. *c.* The acetylated form, experimentally injected intramuscularly for a short period, showed promising results from a clinical, bacilloscopic and—occasionally—histological point of view. *d.* In general, tolerance was good. *e.* It is believed that this slow-acting sulfonamide should be placed on a level with sulfadimethoxin and not far below the sulfones in therapeutic value. Treatment of a larger number of cases over a longer period of observation may serve to rectify or ratify this assertion. *f.* In the authors' opinion, it is the most suitable medicine for use in cases of intolerance, resistance, habituation or for alternating with any of the antileprotic drugs of proven efficacity. *g.* Experience tends to show parity of therapeutic action between sulfamethoxypyridizin and the diphenylthiourea derivatives, but the authors prefer the former on the grounds of better tolerance. *h.* In conclusion, the retard-action sulfas should rank as second-line weapons in the attack on leprosy.

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A study of methods used in controlled chemotherapeutic trials in lepromatous leprosy

M. F. R. Waters—R. J. Rees—Ian Sutherland

Though controlled clinical trials were used from the first introduction of

successful chemotherapy of tuberculosis, such methods have been frequently neglected in the study of the treatment of leprosy. From experience gained in two drug trials performed at Sungei Buloh Leprosarium on behalf of the Malayan Ministry of Health and the British Medical Research Council, a reappraisal of trial methods in lepromatous leprosy is presented. It is considered that untreated L_2 and L_3 lepromatous leprosy patients remain the most suitable for such trials, and that accurate classification is essential. Methods of assessment, clinical, histological and bacteriological, are evaluated, and the importance of recording morphological changes in *Mycobacterium leprae* is emphasized. The general design of leprosy chemotherapeutic trials is discussed, including the advantages and disadvantages of the method of "matched pairs", and the difficulties resulting from reactions, especially erythema nodosum leprosum. Finally it is suggested that the object of the drug treatment of leprosy includes not only the killing of bacilli, but also the sucessful removal of dead bacilli, the prevention of relapse and emergence of drug resistance, and the achievement of bacterial cure.

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The retard-action sulfonamides in the treatment of leprosy and the efficient action of acetylsulfamethoxypyrazine

J. Schneider — J. Languillon

After having demonstrated the antileprotic activity of sulfamethoxypyridizin in 1959 (by personal experience with more than 150 patients, confirmed widely in the literature), the authors pursued their experiments using a sulfonamide superior to sulfamethoxypiridizin by reason of its slower rate of elimination. This drug, acetylsulfamethoxypyrazine*, was injected in insoluble suspensions and above all administered by way of mouth in the form of tablets.

Trials begun in April 1961 covered the treatment of more than 60 patients suffering from the lepromatous, tuberculoid and indeterminate forms of leprosy and in each case the improvement was highly remarkable and many of the patients are now apparently cured. The most striking feature of this drug is that it can be administered orally, owing to the maintenance of a high, lasting degree of sulfonamide activity; thus, most of the patients treated were given a single weekly dose of 2.5 grams. Another important advantage of this therapy is the rarety—not to say the absence—of leprous reactions.

All the patients were given quarterly biological check-ups, including hemograms, functional exploration of the liver, kidneys, etc. These check-ups revealed no signs of harm and confirm the excellent clinical tolerance of the drug. The authors consider that, at the present stage of antileprotic therapeutics, the new retard-action sulfamide, as compared with sulfamethoxypyridizin, is an undeniable step forward.

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* 11,589 R. P. acetyl-Kelfizine.

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First results of the treatment of leprosy with sulfadimethoxin, sulfaphenazol and diphenylthiourea

A. L. V. Marques — D. V. A. Opromolla

A group of 25 patients (19 men and 6 women) suffering from lepromatous leprosy was treated with sulfadimethoxin in doses of 1.5 grams per diem without interruption for one year, with the exception of 4 of them who only took 6 months of treatment. The maximum dose administered totaled 1151 tablets (575.5 grams) and the minimum 510 tablets (255 grams), the latter corresponding to the cases only followed for 6 months.

The patients were examined by a team of technicians by the method of "blind evaluation" in the middle and at the end of the treatment and the results arrived at were the following: *a.* Sulfadimethoxin is very well tolerated in

daily doses of 1.5 grams. *b*. The incidence of reactions of the erythema nodosum type is high, but they are not so intense as in the case of other antileprotic drugs. *c*. The results observed in the 25 patients from a clinical, bacilloscopic and histopathological angle, viz. 15 patients improved, 5 not much improved and 5 unchanged, with 8 patients out of the total displaying erythema nodosum type reactions, leads to the conclusion that sulfadimethoxin is a drug of definitely antileprotic activity which should be included among the resources that can be relied upon either for use in associations of medicines or else in the treatment of sulfone-resistant cases.

The sulfaphenazol treatment lasted 6 months and was tried out on 11 patients with lepromatous leprosy (8 men and 3 women) who were given daily doses of 3 tablets (1.5 grams) without interruption. The following conclusions were reached: *a*. The drug is very well tolerated, as was seen from an analysis of the blood and urine. *b*. The results secured in 11 cases, viz.: 5 patients unchanged, 2 not much improved and 4 improved, allied to a description of the improvements observed, are grounds for supposing that sulfaphenazol has no more than a slight action on lepromatous leprosy.

Diphenylthiourea, injected intramuscularly in doses of 1.0 grams (5 ml.), was used in the treatment of 11 patients (3 women and 8 men) with advanced lepromatous leprosy throughout one year. Of these patients, only two had been given sulfones previously and, as a result of stopping the treatment, were suffering from a reactivation of the disease. In view of a good degree of tolerance—despite the formation of abscesses at the site of injection in some cases—combined with antileprotic activity and convenience of administration, the drug should prove useful in mass compaigns and dispensary treatment. Admittedly, the treatment needs to be given to larger groups of patients in order to confirm these results and compare the degree of activity of the drug according as to whether it is injected or administered by way of mouth.

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First results of the use of Rifamycin SV in the treatment of lepromatous leprosy

D. V. A. Opromolla

Rifamycin was tried out in the treatment of 10 patients in advanced stages of lepromatous leprosy (7 men and 3 women), only two of whom had had anti-leprosy treatment before, in each case the therapy having been stopped prematurely and followed by a reactivation of the disease.

The drug was administered intramuscularly in doses of 500 mg. every 12 hours. The majority of the patients took the treatment for a length of time that averaged 120 days, and the antibiotic was very well tolerated on the whole, although in some cases indurations did develop at the site of injection from the beginning of the fourth month. After a fortnight of treatment, the lepromas began to flatten out and these early clinical results are proof of the remarkable antileprotic activity of the drug. They were not however, accompanied by parallel bacilloscopic and histopathological improvement, although a final examination showed predominance of involute forms of the bacilli.

The great antileprotic activity of the drug leads one to suspect rapid development of resistance and this is an indication in favor of its use in association with other medicines.

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Seventeen years of experience with sulfones in the treatment of leprosy

S. Schujman

1. This therapeutic evaluation only covers lepromatous cases. 2. The author has treated many hundreds of cases, but out of them he has chosen only about a hundred that he has been able to keep under observation for periods ranging from 4 to 17 years. Many of them had been given no previous treatment, but

the majority had already been treated with other drugs before being started on sulfones, after which this therapy was applied exclusively. 3. The majority of the patients were treated with DDS by mouth and others intravenously with promin. 4. Nearly all the patients improved increasingly rapidly during the first year of treatment, after which the rate of improvement was slower. 5. Mild lepromatous cases (L-1) gave a negative reaction after 2 years of treatment, but a fair percentage needed only 1 year, while others took 3 years to reach this stage. 6. Most fairly severe lepromatous cases (L-2) needed 3 to 5 years of treatment to be cleared clinically and bacteriologically, and in some cases treatment was admininistered for as long as 8 years without showing negative results bacteriologically. 7. The advanced lepromatous cases (L-3) demanded for the most part 4 to 7 years to become negative, but quite a large percentage of patients have been given sulfones for 10 to 15 years without any success bacteriologically. 8. The great majority of cases with optical lesions of leprotic origin (keratitis, iridocyclitis, etc.) failed to show improvement, and at times the disease pursued its course unaffected by the treatment. 9. The sulfones set up a leprosy reaction in a high percentage of the patients, but the author asserts that this reaction is beneficial so long as the nerves and the eyes are not involved. 10. Neuritic lesions and manifestations were less subject to improvement than those of the skin and mucous membranes. 11. The great majority of lepromatous cases owing their negativity to the treatment relapsed after it was stopped, especially in the L-2 and L-3 class. The relapse most often occurred from 1 to 3 years after stopping the drug, but in some cases the delay is as much as 5 years. 12. In most cases, when lepromatous patients continued the treatment after the negative reaction, they remained clinically and bacteriologically negative, but in some cases, leprosy reactions reappeared together with severe lesions that proved to be bacteriologically positive. 13. The treatment of lepromatous cases should be pursued all through life, with the sole exception of secondary neural cases (NS) with a lepromin-positive reaction. 14. Sulfones are the most active drugs available up to date, but unfortunately their action is bacteriostatic and the effects are very slow. What is needed is a drug that is not only more active but also bactericidal. 15. To evaluate therapeutical action in a disease with so chronic an evolution as leprosy, it is necessary to bear in mind not only the immediate but also the long-range effects and to follow the patient's progress through many years of observation.

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The action of lipoidic peroxides in the treatment of leprosy

P. M. Baranger

The fixing of peroxidic oxygen on the oil of *Hydnocarpus wightiana* gives this oil a much higher anti-leprosy activity than the non-peroxided oil. The point is that it is an entirely new remedy, chemically different to chaulmoogra oil. The peroxided oil may be used for unctions and massages, or, as an ultramicroscopic aqueous emulsion, for intravenous injections. Other peroxided oils have similar properties. The clinical results obtained with the new derivatives are described.

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Synthetic antimalarial drugs and other antiparasitics in the treatment of the erythema nodosum type of lepromatous leprosy reaction

F. F. Wilkinson — J. Ferrer

A therapeutic trial was made of the lepromatous leprosy reaction to two synthetic antimalarial drugs and one antiparasitic intestinal disinfectant. The results compared favorably with those obtained using accepted medicines, and the drugs tested were found to be useful and practical. Further investigations with the object of ascertaining the causes of this activity led to the con-

clusion that chemically no relationship could be established between the antimalarials and the antiparasitic, the only factor in common appearing to be the antiparasitic action, and it is suggested that research be undertaken to clear up the matter.

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Clinical and laboratory study of the treatment of leprosy with the drug Ro 4-4393

S. J. Falciani — C. A. Barclay — F. F. Wilkinson

The progress of investigation in the field of chemotherapeuticals has led to the synthesis of the so-called "deposit" sulfonamides, which allow the frequency of administration to be reduced without lessening the therapeutical activity, a feature that is of major importance in the treatment of chronic disorders, especially leprosy. The drug Ro 4-4393 remains in the organism considerably longer than any of the slowly eliminated sulfonamides discovered up to date, and can therefore be given in weekly doses, an advantage which is particularly appreciable in the case of maladies that require lengthy treatment.

The authors describe the results obtained by determining the free sulfonamide content, derived Ro 4-4393, in the blood of 22 lepromatous leprosy patients divided into four groups which were given doses ranging from 1 to 1.5 Gm. (weekly in 20 cases and daily in 2). A mean content was established for each group, and it was observed that, with the doses given, the sulfonamide content in the blood remained constant throughout the week, increasing gradually with sucessive doses by reason of the slow rate of elimination.

A comparison of the clinical, bacilloscopic and histopathologic changes observed in the 14 patients who have been taking the treatment for two years lead to the conclusion that in view of the excellent results, allied to perfect tolerance, ease of administration and maintenance of an efficient sulfonamide content in the blood, the drug Ro 4-4393 should be granted a predominant role in the treatment of leprosy.

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Three years' observation in the treatment of leprosy with sulfadimethoxin

C. A. Barclay — F. F. Wilkinson

This paper records the observations made on 46 leprosy patients treated with the delayed-action sulfonamide, sulfadimethoxin in the form of the proprietary drug Madribon "Roche", 21 of which have been under treatment for 3 years. The dose administered was adjusted for weight and evolution, varying from 1 to 2.5 Gm. per diem, figures that were arrived at by taking into account not only the sulfonamide content in the blood, but also the evolutive aspect. The clinical, bacilloscopical, histopathological and immunological results obtained with this new therapy are carefully noted with particular reference to the leprosy reaction, which is described as regards incidence, type, severity and influence on clinical developments.

The conclusions to be drawn from this trial are judged to be sound in view of the ample period of observation and the exceedingly strict rules of practice adopted for control of the patients. Thus it is that the authors consider sulfadimethoxin to be a drug that should be given prominence in the treatment of leprosy, on the grounds both of its efficiency and long-range tolerance, and also because the treatment need not be interrupted during the reactional phase.

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Selection of new drugs for experimental chemotherapy in leprosy

N. Dat-Xuong — N. P. Buu-Hoï — Th. Staron

On the basis of an assertion by one of the authors (Buu-Hoï, in the Internat. J. Leprosy, 1954, *22*, 17) the effect

that chemicals with antileprosy properties also exert an antifungal and tuberculostatic activity, an examination was made of several mercaptans derived from benzimidazole, benzothiazole and benzoxazole. The 2-mercaptobenzothiazole and the 2-mercaptobenzoxazole seem to be particularly promising compounds on account of their powerful fungistatic action on numerous strains of fungi, allied to their tuberculostatic activity.

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Comparative electron-microscope study of the therapeutic effects of sulfone and Ciba-1906 on lepromatous lesions

M. Nishimura—J. Ogawa—
F. Kanetsuna—E. Toda—M. Furuta

To find out the reason why lepromatous lesions are so quickly absorbed in the treatment with Ciba 1906 as compared to the sulfone treatment, we have made a comparative electron-microscope study of various stages of lepromatous lesions when under treatment with these anti-leprosy drugs.

In the sulfone treatment, electron-transparent zones increase around leprosy bacilli in the cytoplasm of lepra cells, but elsewhere in those cells the cytoplasm remains relatively intact except for varying amounts of opaque droplets. The disintegration of bacilli is shown by coagulation of bacillary cytoplasm and disappearance of the bacillary nucleus. The bacillary cell wlls are dissolved only in the final stage of bacillary desintegration.

The therapeutic effect of Ciba 1906 differs widely from that of sulphone. In particular, it breaks down the cytoplasm of lepra cells. Electron-transparent zones collapse and bacilli are also very quickly destroyed This mechanism explains the rapidity of absorption of the lepromatous lesions when treated with Ciba 1906.

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Preliminary report on lysozyme and its combination with DDS in the treatment of leprosy

N. C. Silva—R. S. C. Andrade

The authors report studies on the use of lysozyme and its combination with DDS in the treatment of ten lepromatous leprosy cases at the Frei Antonio hospital (Rio de Janeiro) and another group with perforating ulcers.

Lysozyme was given intramuscularly in the form of an acqueous solution in doses of 80 mg. every 3 days. The diaminodiphenylsulfone (DDS) was administered in fortnightly intramuscular injections of 1.2 Gm., as an acqueous microcystalline suspension also containing carboxymethylcellulose, as well as wetting, detergent and preservative agents. 59% of the crystals measured less than 5 microns, 29.5% ranged from 5 to 20 microns, and 11.5% exceeded 20 microns. A 25 × 8 needle was therefore found quite satisfactory for injections. The systemic and local tolerance was good, except for one patient who was excluded from the group after a mild allergic reaction which subsided after withdrawal of the drug. Acute and chronic toxicity was, however, determined in rats and guinea pigs. All the patients were suffering from advanced lepromatous leprosy and had already been given sulfone therapy; no improvement had been noted and reactions frequently made it necessary to interrupt the treatment. The period of observation was 100 days.

Three cases showed marked clinical improvement evidenced by flattening and regression of the nodules and areas of infiltration, together with changes of color. In the others, up to now, the condition has remained stationary, but in every case it has been possible to continue the treatment in spite of mild flare-ups of a lepra reaction of the erythema nodosum type. In the cases with clinical improvement, correlated changes in the morphologic aspects of the bacilli were observed and in some skin areas the smears began to be negative.

The authors conclude that further clinical and bacteriological evaluation is

necessary before lysozyme can be regarded as a leprostatic agent, but the antibiotic enzyme appears to be useful for increasing the susceptibility of *M. leprae* to the specific activity of sulfone drugs and lessening the frequency and intensity of the reactional states to a point where it is no longer necessary to interrupt the sulfone treatment.

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Report on the ambulatory treatment program at the Mennonite Health Center at Km. 81, Paraguay

E. Rodriguez — J. R. Schmidt

Paraguay has made great advances in its leprosy treatment program in the last ten years. Whan we started leprosy control work in 1951, there were only five doctors specifically treating leprosy patients. The number is now many times as great. The Health Department had one active clinic and one old, outdated colony. These were the only establishments for the treatment of leprosy remaining in operation after the 1947 revolution. Faced with the immensity of the problem in Paraguay, we determined to start ambulatory work, not with rural clinics, but with a service of trained laymen (refugees from Russia) who would give the patients home medicinal treatment. We found our first patients in 1954. It had been our intention to give instructions for isolation in the home, but this was immediately seen to be impossible. We also hoped to persuade mothers to give up their babies for the first two years, or at least to see that the babies did not take the breast from open leprosy cases, but in vain.

From the very first our main aim was to avoid doing anything that might keep people from coming to us for help on account of their fear of possibly having contracted leprosy. Every effort was made to show love and consideration in word and deed. We took pains to announce repeatedly that we had not come to remove the sick from their families, for this was what the people were chiefly afraid of, and neighbors would always misdirect us away from a leper's home, under the impression they were protecting him.

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Treatment of leprous ulcers with a papain compound *

J. Ferrer—F. F. Wilkinson—J. S. Falciani

This paper describes the treatment of ulcers in leprosy cases with a cleansing enzymatic agent; papain, made up to a formula containing neomycin, cystine, benzalkonium chloride, total amino acids and vitamina A.

Material and method: The treatment was given to 23 patients suffering in all from 38 ulcers, 30 of which had shown no improvement with the usual remedies, while 8 had been previously treated with asiaticoside, granulation being obtained but not epidermization. Daily dressings: powder in the center and ointment around the edges. Length of treatment: 1 to 9 months, mostly ambulatory. *Specific medication*: Sulfones, 6 patients; Sulfadimethoxin, 8 patients; Nicotibin, 1 patient; RO4-4393 experimental), 1 patient; Sulfadimethoxydiazine, 5 patients; Untreated, 2 patients.

Results: Cure (completely healed), 8 ulcers; Outstanding improvement (60% healed), 10 ulcers; Good (improved about 50%), 15 ulcers; Fair (improved 20-30%), 5 ulcers. To maintain the success achieved, it was necessary to study the ulcers bacteriologically and apply the antibiotics and drugs exerting a specific action on cach case. It is believed that the treatment discovered is useful and easy to administer, hence a valuable tool for alleviating a serious complication that often leads to disablement for the patient.

* Pan-Bión, manufactured by Laboratorios Ocefa S. A. (Argentina).

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Comparative analysis of the dapsona acetaldehyde bisulfite treatment

D. E. Salazar

In all, 304 cases of lepromatous leprosy (239) and early indeterminate leprosy (65) were investigated at various times in the course of 12 years, and the bacilloscopic results of treatment with sulfone compounds were compared at the end of 6 and 12 months. Inasmuch as no more efficient drugs than diaminodiphenylsulfone and its derivatives would seem to have come to light, it was thought interesting to determine, by comparative analysis, which was the best. It should be noted, moreover, that each social group has its own characteristics in the way of biological conditions and those of climate, nutrition, etc., factors that influence the posology and the tolerance of the various treatments.

Trials were made with: 1. The disubstituted derivative of dapsona acetaldehyde bisulphite injected intramuscularly in 76 cases. 2. Diaminodiphenylsulfone by mouth in 80 cases. 3. The disubstituted derivative disodium formaldehyde sulfoxylate of 4,4'-diaminodiphenylsulfone (diasone) in 148 cases. The comparative analysis of these compounds as regards bacilloscopic modifications is reported in Table N° 1, whereas Table N° 2 gives the tolerance, viz.: *a*) Avlosulfone by injection, 77%; *b*) Diasone, 54,2%; *c*) Avlosulfone by mouth, 46.59%. In Table 3, it will be seen that the number of conditional discharges is greater at 6 and 12 months with injections of avlosulfone. The degree of bacilloscopic positivity is estimated conventionally in x's (Table N° 1). Intolerance (Table N° 2) is measured by leprous reactions, allergic manifestations and organic disorders. By clinical result (Table N° 3) is to be understood a satisfactory condition for transfer.

Different doses were used for the two oral preparations but in every case the effects were found to be much the same. The disubstitute of diaminodiphenylsulfone gave the best results from every point of view. These disubstituted preparations of diaminodiphenylsulfone were administered in two forms: 600 mg. every three days and 200 mg. daily.

A careful examination of the graphs corresponding to application of the drug by mouth or by injection shows that the best results, obtained by injection, are due to the intermittent action of the drug on the bacillus, whereas it is considered that the treatment with the preparations by way of mouth may very well induce an adaptation of the micro-organisms to the medium. As may be seen in Graphs N° 6 and 7, the 200-mg. daily injections gave better results than the 600-mg. injections every 3 days, and it is assumed that this is due to the more frequent intermittence of the action of the drug on the bacillus, since bacterial reproduction gains headway when the concentration is very weak for a longer time. Hence, it is considered that the beneficial action of these drugs is not to be attributed to the concentration in the blood but rather to the intermittence of the drug.

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Drugs and drug trials In leprosy

S. G. Browne

The variations in reported results in drug trials in leprosy may be due to unemphasized factors, in addition to those generally recognized.

Among such factors tending to produce variable results from one center to another and from one country to another may be mentioned: the importance of including only untreated patients suffering from typical lepromatous disease, with no atypical clinical or immunological features, and with standard extent and depth of granulomatous infiltration. Variations in the degenerative changes in the bacilli, and localized persistent foci of morphologically normal forms, may complicate both the therapy and its results as generally expressed.

The indication of the degree and rapidity of improvement presumably due

to therapy, is a complicated matter, and existing notations (bacteriological and clinical) are not wholly satisfactory. They may give a false and misleading and non-comparable picture. The phase of leprosy during which therapy is initiated is also important, whether progressive or stationary or regressing. Variations in *M. leprae* itself are possible, and indeed likely, on analogy with other mycobacteria.

Hormonal, dietetic, environmental and seasonal factors may also be concerned.

Resistance of *M. leprae,* reactional episodes and sensivity reactions, may all complicate and even vitiate therapeutic trials.

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Criterion for the choice of drugs in the treatment of the different clinical forms of leprosy

F. T. Guasp

The various stages and episodes in the evolution of leprosy are reviewed in the light of the suitable therapeutic indication for each of them. Emphasis is laid on the great future interest for the patient in avoiding the spread of visceral lesions (of the liver and kidneys) during the reaction period; by treating the patients before such lesions become generalized, they turn negative without incurring leprosy reactions, which results in a cure without after-effects. On the contrary, the specific treatment now so widely adopted determines the appearance of leprous reactions and consequently visceral lesions that subsequently make it impossible to accept the cure of patients even though they have become bacteriologically negative in skin and mucus.

Attention is drawn to the great possibilities ofered by the use of corticosteroids in the treatment of the reactional syndrome to prevent the inception of the aforesaid hepatorenal lesions, viz.: specific local inflammatory lesions (liver) and pathogenic lesions with an allergic background (kidney), which leader on to connective hyperproduction (cirrhosis of the liver and renal sclerosis).

On many occasions it is wise and sometimes necessary to abstain from administering specific drugs (old age, severe renal or hepatic lesions). It should always be borne in mind that the extent of hepatorenal lesions should govern the therapeutic inidications throughout the reactions period.

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Treatment of leprosy with sulfadimethoxine, a retard-action sulfa

R. Culasso—A. R. Mercau—
E. A. Carboni—E. Depaoli—
P. M. Prieto

The drug was given to thirteen patients, ten of them without prior treatment; the form of the disease was lepromatous in 12 cases and indeterminate in one. The drug was administered by mouth in doses of half a gram every 12 hours (1 Gm. per diem). Sulfonamidemia was controlled in ten patients. The duration of the treatment ranged from one year for the most recent to 2 years for the earliest patient. The results were as follows: *Clinical*: Evident regression of the lesions, disinfiltration of spots, patches, tubercles and nodules. Cure of rhinitis and improvement of neuritis. Bacteriology: No case turned negative, but the morphology of the bacillii altered with the appearance of fragmentary and granulated forms. *Histopathology*: Diminution of infiltrates and vacuolization. *Tolerance*: excellent. Hemograms, erythrosedimentation and urine practically normal. *Reaction*: Three patients sufferred from acute episodes of varying intensity. *Comments*: Sulfadimethoxine is clearly an active drug and it seems to be more effective than the similar product, sulfamethoxypyridizin.

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Sulfonamidemia and treatment of leprosy with diaminodiphenylsulfone

C. E. Corbett—A. C. Mauri—
D. V. Opromolla—A. P. Brisola

Though diaminodiphenylsulfone gives good therapeutic results with a relatively high number of patients, some of

them are only initially benefitted, ceasing to show clinical improvement while others receiving the same dosage progress steadily.

In order to study this disparity, 80 patients were tested for sulfonamidemia, half of them (Group I) presenting an involutiona. clinical picture, and the other half (Group II) a stationary or evolutional morbid condition. All were given a daily dose of 200 mg. of DDS (product A) by mouth. The sulfonamidemia was determined by the Bratton-Marshall method with modifications and the blood samples were taken 3, 6 and 24 hours after administration of the drug. The mean sulfonamidemia in Group A was considerably higher after 24 hours in Group I (0.483 mg.%) than in Group II (0.262 mg%). In the case of 10 patients the treatment was stopped and resumed 30 days later with DDS from a different source (product B), in the same dosage, whereupon the average rose to 0.420 mg. 24 hours later. The increase of sulfonamidemia in these patients with the use of a drug of a different make would, however, appear to be due to the pharmacochemical nature of the previous drug which made it difficult for the patient to absorb it. In fact, the blood concentrations obtained after 3, 6 and 24 hours of treatment with product A were more constant, though low, and no fluctuations were observed during the day. This did not hold good for product B, for which the highest readings were obtained 6 hours after administration, subsequently falling off. On the other hand, the administration of product B enabled far higher blood concentrations to be reached than those formerly obtained with the same patients, the values almost exceeding those of Group I.

In order to ascertain whether or not the absence of therapeutic reponse in Group I should be attributed to a lack of absorption of DDS, the ten patients which showed a rise in sulfonamidemia when product A was replaced by product B were carefully examined, with the following results: one of the patients continued to get worse, one remained unchanged, two improved slightly and the rest got distinctly better.

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Methodology for therapeutical experimentation at the São Paulo Leprosy Prophilaxis Department

J. M. A. MADEIRA

The author, as Director of the Leprosy Prophylaxis Department of the State of São Paulo and member of the Organizing Committee of the VIII International Congress of Leprosy, presents the Methodology adopted for the studies in the field of experimental therapeutics pursued by the leprologists in this department with the object of standardizing them and ensuring that the results were comparable with those obtained with the same drug in other centers.

This methodology is concerned with: 1. The process of selection cases and forming the various pilot experiment groups so that they may be statistically valid. 2. The schedule of treatment to be adopted for each drug employed alone or combined with other drugs. 3. Documentation at the beginning of the treatment, brought up to date every 2 months to keep in touch with the evolution of the disease. 4. The method of "blind assessment" for evaluating the results after 6 and 12 months. 5. The criterion for the evaluation of bacilloscopic results by means of a bacilloscopic index, both for skin lesions and for the nasal mucosa. 6. The taking of biopsies at the start of the treatment and after 6 and 12 months, on the occasion of the blind assessments. 7. Laboratory examinations, considered as routine, and certain special ones, e. g. electrophoresis of the proteins in the serum, titration of mucus, proteins, C-reactive proteins, etc.

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Notes on the treatment of lepromatous leprosy with Ro. 4-4393

C. F. LOPES—O. DINIZ

The authors report the results obtained by treating three lepromatous pa-

tients with the preparation Ro. 4-4393, the active principle of which is a sulfonamide like sulfadimethoxine belonging to the same group as sulfadiazine. The present experiment started nine months ago, when the patients were given a dose of 200 mg. per diem. ULISSES M. SANTOS and CID FERREIRA LOPES having ascertained that a weekly dose of 1½ to 2 grams maintained a blood level equivalent to that secured with the daily dose mentioned, the authors decided to change the schedule accordingly. The regression of the clinical lesions from which the patients were found to be suffering at the start of the treatment proceeded steadily and progressively. Bacilloscopy of the nasal mucus and skin lesions was at first strongly positive, but regressed rapidly until now only alcohol-acid-resistant fragments remain. The tolerance of the drug has been good and no untoward symptoms have developed worth mentioning. The results obtained in so short a time are extremely encouraging and clearly show the value of this therapy, though they are subject to some reserve in view of the small number of patients treated. The authors realize that they have made but a slight contribution to the subject, but trust that their findings will be confirmed by other workers in the same field.

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Observations on some modern anti-leprosy drugs

G. FARRIS—A. BACCAREDDA-BOY

For the last 5 years we have been treating several groups of lepromatous patients with Ciba 1906 and cycloserine so as to gain a better notion of the practical applications of these two drugs. Ciba 1906 has been found the most suitable for long treatments after hospitalization; cycloserine has been used with very good results in cases of serious lepromatous diffusion with kidney involvement where other drugs are not tolerated. About 6 months ago, experimental treatment with a cycloserine derivative (terrazolidone, manufactured by Bracco) that seems likely to be better tolerated than cycloserine itself has been started with a group of 8 patients affected with lepromatous leprosy. Though the period of observation is still too short, it may be said that the anti-leprotic activity of this drug is quite effective and that a dose of 500 mg. per day is very well tolerated for treatments and research into pharmalogical synergism.

About 8 months ago, a start was made on a group of 15 lepromatous patients with rifamycin SV (Rifocin Lepetit), an antibiotic derived from that produced by *Streptomyces mediterranei,* in experimental treatment. This drug, which has given proof of good antitubercular activity, has also been found efficacious in the treatment of leprosy and well tolerated in intramuscular injections of 500 to 1000 mg. per day given every 12 hours for periods of 15-45 days alternating with rest periods of 10-15 days. Despite the encouraging clinical and bacteriological results, a few cases developed a lepra reaction with signs of erythema nodosum and a rise in body temperature.

It is thought that the communication of the antileprotic activity of these two drugs may open the way to associated treatments and research into pharmalogical synergism.

As standard practice in treating the lepra reaction, novocaine has been given intravenously with excellent results, to the exclusion of corticoids, which impair immunity and have only been used with caution in the most serious cases (iridocyclitis). Neuritis and neuritic pains have been alleviated to some extent with the administration of the usual heavy doses of vitamins B_1 and B_{12}, associated with intramuscular injections of galantamine bromohydrate (1.5 to 5 mg. per day) for periods of 30-60 days.

PANEL ON EPIDEMIOLOGY AND CONTROL

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Leprosy control in Brazil

F. G. Castelo Branco

1. In this paper the serious public health problems of endemic leprosy in Brazil is discussed. About 6,000 patients were card-indexed on the average in the period 1950/1962, which gives a mean coefficient of incidence of 9.5. The number of patients and contacts in all are estimated at 98,570 amd 192,158 respectively, indicating a prevalence of 1.3.

2. In view of the failure of the former costly three-fold method of prophylaxis to control endemic leprosy, a "pilot-campaign" was launched successfully, to be followed by the institution of a new prophylactic system, campaign-style, in which an executive role was played by the doctors and orderlies of the local sanitary units, not specially trained, but always under the guidance, coordination and control of the leprologists of the National Leprosy Service. The advantages of this pratice proved to be both technical and economic. Merely in the area covered by the Campaign—18.56% o fthe extent and 47.12% of the population of Brazil—there was a substantial increase in early diagnosis and an unprecedented rise in the control of patients and contacts—77.9% and 60.1% respectively. Conclusions may therefore be drawn in favor of the feasibility of the new method and the benefits to be derived therefrom, which would seem to justify a greater outlay of funds and energy to extend it to the other areas of the country where the epidemiological situation is of recognized importance.

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Prophylaxis of leprosy in the state of Paraná

A. Scheidt—A. Arantes—G. Mourão

The authors survey the work of leprosy control in the state of Paraná over a period of 11 years in which these activities were pursued according to two different systems: at first, the old-fashioned three-fold combination of prophylactic measures, and subsequently, the modern system of home treatment, i.e. the National Anti-Leprosy Campaign. The sampling under consideration clearly denotes the different working methods. The authors worked under both systems, getting to know them thoroughly.

The population of the area under investigation is a cross-section of the national population and the total of 4,905,000 inhabitants includes representative groups from nearly all the nations in the world. The climate is subtropical and temperate, and the area, amounting to 199,554 km² (77,049 sq. miles), is in a plateau region.

Up to the last year of the first period under survey, i. e. up to 1956, 5,959 patients had been card-indexed, since the Service was begun, whereas in the period of activities under the new system, i. e. up to 1962, the number of patients card-indexed amounted to 4,496, bringing the total up to 10,455. Statistics show, therefore, a remarkable increase in working activities.

The diminution in the lepromatous forms from an average of 70% in the five earlier years to 45% in the last five is an indication of the greater value of the work. The indeterminate forms increased from 17% to 37%, which is another achievement of the new doctrine. The control of the sick in the Dispensaries, formerly 40%, was raised, under normal working conditions, to 90% with the new methods. Thus comparative data and studies reveal a noteworthy improvement in the efficiency and quality of the work, with a marked saving in outlay and a far-reaching social effect.

The value of the new system is shown to be even more significant in view of the fact that the lack of funds hampers the pursuit of regular activities and their extension all over the area. The authors conclude, therefore, in favor of a working system along the lines of

the National Anti-Leprosy Campaign, laying emphasis on greater extension and the need for sufficient funds, and further stressing the importance of the Sanitary Units taking a share in leprological activities.

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The origin and antiquity of leprosy

V. MOLLER-CHRISTENSEN

Since 1953, when the syndrome of bone changes in the skull was discovered—and named facies leprosa (V. MOLLER CHRISTENSEN—it has been possible to trace cases of leprosy in many large archeo-osteological collections the world over. About 80 to 90% of the material in these museum and university collections consists entirely of crania, i.e. skulls without the mandible, and diseases such as leprosy and syphilis must therefore be diagnosed from characteristic changes in the skull alone. In leprosy, pathological changes in parts of the skull other than the maxillary bone (facies leprosa) have never been observed, except for the orbital anomaly known as usura orbitae. In syphilis, the skull vault is the predominant part of the skull to show characteristic changes, i.e. calvaria syphilitica.

In 1962, I spent six months as a Carlsberg Research Fellow traveling in England, Scotland and France in search of cases of leprosy among the extensive archeo-osteological collections. Alone or in teamwork with six English, Scottish and French anthropologists, leprologists and pathologists, I examined in all about 18,000 skulls, skeletons and mummies, with the following results:

Leprosy: The earliest cases, six in number, from the British Isles date back to 500-700 A.D. as far as can be while in Egypt there is a male mummy some in Roman times. One case from about 500 A.D. was found in France, while in Egyte there is a male mummy with lepromatous leprosy and a female skull with facies leprosa, both of aboult the same date and from the same cemetery near Aswan; leprosy, has nota, however, been met with among the other thousands of mummies and skeletons from ancient Egypt and Palestine. In medieval European leper churchyards, traces of the disease are not uncommon, in Denmark for instance.

Tuberculosis: The disease has been described in ancient Egyptian specimens, some over 5,000 years old, and in others of about the same age found in Europe (Germany and France).

Syphilis: No well-dated cases of caries syphilitica is known from European, African or Asian material prior to 1500 A.D., but after this traces of the disease are increasingly common.

From the available data it may be deduced that tuberculosis is a very old disease in the Old World; leprosy probably began two or three centuries B.C.; and syphilis after the discovery of America (1493).

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Results of antileprotic prophylaxis in Martinica from 1954 to 1963

E. MONTESTRUC

Since 1954, the year in which measures of control (e.g. case-finding, segregation, treatment, biological prophylaxis with BCG vaccin and medicine, social work) were greatly reinforced, the following trends have been noted: 1. A drop in the total number of cases of leprosy found annually. This figure was 4 times lower in 1962 than in 1955. 2. An even greater drop in lepromatous patients (53 in 1955 as against 8 in 1962). 3. An increase in the proportion of tuberculoid leprosy among the total number of new cases found. 4. The undeniable diminution in the prevalence of leprosy in Martinica shown by these figures is even more marked in the age group of adults over 20. 5. Leprosy has almost disappeared from among children under 5 years of age.

It is truly regrettable that these promising results, which might lead one to expect leprosy to be practically eradicated in Martinica within a short space of time, are offset by a state of affairs

only too likely to prevent this; the adverse factor is the number of clinical and bacteriological relapses among patients who stop the treatment too soon in the belief that they are cured, and now amount to a source of contagion more serious than that of the new cases of bacillogenous infection detected.

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Control of endemic lèprosy by mobile sanitary units

J. A. PUPO

Starting from the traditional concept established by ARMAUER HANSEN in 1886 that leprosy is a disease spread by contagion within the family, the author suggests a prophylactic system supported by irrefutable epidemiologic arguments and with an ecologic basis in the field of preventive medicine, to work as follows: *a*. Perodical inspection of domestic foci by mobile sanitary units. *b*. Intensive treatment of indeterminate cases so as to break the cycle of contagion and avoid development into the lepromatous type, the majority of which evolve from this, the most numerous group of sufferers from *lepra incipiens*. *c*. Higher efficiency and more facilities from sulfone therapy when the lepromatous form is diagnosed in its initial evolution, avoiding highly infectious open lesions by intensive treatment. *d*. Abolition of compulsory isolation, which, besides being extremely expensive for the campaign, leads to the hiding of foci, existing sanatoriums being maintained with an *open door* regime for advanced cases, the only condition compatible with *selective* isolation as advocated by the VIIth International Leprosy Congress (Tokyo, 1958). *e*. Transformation of preventoriums into polyvalent educational and assistential institutions for the children of poor families, so as to protect the descendants of lepers from the stigma of millenary tradition. *f*. Integration of leprosy prophylaxis within the Public Health Service to be coordinated as a specific unit in polyvalent organizations with sanitarian, assistential and scientific aims, of official, semi-official and voluntary institutions, furthering close collaboration between clinicians, pathologists and sanitarians specializing in leprosy, and technical Public Health personnel. This will tend to raise specific standards and gradually dispel popular prejudice, which is particularly strong against leprosy and tuberculosis.

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Biotypology and leprosy

M. L. SALOMÃO

The work described in this paper was originally undertaken with the object of comparing the results of a biotypological investigation made at the Krutje Rutschji Leprosarium in the USSR with data collected from a Leprosy Sanatorium in the state of São Paulo, Brazil, where the inmates belong to groups of very different racial origin. This comparison was found to be impossible for various reasons, amongst others the fact that there was not a significant number of leprosy patients of the tuberculoid type to be compared with those of the lepromatous type.

A comparison was, however, made between the distribution curves of: 1. A group consisting of a sample of 351 inmates of the Sanatório Cocais (São Paulo state), suffering from the lepromatous form of leprosy. 2. A control group consisting of a sample of 383 individuals not suffering from leprosy or tuberculosis, of the same social class and accustomed to the same general type of nutrition as the patients under investigation. The calculations were made on the basis of Pignet's formula.

The author concludes that there is a striking relationship between the biotype and the lepromatous form of leprosy. Among individuals suffering from this form of the disease, there was a greater incidence of the longilineal type than among the members of the control group.

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Assistance to the children of lepers (in mixed family groups)

F. C. MENDES

The problem of separating the minor progeny of a leper from the family is examined from the prophylactic and social-economic viewpoint. This analysis is based on observations made at the educational establishments (*educandários*) of Santa Terezinha and Jacarei. The advantages of the ordinary school and the special training school (*educandário comum* and *educandário especializado*) are reviewed, together with the importance of the role of the Social Worker and the Health Instructor. Emphasis is laid on the wisdom and the need of preserving the link between the minor and his parents and other relatives.

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The mission to lepers in South Korea

G. K. WILSON

There have been many surveys of leprosy patients in South Korea, resulting in estimates of incidence of 4 to 10 per thousand.

In March 1957, the Mission to Lepers began a weekly clinic in Taegu followed by the first of 13 rural clinics. Of over 1,250 patients the average attendance is 66%. Of the 30 new patients seen each month, 10% were classified as Indeterminate, 1% Borderline, and 1/3 were bacteriologically positive (modification of Wade's method). About 1/3 have eye disease, mostly associated with leprosy. After a 3-year experiment with a 4-bed unit, a 20-bed Leprosy Centre with operating unit was opened on December 1, 1962, inside the compound of the Provincial Government College Hospital Although every opportunity is used for propaganda, this small project is not a mass campaign, each patient being seen individually with separate notes and treated for concurrent disease also. Paramedical workers are needed to fulfil the requirements of this project —Propaganda, Treatment, Survey—but their selection remains a big problem. Meantime absolute regularity of clinics and individual treatment remain the characteristic features of this program.

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The importance of anesthesia in a leprosy control program

R. S. BUKER

A leprosy control program requires two things finding the patients and treating them long enough to prevent relapses. The procedure of finding cases demands a simple positive sign which invariably confirms the diagnosis of leprosy.

The histological basis of this clinical sign has been repeatedly shown by different leprologists who have made a study of leprosy biopsies. GASS in 1952 made a detailed clinical study of anesthesia, comparing his clinical findings with histological observations. We applied this fact clinically in a field survey of four tribes in Burma. We examined over 1000 people for anesthesia resulting in the diagnosis of leprosy in 609 cases. Again in 1951-1955 paramedical workers, carefully trained in this method, made the diagnosis of leprosy in over 10,000 cases of leprosy, in North East Thailand.

The method of examining for anesthesia is important. The patient should be blindfolded. Cotton and light downy feathers may give false positives. Pins, needles and stiff objects may miss definite early cases. A piece of paper, a leaf or a blade of grass should be used. By testing for light anesthesia difficult skin diseases, beriberi, and poliomyelitis are quickly and easily ruled out. It is the only field method, usable by paramedical workers, which will definitely confirm the diagnosis in the earliest cases of leprosy.

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Present status of leprosy in Cuba and program of control

B. S. Delgado
M. A. G. Prendes

An analysis is made of the present overall conditions and technical basis of prophylaxis, and a description is given of the organization of a program of leprosy control in Cuba.

Emphasis is laid on the scarcity of skilled personnel, with the recommendation that the study of leprology be intensified in the universities and that workers be prepared by means of special training courses. Importance is attached to early diagnosis, case-finding and bacteriological examination. The classification of the disease into the forms "open" and "closed", as being the sanitarian frontiers of leprosy, is also considered of great importance. The technical background must cover a knowledge of: 1. Features of the endemic. 2. Guiding principles of the campaign. 3. Organization of medical services. 4. Assessment of the results of the campaign.

The control program should embody the following essentials: integration of the services in the General Agencies of Public Health, coordination with other departments, regulations, and connection with Mass Organisms. International norms have been followed in building up an organizational framework, with special emphasis on dynamic promotion of epidemiological assistance in specialized dispensaries. The importance of health education at all levels is unanimously recognized.

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Epidemiological study of leprosy in Cuba (geographical distribution)

M. A. G. Prends — B. S. Delgado

The total area of Cuba is 114,525 sq. km. (44,178 sq. miles) and the population amounts to 7,022,350 inhabitants, the races, by order of numerical predominance being: white, halfcaste, black, yellow. "The climate is healthy, moderately warm and humid, without the extremes of cold and heat found in other climates," according to P. Gutierrez Lanza. The average temperatures are: annual, 25°C (77°F); winter, 21°C (70°F); summer, 27°C (81°F); the mean annual rainfall amounts to 1.40 m (55.12 ins.) and the mean relative humidity 72%.

Endemic leprosy is to be found spread all over the country. There are about 4,810 lepers, 4,299 of whom are under sanitarian control in their own homes while 511 are in-patients at one or other of the hospitals. The prevalence per 10,000 inhabitants is 6.8, while the number of lepers per 100 sq.km is 4.2 (10.9 per 100 sq miles). The Cuban climate has no influence on the frequency of the disease, nor has race, sex or birthplace. The age most seriously affected is 16 to 35 years. The low standard of living, which leads to a lack of personal and domestic hygiene, overcrowding, physical exhaustion, deficiency diseases, parasitism, etc., diminishing or exhausting the natural resistance of the organism—all this is what does have a bearing on the incidence, development and spread of the malady when these factors are concomitant in individuals living in regions where the endemic remains active, as is the case in poorly developed countries.

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School surveys in Burma

F. M. Noussitou

1. Methodical school surveys have been carried out in Burma in 1961-63 as part of the regular leprosy control project activities. 2. Out of 350,798 students examined, 9,375 typical cases of the disease (26 o/oo) were detected. 3. Prevalence was 23 o/oo in the 5-9 year group, and 28 o/oo and 21 o/oo in the 10-14 year and 15-9 year age groups respectively. 4. Prevalence was 29 o/oo among the males and 18 o/oo among the females. 5. Clinically 65% of the cases

were classified as indeterminate, 32% as tuberculoid and 2% as lepromatous. 6. Epidemiology of leprosy in children is briefly discussed and the importance of methodical examination of children in hyperendemic areas stressed.

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First experience in Mexico of mobile units for leprosy control (1960-63)

AMADO SAÚL

In 1960 a new Campaign was started in Mexico on the basis of specially designed *mobile units*, consisting of a doctor-and-nurse team specially trained in dermatoleprology and provided with a jeep to enable them to reach the most out-of-the-way places in the endemic zones of the country, and seek out new leprosy cases for treatment, in the belief that for the time being the only efficient prophylaxis for the disease lies in treating as many lepromatous cases as possible.

The apathy and carelessness of sick people in Mexico, the lack of communication in many parts of the country, the inability of the patient to afford transportation to the big cities where proper medical attention is available, and the absence in many neighborhoods of health centers with sufficient trained personnel to handle such patients, are the reason that led to the establishment of these mobile units.

The work of the mobile units may be summed up as follows: 1. Sensitization. 2. Dermatological consultation to detect new cases of leprosy. 3. Ciinical and epidemiological study of leprosy patients. 4. Examination of contacts. 5. Examination of population centers, above all from an educational point of view. 6. Education in hygiene.

Three years of work (1960-63) have yielded the following results: *a*. With the help of the mobile units, four times as many patients have been discovered as when the work devolved upon a few dermatological centers. *b*. 50% of the new patients were discovered through dermatological consultation. The remainder were detected when examining contacts or through information supplied by other patients. It is considered that the operation of mobile units is useful and indeed indispensable in any attempt to control leprosy in countries like Mexico, where conditions make it extremely difficult to attend to the sick in specialized centers.

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Organizatio. activities and results of the Leprosy Control Program in Mexico (1960-62)

F. LATAPÍ

In 1960, the Secretariat of Health launched a new Program for the Control of Leprosy in Mexico and assigned the organization and management of the undertaking to the author of this paper. Antecedents and the ideas of Mexican leprologists are cited, with emphasis on the role of the distinguished Brazilian leprologist Lauro Souza Lima, adviser in 1949, the enthusiasm of Dr. Alvarez Amézquita, Secretary for Health, and the efforts of the dermatoleprologists of Mexico City and Guadalajara to set up this program on a sound and durable foundation. A description is given of the training of doctors and nurses, the formation of 39 mobile units and their activities in endemic foci, gaining the confidence of the country folk through the consultation "for skin diseases". The results in the first three years, amounting to 4,000 new cases detected and treated, are compared with those of earlier periods, and certain factors, favorable and unfavorable, are noted. It is affirmed that the technical training and stamina of this personnel, entirely devoted to their work, is high enough to overcome the burocratic and political obstacles that, in Mexico and elsewhere, frequently bar the advance of such ventures in the cause of public health.

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Epidemiology and control of leprosy in Paraguay

A. A. González

Paraguay presents its experience with 4,367 patients registered from February 18, 1949, to December 31, 1962.

From the epidemiological study, it may be seen that: 1. The recording and the rate of incidence are in strict proportion to the scope of the work carried out. 2. In the case of 698 patients, the records have been closed on the grounds of death, cure or immigration. 3. In the leprosy area of Paraguay, the lepromatous form is predominant (48%). 4. 40.7% are within the area of the First Sanitary Region and one-fourth (27.7%) thereof in Assunción. 5. The rate of prevalence throughout the country is 2.0 per thousand inhabitants. 6. The prevalence according to area works out at 0.8 patients per 100 sq. km for the whole country, with a peak of 507 patients per 100 sq. km. in Assunción. 7. 74.1% are between 20 and 59 years of age. 8. More males contract the disease than females. In both sexes, the tuberculoid and indeterminate forms are more common up to 15 years of age, after which the lepromatous form predominates. 9. The prevalence rate in Paraguay makes it a country where leprosy is extensively endemic, though relatively benign in view of its low spreading potential and tendency towards stabilization, as shown by the fact that 74.1% of the sick are between 20 and 59 years of age. 10. Since 1955, there has been a plan of control in operation, based on ambulatory treatment without compulsory segregation. 11. In 1958 the program was revised with a view to ensuring coordination with other programs of the Ministry of Health, a lower cost per patient detected and controlled, better utilization of the technical and direct participation of the local Health Services. 12. The program was adapted to fit into the Sanitarian Organization of the country, with positions in the public service for the regional leprologist, doctors and auxiliary personnel. 13. 73,3% of the sick are under control. Of the known lepromatous cases, 86.6% are under control. 14. The control of contacts amounts to 16.1%. The contagion index stands at 1.1%, the source of infection in all cases being lepromatous. 15. The system of community examination has led to the detection of 83 new cases of leprosy.

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Suggestions for a basic reform of the National Leprosy Service

M. Silva Júnior

I. *Sanitarian policy*

1. Energetic prophylaxis to be pursued by direct federal action under one management, with centralized regulations and decentralized executive. Autonomy in the movement of personnel, viz.: engagement, transfer and dismissal. 2. Positions of responsibility (director, chief, etc.) to be held exclusively by full-time sanitarian doctors (at a salary of ten times the highest minimun wage, plus auxiliary benefits). 3. Effective institution of a system of intellectual and cultural merit as a basis of public service promotion. 4. Direct subordination of the NLS to the minister's departmental staff, with incorporation of the present unconstitutional or superannuated agencies in the National Health Department. 5. Reestablishment of the three-fold Dispensary-Leprosary—School organization, but on an effective doctrinarian working basis. 6. Effective adoption of temporary selective isolation in high-standard leprosaries (with attraction conducive to isclation), progressively and strategically installed (according to the extent of prevalence) in the endemic areas. 7. Reorganization of the Leprology Institute.

II. *Assistential policy*

Institution of a sick wage (equivalent to the regional minimum wage) conditioned to regular treatment, with extension of prophylaxis to patients that have

been rendered negative whenever advisable and possible. 2. Institution of a special family allowance (equivalent to half the minimum wage) for the maintenance of co-educational technical professional schools for the children of lepers. 3. Institution of sickness insurance policies (with private companies) for Mitsuda-negative subjects living with unhospitalizable sources of leprosy.

III. *Financial policy*

A. Revenue: 1. Five-year budget assignments, with compensation for currency depreciation. 2. Establishment of the "Leprosy Control Week" to collect additional funds from popular support. 3. Creation of a National Leprosy Control Fund, made up of both national and international contributions (US AID, FISI, NIH, etc.). *B. Expenditure*: Application of assignments deposited in government bank accounts by the system of "advance installments", according to the principle of *full freedom subject to effective verification of responsibility*. 2. Credit balances at the end of the financial year to be carried forward automatically to the NLCF for the following year.

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Leprosy survey in the village of Limas

D. G. Tinoco—A. A. Henriques—J. T. Coelho

The authors proceeded to a leprosy morbidity survey in the satellite village of the largest leprosary in Brazil, situated in the state of Minas Gerais. The village has 433 dwellings and 1,361 inhabitants. Most of the houses are brickwalled and tile-roofed, with a tamped earth floor. Sanitary conditions are very bad. There are two grade schools with a total enrolment of 96 children. 58% of the adult population are quite uneducated; 67% are undernourished. There is a high infant death rate, and no medical care available. The examination of 1,259 people showed that 431 were lepers, most of them lepromatous, but only 44,8% receive regular treatment. The contact/patient ratio is 1.9:1. 14 new cases were diagnosed, 8 belonging to the Indeterminate Group, 4 of which had been developing for about a year. Of the new cases, 5 are children, one of whom, a five-year-old, was born in the village. Of the 828 contacts, 31% were born in the village. A serious hazard from a health point of view lies in the fact that 56.2% of the contacts belong to the 0-14 age group. The susceptibility of the exposed population was investigated and it was found that, where the contacts were living in surroundings involving massive exposure to the disease, the lepromin test was positive in 40% of the 400 cases examined, a result that was no different from that obtained in the unexposed areas. It is suggested that a clinic be set up in the village and staffed by qualified public health workers, impressed with the importance of a program of sanitary education designed to change the unhygienic habits of the population. The sick should be encouraged to do such work as is compatible with their condition. It is recommended that an enquiry be made into the possible positive correlationship between lepromin positivity and nutrition.

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Epidemiological and clinical characters of leprosy in West Africa (Haute-Volts)

H. Sansarricq

This paper describes the initial results of an enquiry pursued in a canton of Haute-Volta, selected because of the absence of certain sources of error generally encountered in West Africa. These results may be summarized as follows: 1. In 8 villages grouping 7,705 inhabitants, the overall prevalence amounts to 58 35 o/oo for the population as a whole, breaking down into 55.1 o/oo for the male sex and 61.0 o/oo for the female. 2. The lepromatous index is twice as high for males as for females. 3. The demographic

group pattern of the endemic reveals no disagreement with modern ideas on the spread of the disease. 4. Primary lesions do not appear to be located preferentially on clothed or unclothed parts of the body. 5. The proportion of lepromatous cases amounts to 5.6% of all cases of leprosy. 6. Disabilities of leprotic origin only affect 11.9% of the patients. 7. Results of treatment list "cured" cases as 80.6% of all patients. There would seem, however, to persist a heavy proportion of cases that remain bacteriologically positive in spite of regular treatment over a long period, and these cases may well be an important source of endemic renewal.

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Diagnostical investigations into early tuberculoid lesions in North Ghana

J. Walter

24 early tuberculoid cases chosen at random were clinically, histopathologically and immunologically examined. Special accent was put on clinical signs of disturbance of sensitivity and 10 out of 24 cases showed no such disturbances. In spite of the small number of cases examined, attention is drawn to the fact that in Northern Ghana and probably in West Africa the cardinal signs of changes of sensitivity in tuberculoid leprosy are not always a realiable diagnostic aid.

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Leprosy epidemiological statistics in Nigeria, Cameroon and Thailand

L. M. Bechelli — V. M. Domínguez

In this paper some epidemiological data collected by the WHO Leprosy Advisory Team in random sample surveys in North Nigeria (Katsina), Cameroon and Thailand (Khon Kaen) are reported and commented upon as follows:

Prevalence and lepromatous rate: It appears from the data that there is no correlation between the lepromatous rate and prevalence. However, such correlation was observed in Thailand, in the different districts of Khon Kaen province where the factors involved in the transmission of leprosy act on the population in the same way and exposure is similar.

Proportion and rate of lepromatous and tuberculoid cases. In Cameroon and Northern Nigeria, as in many other African countries, the proportion of lepromatous patients is relatively low as compared with South American countries and some countries in Asia. However, the lepromatous rate in Cameroon and N. Nigeria is relatively high and would explain the persistence or spread of leprosy in the two countries and probably in other African countries. In addition to lepromatous patients, tuberculoid patients in reaction (Major T) might also play a role in the spread of leprosy, as they are numerous and may be temporarily bacteriologically positive.

Leprosy and sex: The leprosy prevalence rate was higher in females in Katsina but higher in males in Cameroon, while in Thailand the rates were similar. There was no difference in the tuberculoid rate in Cameroon and Thailand, but in Nigeria the rate was higher in females. The lepromatous rate was significantly higher in men in Cameroon, Nigeria and Thailand. Considering the available data and especially the results of lepromin reactivity, it seems that in a general way, males and females have a similar resistance to leprosy but the factors involved in the transmission and spread of the disease, including those connected with genetic mechanisms, could determine in certain countries and areas the different epidemiological aspects noted in males and females.

Leprosy and age: The onset of the disease was more frequent in the age-group 15-44 years, followed by the 5-14 group, in both N. Nigeria and Camer-

oon, while in Thailand it was more frequent in the 5-14 age-group followed by that of 15-44 years. A higher rate of lepromatous, tuberculoid and indeterminate leprosy was observed in the older age-groups. This would be explained by higher prevalence rates also observed in the older age-groups. In the light of these data, it appears that: 1. The difference in prevalence in the various age-groups would depend chiefly on earlier or later exposure to *M. leprae*. 2. In the three countries, individuals would have similar resistance to *M. leprae* in the different age-groups and are similarly capable of developing tuberculoid or lepromatous leprosy. 3. In highly endemic countries where children and young adults have the opportunity of being exposed to leprosy, the onset of the disease is more often observed up to 20 or 25 years of age, as the more susceptible individuals will acquire the disease and those with more resistance will be able to resist it throughout their lives. Therefore, the oldest group of the population is formed by a majority of people already exposed to leprosy and resistant to it, and of a minority in which a proportionately reduced number (the lepromin-negatives) is prone to acquire the disease after exposure.

Leprosy in ethnic groups: From the data obtained there is no indication of any difference concerning prevalence and lepromatous, tuberculoid and indeterminate rates in the Hausa and Fulani groups (N. Nigeria).

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Evolution of contacts under home control over a period of six years

J. Almeida Neto — C. A. M. Leite — P. Bello

control of contacts under home supervision. The study was effected in three different regions with a certain amount of variation in social and economic development, but the working methods employed were the same. The paper is presented in the form of graphs and tables accompanied by concise explanations.

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Evolution of patients under home control, and clinical and bacilloscopic situation after six years work

P. Bello—C. A. M. Leite—J. Almeida Netto

This paper reports the clinical and bacteriological results observed in patients brought under home supervision over a period of six years. The study covers three different regions with a certain amount of variation in social and economic development, but the working methods employed were the same. The paper is presented in the form of graphs and tables accompanied by a brief explanation.

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Suggestions based on a study of epidemic cards compiled from field work

C. A. M. Leite

This paper discusses suggestions arising out of the analysis of a group of epidemiological data cards summarizing the results of six years work in a region of the state of Minas Gerais. The informative elements recorded on the type of card used in Brazil are analysed in the form of graphs and tables. The study, which is entirely concerned with the epidemiological and, above all, the prophylactic aspects of the subject, employs universally accepted indices, but goes on to make other surveys and raise various points of issue.

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Leprosy control: details of a prophylactic work program

J. X. PINTO—C. A. M. LEITE

The authors analyse the outset, development and situation after years of prophylactic activities in a small, high prevalence area, carried out by a work group belonging to the specially trained Brazilian service known as National Leprosy Campaign (*Campanha Nacional Contra a Lepra*). The study comprises a set of graphs and tables, accompanied by brief explanations.

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Field work manual

I. T. A. MARTINS—C. A. M. LEITE

This paper describes in careful detail the planning of a prophylactic control service. A comprehensive system of work is proposed with the object of ensuring early diagnosis and maintaining leprosy control and assistance to patients.

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Leprosy Control in Ghana

B. D. MOLESWORTH

The problems of leprosy control are considered with regard to objectives, results obtained, the means by which they are obtained and the cost involved. Comparison is made between out-patient service, wholly in-patient service and a combined operation of mobile units based on hospital facilities. The Ghana Leprosy Service is an example of a combination of case-finding and treatment on out-patient lines, but based upon full hospital facilities in existing leprosaria, laboratory control being maintained throughout. Extensive use is made of para-medical personnel and their training is discussed. With regard to results the problem of deformity and resulting incapacity for earning a living presents a major problem, prevention of which is better than cure.

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Leprosy control at Usina Ester

R. QUAGLIATO

The author reports an intensive leprosy survey carried out at Usina Ester, in the county of Cosmópolis, São Paulo state, Brazil, from August 1959 to January 1960, by means of a dermatological examination of the population. The assessment may be deemed accurate on the whole, inasmuch as all of the residents are recorded by name.

The work was divided into three stages: 1. Dermatological examination and Mitsuda reaction on schoolchildren. 2. Calling on other persons to present themselves for examination at appointed places. 3. Localization of about 100 individuals who failed to attend, with the help of a woman doctor.

On checking the various colonies of the estate, it was found that 100% of the inhabitants had come up for examination without any new case of leprosy being discovered. A great many other skin diseases were recorded. The Mitsuda reaction on contacts of school age revealed on the whole 75% positivity (+, ++ and +++), but this positivity only extended to 30% of the children.

In 3 out of the 8 school grades, the children received 6 doses of fresh BCG between the application and the reading of the Mitsuda reaction. The author noted no difference between the results of the lepromin test in the grades that were or were not given BCG. This community has been under regular extensive observation since 1950, so that all the cases of leprosy and their contacts that have been recorded are kept under control. Among the various aspects of an enquiry of this kind, the population of Usina shows a high degree of stability, for only 5% of the 658

families living there have less than 5 years of residencé. Notwithstanding the high local index of leprosy prevalence (nearly 4.3% inhabitants), the examination of 100% of the population has not revealed a single new case of leprosy, a result that is most certainly due to the regular control of foci by the hard-working staff of the Campinas dispensary.

PANEL ON BACTERIOLOGY AND IMMUNOLOGY

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Sensitive myocontraction test for leprotic sera

L. Castro
S. M. Silvera
N. Castro

The authors undertook a detailed study of the Rubino reaction and, starting therefrom, by suitable adaption of the Schultz-Dale method, they arrived at a new test that was very sensitive to the sera of lepers. In order to explain the facts observed while developing this test, the authors suggest a theory, which fits in with the modern concept of auto-immunization. It is suggested that three essential factors may coexist in leprotic sera, viz.: *G* — Normal complementary factor; thermolabile; auto-antibody activator. G_a — Factor G altered by the leprotic process; thermolabile; antigenic. Necessary for the test and immunologically similar to sheep globin. *Anti-*G_a — Auto-antibody; thermostabile; determining factor of the Rubino reaction. Reacting specifically with G_a, it is equally essential to the myocontraction test.

The test has been found to be sensitive and constant in leprosy, quite apart from the clinical form and/or severity of the skin symptoms. It is possible that this simple test may serve to reveal an evolutive stage of the disease prior to symptomatic exteriorization. If so, this will be a valuable contribution to the elucidation of certain points that are still obscure in the pathogenesis of leprosy.

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Behavior in vitro of Mycobacterium leprae in the whole blood or plasma of lepers of various clinical forms

M. H. Treo — C. Oliveira e Silva

The authors analyse the resistence of *M. leprae* to disintegration when incubated in the whole blood or only in the plasma of sick carriers of leprosy of the following forms: lepromatous (15 cases), tuberculoid (17 cases), borderline (2 cases), reactional tuberculoid (4 cases) and indeterminate (7 cases).

They state that *M. leprae* remains intact after 45 days in the whole blood of lepromatous, reactional tuberculoid and borderline cases, whereas in the blood of tuberculoids the germ is no longer to be found after 25 days at the most. The plasma in the same cases was seen to be always inactive, for the germ remained intact in it throughout all the time of observation, which varied from 20 to 60 days. This fact suggests the presence of some active factor, perhaps enzymatic, linked to cellular components of the blood of carriers of tuberculoid leprosy and some indeterminates. In lepromatous cases this does not appear to hold good.

The authors observe that in the tuberculoid cases there is a probable correlation between the degree of intensity of the positive Mitsuda reaction (in mm.) and the number of days necessary for the destruction of *M. leprae in vitro*.

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Resistance of antihistamine-treated guinea-pigs against infection with M. leprae and M. lepraemurium

W. F. KIRCHHEIMER

KATO (Int. J. Lepr. 1957, 25:193) reported enhancement of infectivity of *Mycobacterium lepraemurium* by antihistamines for naturally resistant guinea pigs, if the bacteria were introduced directly into macrophages of the animals. He stated that in the presence of antihistamines guinea pig macrophages failed in their ordinary function to rapidly disintegrate the phagocytized bacteria. Because of the significance of these observations for elucidating mechanisms of natural resistance against mycobacterial disease KATO's experiments with *M. lepraemurium* were repeated, and extended to include *M. leprae* as the infecting agent. The results showed that guinea pig macrophages fail to disintegrate either of the two mycobacterial species *in vitro* or *in vivo* within 72 hours. Antihistamine-treament failed to alter the resistance of guinea pigs against either of the two mycobacterial agents even if they were introduced directly into the animals' macrophages.

It is concluded that genetic resistance against these Mycobacteria depends on mechanisms other than rapid intracellular disintegration.

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Fecundity and leprosy

T. HAMA — B. BEIGUELMAN — C. C. AMIN—M. N. C. GODOI—T. A. BAPTISTA

270 lepromatous females married to healthy males and 75 lepromatous females married to lepromatous males were the object of a fecundity survey. The data collected covered the number of pregnancies, number of living progeny, declared causes of mortality in the filial generation, age of parents at time of marriage, how long the couple had been living together, contraceptive methods employed if any, number of natural abortions, number of induced abortions and number of stillborn children. An analysis of the data indicates lower fecundity among lepers.

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Hereditary nature of the Mitsuda reaction

B. BEIGUELMAN

After analysing the distribution of the Mitsuda reaction in 220 married couples, chosen at random, and their 762 offspring, all residing in the rural zone of Rio das Pedras in the state of São Paulo, Brazil, the authors conclude that there is a familial relationship in the reaction to lepromine. After examining the evidence in favor of environmental influence and that supporting the hypothesis of a hereditary component in the manifestation of the Mitsuda reaction, the author proposes a genetic component to explain the familial nature of this character. The analysis of the data was modeled on a method suggested by TRANKELL (1955), and it was found that the distribution encountered was compatible with the hypothesis of the existence of a main pair of fully dominant genes controlling the responses to lepromine, admitting that the negative response to the Mitsuda test is caused by a recessive gene, albeit a fraction of the recessive homozygotes may show the opposite phenotype, under the action of environmental factors, especially contact with leprosy or tuberculosis bacilli. Assembling familial data and others collected in the same rural population, an analysis was made of the distribution of the Mitsuda reaction according to age and sex groups, which showed that the proportion of Mitsuda negative individuals was greater in rural than in urban populations. The results obtained indicate the need of further investigation into induced positive reactions.

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The immunocytogram in leprosy

C. E. Rudge — A. C. Marques — E. A. L. Wanderley — T. Kliemann

1) The variation in early (2 — 48 hours) immunocytological behavior was ascertained in individuals with either a negative or a positive response to the lepromin test. 2) This behavior was observed by making a skin abrasion upon which a drop of lepromin was placed and the preparation covered with a microscope slide. 3) In order to take a reading of the matter adhering to the slide (immunocytogram), the latter was changed periodically and stained by the Leishmann and Ziehl methods. This procedure enabled the cytological alterations to be observed in function of the time lapse. 4) The authors discuss the significance of a series of morphological and quantitative cellular differences in relation to the reactivity to the lepromin stimulus, showing the existence of a clear-cut tendency toward tuberculoid granulomatosis in lepromin-positive cases.

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Experiments on bacilli separated from human lepromas

T. Nojima

The author has succeeded in growing lepra bacilli from human lepromas on potato medium, as may be seen from progress reports made at Japanese leprosy conventions since 1930. In 1934/44 he separated 3 strains of acid-fast bacilli from human lepromas; though doing so with different patients and at different times, he found the characters of all three strains to be the same. With this cultured bacillus as antigen, leprotic serum gave results 95% positive in complement tests. The figures for agglutination with most leprotic sera ranged from 400 F. to 6400 F., nor have they decreased up to date. The skin reaction to this cultured bacillus was not the same as to lepromin (Mitsuda test), but when chickens were inoculated with the bacillus, injection of a suspension of tissue from the resulting nodules gave practically the same results as with lepromin. The injection of granulation tissue produced in chickens by the cultured bacillus into other chickens was followed in four cases by the appearance of positive nodules elsewhere on their bodies. Similar nodules were produced on rats with the cultured bacillus and the infectious material has been passed from rat to rat from 1949 until the present day. In the course of experiments on rats with the cultured bacillus, we have found specific alterations similar to those in leprosy in: skin nodules, ulcers, the liver, spleen, lungs, testicles, kidneys, pancreas, lymph glands, schneiderian membrane and peripheral nerves.

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Serological studies in leprosy

R. J. W. Rees — C. Fildes — — J. Pepys — R. Tee — M. F. Waters

The studies were undertaken on 75 patients from Malaya. Sera were obtained from 50 previously untreated patients (25 lepromatous and 25 borderline or tuberculoid cases) and then every 3 months for 12—24 months during treatment further samples of sera were taken. Sera from another 25 patients with lepra or E. N. L. reactions were obtained during different phases of their reactions. All of the sera were tested quantitatively, using agar-diffusion techniques, for the presence of precipitating antibodies against a variety of mycobacterial antigens and also for the presence of C-reactive protein (CRP). The lepromatous or borderline patients had high titers of antibodies to a variety of mycobacteria but most tuberculoid patients had no antibodies. Thus different types of leprosy can be identified by their antibody response. The

same antibody response was found in patients from Jamaica. Two lepromatous patients also had circulating mycobacterial antigens. Because patients with active tuberculosis were excluded from the study and because the presence of antibody was unrelated to the tuberculin sensitivity of the patient it was assumed that the antibodies resulted from infection with *M. leprae.* CRP was found in high concentration in patients during active phases of lepra and E.N.L. reaction.

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Fine structure of M. leprae, with special reference to modes of cell division

SABURO SATO

Peripheral halo: This may have been a sort of artifact, but seem more likely to have been a product of both bacillus and tissue. *Cell wall*: Consisted of 3 layers. On the wall a rough network of fibers was 40º angstroms wide and clearly demonstrable by grinding a bacillus with powdered silica. *Cytoplasmic membrane system (ICMS):* The CM also consisted of 3 layers, extending into the cytoplasma and forming the ICMS, viz.: many spherical and semispherical organelles (100-400 × 200-800 mμ), known to be the equivalent of mitochondria. Besides these, thick tubular organelles (400-€00 × 200-800 mμ) were found running longitudinally through the nuclear site (two cases). *Homogenously dense bodies:* These were seen in a few acute exacerbation cases, showing somesurrounding them. *Modes of cell division:* The process usually occurred in the middle of the bacillary body, but this was not necessarily always so. In fact, it was possible to distinguish 3-4 what dense ovoid bodies (80 × 100 and 200 × 350 mμ) located in the cytoplasm. There was, however, observed to be no limiting membrane, or practically none, variations of this pattern. It should be emphasized that another mode of cell division, viz.: longitudinal fission, was found but it was quite rare (only one case).

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Lepromin reaction in native villages in the state of Pará

M. V. PADIN

In this paper a comparative study is made of the lepromin reaction in 4 native villages of Pará not exposed to *M. leprae,* but exposed to *M. tuberculosis;* inhabitants in three of them were vaccinated with BCG, while those in the remaining village were not. In all, 329 Indians were tested, 91 in the first test and 269 in the second, including 31 retested, a number which is small because of the difficulties of approach. The BCG vaccin was given 12 months before testing in two villages; 3 months before the second test in one village; and not at all prior to either test in the fourth village. As regards the total number of Indians tested, the numerical results were as follows:

Village	First test	Second test			
	Total tested	Total tested	Number —	Number ±	Number +
Tapirapé	4	54	29	11	14
Karajá	22	27	24	3	0
Kubenkrankem ...	20	74	65	1	8
Garotire	45	83	81	2	0

Breaking down the population into adults and children (up to 12 years of age), the following percentages were obtained:

Village	First test		Second test			
	Number tested	% —	Number tested	% —	% ±	% +
Tapirapé:						
Adults	3	100	32	59.4	9.4	31.2
Children	1	100	22	45.4	36.4	18.2
Karajá:						
Adults	18	100	18	94.4	5.6	0.0
Children	4	100	9	77.7	22.3	0.0
Kubenkrankem:						
Adults	5	100	46	84.8	0.0	15.2
Children	15	100	28	92.8	3.6	3.6
Garotire:						
Adults	28	92,6	48	96.0	4.0	0.0
Children	17	100	35	100.0	0.0	0.0

Comparing the results of the second test in the four villages, the percentages, in relation to vaccination with BCG, are as follows:

Village	Vaccinated with BCG	Percentage positive	Percentage doubtful
Tapirapé	12 months ago	25.5	20.4
Karajá	12 months ago	0.0	11.1
Garotire	3 months ago	0.0	2.4
Kubenkrankem	Not vaccinated	10.8	1.4

Wishing to contribute to a knowledge of the reaction to the lepromin antigen in individuals not suffering from leprosy, the author examined the results before and after the application of BCG, and reached the conclusion that the BCG factor was not the only one that led to the development of a positive lepromin reaction in those groups. Both the groups vaccinated and the group unvaccinated with BCG showed positive reactions. Of the two villages vaccinated at the same time, the reaction was favorable in one, indifferent in the other. From a practical point of view, it would be interesting to know to what extent individuals free from leprosy up to the present can keep themselves free with such a low response to the lepramin reaction, and what means can be used to help them to do so. From a doctrinal point of view, the author seeks to furnish new data for a closer consideration of the reactivation of the lepromin reaction in the presence of various factors: BCG, tuberculosis.

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A cytological study of the lepromin test

R. G. Neves

A cytological examination of the lepromin reaction was carried out by the author on leprosy patients and healthy individuals. The samples were taken at the same time as the Mitsuda readings, ethyl chloride being the anesthetic used. A bistouri of the safety razor type with a triangular blade was used to make the superficial incision, and the edges were then scraped. The smears were made by using the blade of the bistouri. A 50% mixture of alcohol and ether, and methyl alcohol, were the fixatives chosen, and the preparations were then stained by the Ziehl-Gabbet and Giemsa methods.

Comparative analysis, not only of the cellular elements, but of the quantitative and qualitative bacillary changes, too, revealed clearly divergent aspects *tive*: Predominance of epithelioid cells, in the preparations; viz: 1. *L. R.* positive: Predominance of epithelioid cells, giant cells nearly always of the Langhans type, and bacilli, not very numerous morphologically altered. 2. *L. R. negative:* Predominance of the macrophages, giant cells, when present, of the foreign body type and bacilli, numerous, with more or less unchanged morphology.

Some lepromin tests, considered indeterminate, on being examined cytologically, suggested the existence of a dermic tuberculoid structure. To gain a better appreciation of the bacillary modifications, the author recommends examining a Ziehl-stained smear of inoculated lepromin. He believes that cytobacterioscopy in leprosy, on the grounds of simplicity and minimal traumatism, deserves to be further developed, inasmuch as it may be found a practical method of: *a.* Completing the mere visual evaluation of the test. *b.* Helping to interpret doubtful reactions. *c.* Aiding the diagnosis of clinical forms or else for a systematic control of the treatment.

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Comparative study of the reactions to lepromin, marianin and the BCG test

A. Basset—R. Pradinaud

The experiments were made on 50 lepromatous, 16 tuberculoids, 9 indeterminates, 5 borderlines, 49 children of lepers and several patients suffering from sundry ailments. All these products can give rise to early and late reactions. Out of 33 children of lepers vaccinated previously with BCG, 30 showed a Mitsuda positive reaction; on the contrary, of the 16 not vaccinated, only 8 had a Mitsuda positive.

This confirms the action of BCG in inducing a positive Mitsuda reaction and in children the concordance between the BCG and Mitsuda tests is almost complete. In lepromatous patients, however, there is wide divergence between the BCG test, the marianin test and the Mitsuda reaction. The Mitsuda reaction was negative in 94% of the cases and doubtful in 6%. The BCG test and the marianin reaction were positive in more than 50%, without, however, there being absolute parallelism between the two. In the lepromatous patients, marianin set up very strong local reactions, often accompanied by general phenomena recalling reaction fever. In all the other forms of leprosy (tuberculoid, indeterminate and borderline), the agreement between the different antigens was more frequent without being absolute. Marianin produced reactions that were nothing like so strong in tuberculoid as in lepromatous cases.

All these remarks tend to prove that while there may exist co-allergies between these various bacilli, probably connected with their lipopolysaccharide capsules, there are likewise important divergencies as is revealed by their different behavior in lepromatous cases. It is difficult to gage the role of these bacilli from a therapeutic or prophylactic viewpoint. For the lepromatous patient these antigens, though made up of killed bacilli, do not seem to be free of risk, since they can set up reactive states.

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Observations on the use of lyophilized BCG in the treatment of lepromatous leprosy

O. N. Cruz—D. V. A. Opromolla

Continuous observations were made of 15 patients suffering from lepromatous leprosy, healed and in regression, and leprosy of the dimorphous type, to which lyophilized BCG was administered by way of mouth in weekly doses of 0.1 gram for 21 weeks. All the patients continued the treatment they had been taking previously, viz. parent and disubstituted sulfones given orally or parenterally. Many of them received insufficient doses of the drugs and failed to follow the treatment regularly. Mitsuda's antigen was administered before and after the period of observation. Readings were taken after 40 days of application and doubtful reactions were checked by biopsy and studied from a histopathological angle. In none of these patients were positive Mitsuda reactions observed or any signs of reactivation of the disease.

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Multiplication of Mycobacterium lepraemurium in cell cultures

C. Fildes—R. J. W. Rees—E. W. Garbutt

Cell cultures of rat fibroblasts (strain 14 pf) have been successfully adapted for the continuous growth of *M. lepraemurium*. By repeatedly subculturing the infected fibroblasts continuous multiplication of *M. lepraemurium* has been maintained now for more than 3 years (1,170 days). The total increase of bacilli during a period of 1,015 days was approximately 10^{20}, giving a mean generation time of 14 days. The rate of multiplication, pathogenicity for mice and inability to multiply in bacteriological media of the tissue-culture grown bacilli have remained unchanged all along. The tissue culture growing bacilli have been used to test a number of anti-leprosy drugs. A soluble mycobacterial antigen (polysaccharide) has been isolated from the medium of the cell culture. The possible application of cell cultures for the successful growth of *M. leprae* will be discussed.

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Discovery of a germ of the genus Bacillus in leprosy patients

J. G. Gago—F. F. Wilkinson

Considering that leprosy needs to be revised bateriologically and starting from the principle that investigation should begin directly with the patient, the authors undertook a systematic bacteriological survey of leprosy patients. Their studies led to the discovery of a germ belonging to the genus *Bacillus* for which the name of *propter-mariam* is suggested. It was found 30 times in 78 patients, i. e. an incidence of 38.45%, which may well have been greater to judge by the so-called "unapparent" cultures that, for purposes of this work, were considered negative.

Controls: An investigation among patients suffering from various skin diseases and in-patients in the clinical medical ward failed to reveal the presence of the germ, but among people living with lepers, it was encountered in 45% of the individuals investigated. Attention is drawn to this fact.

A study was made in a Colony for the children of lepers, divided into two groups: 1. Children of lepers who had lived with their parents; 2. Children of lepers, separated from their parents at birth. Each group consisted of 10 children. In the children of the first group *B. p.* was found on three occasions. In those of the second group it was not found at all. The investigation was made by using a syringe to extract material from the subcutaneous cellular tissue.

Furthermore, the research done by the authors includes bacteriological classification, antibiograms, therapeutic trials, and animal and vegetable in-

oculation, and a start has been made with investigation in excreta, immunology, serology and vaccins.

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Origin and character of non-cultivated states in mycobacteria

J. H. HANKS

The pathogenic mycobacteria fall into two great groups: those with preference for pulmonary or oxygen-rich tissue surfaces, and those which cause non-pulmonary diseases. The latter are universally "factor-requirers" or non-cultivated. It may be postulated that the latter, by mutation, tend to delete one or more essential segments of their respiratory chain while growing within host cells in low oxygen tensions.

Present evidence, as obtained from "factor-requirers", such as *Mycobacterium johnei* indicates that the "non-pulmonary" types of mycobacteria are not fastidious because of dependence upon host enzyme systems or complex or labile compounds within host cytoplasm. They prefer to synthesize all their cellular components from the simple nutriments in synthetic media. Their basic needs can be met in either of two ways: by mycobactin; or by miscellaneous fragments of carbon, by high levels of CO_2 and low pH to facilitate transport. The factors promoting growth within tissue cells are similar to those required for growth *in vitro*. Thus, their major peculiarities are readily understood on the basis that organisms of this type are specifically adapted to conditions within the phagocytic vacuoles of host cells.

From these findings it may be surmised that *M. lepraemurium* and *M. leprae* are not truly intracellular parasites; that they also obtain their requirements from host cell membranes which have folded inward to form phagocytic vacuoles. If this be true, the problem of their cultivation *in vitro* may be simpler than has been assumed in the past.

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Circumvention of the mycobactin requirement of *M. johnei*

N. E. MORRISON

Certain of the mycobacteria which cause non-pulmonary lesions can be isolated and sub-cultured only in the presence of a special growth factor—mycobactin. Since *Mycobacterium johnei*, the causative agent of chronic enteritis in herbivorous animals, fails to grow in the absence of this factor, cells deprived of mycobactin (Mb) are in some repects analogous to *M. leprae*. Conditions or compounds which alleviate the Mb requirement of such cells should be of interest in growth experiments on the non-cultivated leprosy species.

The slow growth of 2 "independent" strains of *M. johnei* (long used for production of johnin on a synthetic medium) is stimulated by mycobactin and (in the absence of Mb) occurs only under specialized conditions. Growth rates, for example, are significantly slower at neutral pH or on filtered media. A Mb-dependent strain, given Mb during only one transfer, likewise grows "independently" under the special conditions. Similar experiments with 2 Mb-requiring mycobacteria from Scandinavian wood pigeons permits a definition of the specialized requirements to be as follows: (*a*) complexes and/or carbon fragments produced by autoclaving the medium at pH 5.5, (*b*) incubation at pH 5.5 (to facilitate transport), and (*c*) addition of CO_2 to the atmosphere.

Thus, highly specialized growth requirements can be circumvented by a constellation of unconventional but defaible factors.

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Surface properties as impediments to transport in the mycobacteria

B. S. TEPPER

Recent developments involving the use of the electron microscope and bio-

chemical techniques have thoroughly reconciled the composition and structure of the mycobacterial cell surface with that of other bacterial species. TAKEYA *et al* (J. Bacteriol., 58, 16. 24, 1963) have shown the mycobacterial cell wall to be multi-layered consisting of: (*a*) a "basal layer" which resembles the cell walls of Gram-positive bacteria and gives the wall its rigidity and (*b*) an outer layer, similar to the lipo-protein layer on Gram-negative bacteria, but which is much richer in complex lipids.

The localization of the mycobacterial lipids at the outer surface of the cell strongly supports the hypothesis that the lipid coat acts as an impediment to the transport of nutrients, substrates, stains, etc. into the cell. Variations in the rates of permeation of different mycobacterial species may be correlated with the amount and character of the lipids at the cell surface. Such evidence suggests that problems of permeation and transport should be serious in the least penetrable species. *M. lepraemurium* and *M. leprae*.

To test this hypothesis, uptake rates have been measured using compounds known to be excellent nutrients for mycobacteria. Resting suspensions of *M. phlei* cells take up glucose immediately. However, cells grown on glycerol media take up glucose three times more slowly than cells grown on glucose media. Cells grown on media which promote high rates of lipid synthesis take up glucose at much slower rates than those from media promoting minimal times more bacilli than the poorest; that the amount of surface lipids plays an important role by controlling the entrance of glucose into the cell.

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The concentrations of M. Leprae in currently available lepromins

M. F. LECHAT

Lepromin is employed to assay cutaneous reactivity to soluble proteins of *M. leprae* (Fernandez reaction) and subsequently the response to a depot of bacilli (Mitsuda reaction). Judgments concerning prognosis in patients and levels of resistance in populations are based upon the readings obtained. If these results are to be valid and comparable, it is important to establish an "average" or "standard" for lepromin. This by definition must contain reproducible concentrations of *M. leprae*.

The enumerations in 16 samples of lepromin from 10 sources revealed: that the richest lepromins contained 860 times more bacilli than the poorest; that two lots from individual investigators may differ by 100 and 200 times; that the average and median counts were respectively 35% and 20% of those in other base-line studies. The overall results indicate that problems in the preparation of lepromins are insufficient attention to established methods of selecting and pooling tissues and overdilution.

Modifications of an already described method for enumerations of *M. leprae* will be described in detail. I facilitate the preparation of films and eliminate calibration of the areas of films and of microscopic fields. Simple standards for reducing the work of counting and for assessing the reliability of counts will be given.

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Studies on inversion of the lepromin reaction by BCG

II. A brief review of the literature, present state of knowledge and phophylactic prospects in the light of recent observation on lepromin reaction inversion under the influence of various stimuli

N. S. CAMPOS—W. LESER — A. ROTBERG L. M. BECHELLI R. QUAGLIATO

The literature on inversion of the lepromin reaction (negative to positive) by administration of BCG is reviewed, and attention is drawn to the wide disparity of the results recorded (30 to 100%) which, it is suggested, may be due to: diversity in the make-up of the groups studied; quality, doses, scheduling and way of administering the BCG;

time lapse up to determination of the reaction; quality of the lepromin; interpretation of the reaction. Furthermore, assessment of the results is likely to be difficult if the research has not been properly planned.

This introduction is followed by a commentary on an experiment made by the authors and recently published, in which 112 children, without previous contact with leprosy patients, were divided into 4 groups. The conclusion arrived at was that the administration of BCG (orally or intradermally) induced positivity in percentages that did not very significantly from one group to another, but diverged widely from the results obtained with children that were only given injections of lepromin or made up the control group. There is no appreciable difference between the last two groups. Among the children that received BCG by mouth, the intensity of the reactions and the percentages of positivity decreased markedly with the increase in age from 6 to 43 months; whereas among those that were given only lepromin or figured as controls, the intensity of the reactions showed a marked increase with age. This variation with age was not observed when the BCG was injected intradermally.

As to the practical utilization of BCG in the prophylaxis of leprosy, reference is made to the hypothesis of one of the authors, whereby it is admitted that lepromatous individuals are incapable, perhaps genetically, of turning lepromin positive whatever the stimulus ("anergic margin", devoid of the "N factor" of inversion to lepromin positive). The 100% inversion in children under 24 months of age is unfavorable to this hypothesis; as, however, for the small number of individuals observed (21), the "interval of reliability" of 95% lies between 86 and 100%, it is possible that a certain "anergic margin", such as that indicated by the lower limit of this interval, may be brought into evidence by more extensive observation and so fall into line with the facts recorded in the literature. New investigations into the "anergic margin" and the relationship between age and inversion are necessary to secure more precise information as to the possible importance of BCG in the prevention of leprosy.

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Studies on inversion of the lepromin reaction by BCG

III. Results of the lepromin test in a community of childrea of lepers and attempts to promote inversion in individuals showing a negative, doubtful or slightly positive recation, by varying schedules of BCG administration

N. S. Campos—A. Rotberg—
L. M. Bechelli—M. Ginefra

In a community of children, the offspring of lepers and most of them contacts of those patients, injected with BCG and tested with lepromin, an attempt was made to prove the existence of individuals incapable of turning lepromin positive in spite of various stimuli, and also the possibility of reducing or eliminating the so-called "anergic margin".

A preliminary examination of the records of the 607 children in the Jacarei School (Educandário) revealed that 431 (71%) were lepromin positive, grades ++ and +++. Of the remaining 176 with —, ± and + reactions, 68 minors were still in the the School, and they were given a heavy dose of BCG (400 mg.) by mouth every week for 6 weeks. This massive schedule was followed by 6 (8.9%) inversions or strong intensifications, 29 (42.6%) that were discrete or doubtful, and 33 cases (48.5%) unchanged in their reactivity.

Another group, more recently segregated, consisted of 116 children, contacts or not, almost all of them previously inoculated with BCG, but of unknown lepromin reactivity, were tested. 45 turned out to be lepromin positive. The remaining 71 were —, ± or +, and 68 of them had been previously in contact with lepers (3), BCG (54) or both (11). These children were given 3 weekly doses of 200 mg. BCG, with the result that 18 (25%) inversions to positive or marked intensifications, 26 (37%) mild intensifications and 27 (38%) cases of unchanged reactivity were observed. The inversion or inten-

sification of the lepromin reactions was most likely due to the action of the BCG.

In the group of children treated with heavy doses of BCG, to the extent of about 9%, negative or mild reactions were seen to have become positive or stronger after exposure to leprosy and/or being given BCG in the usual doses.

On the other hand, attention is drawn to the fact that 40 of the children who had been longest in the School, though previously exposed to the stimuli represented by the Hansen, Calmette-Guérin and Koch bacilli, remained anergic or hypoergic and that 25 of them continued to be so, even after being given BCG again in massive doses. These would appear to be the most representative individuals of the "anergic margin", devoid of the "N factor" of lepromin inversion. Of the 116 minors more recently segregated and less intensely stimulated, 26 were and continued to be lepromin negative or only slightly positive after fairly heavy doses of BCG (22.4%), but it is presumed that this percentage would be reduced by a series of heavy doses.

New studies should be undertaken in an attempt to reduce or possibly eliminate the "anergic margin" and arrive at a more accurate evaluation of the utlity of BCG in the prophylaxis of leprosy.

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Studies on inversion of the lepromin reaction by BCG

IV. Correlation between the tuberculin and lepromin reactions in communities of leper children vaccinated orally with BCG

M. Ginefra—L. M. Bechelli—
R. Quagliato—N. S. Campos—
A. Rotberg

A study was undertaken on the children of lepers from 3 months to 19 years of age, many of them previously exposed to *Myco.leprae* and/or vaccinated crally with BCG, with the main object of ascertaining the extent of the influence, if any, of tuberculin sensibilization on the early or late appearance of a lepromin positive reaction. For grading the reactions in the Fernandez and Mitsuda tests the rules of practice suggested at the last International Leprology Congress (Tokyo, 1958) were adopted. The Mantoux reaction (1/100) was graded according to the rules recommended by the V Pan-American Tuberculosis Congress, whereby infiltrations more than 5 mm. in diameter were considered positive. Integral lepromin was used.

The first group studied comprised 35 children BCG vaccinated in 1960 or 1961 with three doses of 200 mg. and never tested with lepromin. The very small number of children showing a Mantoux positive reaction made it unfeasible to attempt to correlate this reaction with Mitsuda's. In the second group of 72 children vaccinated with BCG in 1960 or 1961 and again in 1962—because the Mitsuda reaction was only negative, doubtful or mildly positive—tuberculin positivity was not associated with a greater percentage of grades ++ and +++. The third group consisted of 56 children, BCG vaccinated in 1958 and which had experienced one or more negative, doubtful or slightly positive (+) Mitsuda reactions. They were vaccinated again in May and June, 1962, with 6 doses of 400 mg. BCG and a month later given lepromin and tuberculin tests. The results were similar to those obtained with the second group. The conclusions to be drawn from the experiment were the following:

1. In the three groups of children, BCG vaccination and the result of the Mantoux reaction had no significant connection with the result of the Fernandez reaction.

2. In children BCG vaccinated by way of mouth, the frequency and intensity of the late lepromin reaction did not differ appreciably according as to whether the subject was tuberculin negative or tuberculin positive.

3. The fact of being tuberculin positive or having been exposed previously to *Myco. leprae* did not make any noticeable difference to the Mitsuda

reaction in children that seemed to lack the determining factors of lepromin positivity ("anergic margin").

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The effect of BCG vaccination on tissue reactivity in leprosy

S. W. A. KUPER

It has been shown that tissue reactivity to lepromin in a proportion of lepromatous African subjects can be altered by BCG vaccination. Some elements of the tuberculoid type of reaction become superimposed on the conventional histiocytic response that occurs in lepromatous leprosy when lepromin is injected intradermally. It seem likely that the effect is of short duration and this presumably accounts for the rapid fading of lepromin conversion sometimes produced in lepromatous patients who receive BCG vaccination. It was clearly of interest to ascertain whether the use of BCG vaccination at regular intervals would maintain the altered tissue reactivity, and if so, whether this would confer any clinical benefit.

A small clinical trial has been carried out in Thailand with the help of Dr. Ramon Miquel (World Health Organization), Dr. Molesworth (Specialist in Charge, Ghana Leprosy Service) and Mr. Peter Payne (Director of the South Metropolitan Cancer Registry, England). Approximately 200 lepromatous patients were admitted to the trial. They were randomly allocated to a Control or BCG group and in addition they all received standard chemotherapy. Those in the BCG group received BCG vaccine at approximately three-monthly intervals for a period of one year. A careful clinical assessment was made by Dr. Molesworth at the beginning of the trial and again after one year had elapsed. Bias in the assessment was avoided by masking both arms of all subjects, so that the clinician was unaware whether the patients were in the BCG or Control groups. A biopsy was taken of a lesion at the commencement of the trial and one from another lesion at the termination of the trial. These pairs of biopsies were examined by the author without knowing which of the two test groups the patient belonged to. Every precaution was taken to see that all estimations, clinical and pathological, were made without bias. The biopsies were examined with respect to intensity of reaction, degree of lymphocytic infiltration (with or without giant-cell follicles) and numbers of acid-fast bacilli present.

Any benefit conferred by the vaccination would of necessity have been partly masked by the great improvement resulting from standard chemotherapy. Careful analysis of results has revealed no statistically significant clinical difference between the two groups, nor is there any evidence of an altered histological response. The numbers of bacilli, likewise, are not affected by repeated BCG vaccination. The results described suggest the possibility that the altered histological reponse observed in some Africans after BCG may not be paralleled by any immunological improvement; alternatively, the apparent failure of BCG to excite such response in this trial may be due to the different racial character of the group tested.

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A study of the mechanism of the lepromin reaction

M. TUMA — R. G. NEVES — N. C. SILVA — A. MELLO — C. SILVA

Results are reported of experimental work consisting in comparing the lepromic reaction with reactions induced by other substances in leprosy patients and healthy controls. The purpose was to investigate problems relating to the nature and mechanism of the Mitsude reaction.

Besides integral lepromin, the inocula comprised: *a*) Lepromin with bacilli disintegrated in a Mickle tissue disintegrator. *b*) A suspension of bentonite particles. *c*) A suspension of the mycelia of certain fungi. *d*) A suspension of non-pathogenic mycobacteria. *e*) A suspension of *Bacillus subtilis*. A his-

tological examination was made of all macroscopically positive or doubtful cases.

The results obtained suggest the following conclusions: 1. No significant difference is to be detected in the early stage sof the reaction, apart from the nature and the inoculum and the clinical form of the disease; the early infiltrate is always non-specific and made up of lymphocytes, histocytes, fibroblasts and polymorphonuclear leukocytes. 2. The divergent behavior observed in later stages, ranging from the infiltrate of lymphocytes, histiocytes and fibroblasts to a well-constituted tubercuoid granuloma, appears to depend upon a lipidic substratum in the inuoculum and an enzymatic factor (lipase?) present in the cytoplasm of the macrophage and acting thereon. 3. This hypothesis would explain two facts: *a*) the inability of non-lipidic substances to stimulate the formation of the tuberculoid granuloma; and *b*) the impossibility of the macrophages of lepromatous patients digesting lipidic substances and transforming them into epithelioid cells, owing to the absence of the supposed enzyme.

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Bacteriological status of lepromatous patients treated with DDS in Nigeria, Cameroon and and Thailand

K. M. Patwary — V. M. Dominguez
K. M. Cress

The data were obtained by the WHO Leprosy Advisory Team in surveys carried out in Northern Nigeria (Katsina), Western Nigeria, Cameroon and Thailand.

1. *Duration of treatment and bacteriological results* (*table* 1):

Only patients regularly treated, who had taken at least 75% of the prescribed dose, were considered.

From the data it can be seen that the percentage of lepromatous patients with a negative examination rises from 35% in the first year of treatment, to 82,3% in those treated for 5 or more years. It is important to point out that, even after 5 or more years of treatment, about 20% of lepromatous patients remained positive: in a leprosy campaign it is important to get rid of this source of infection which may be enough to maintain a certain degree of endemicity, especially in countries with a high rate of lepromatous cases.

2. *Regularity of treatment and bacteriological results* (*table* 2):

Only lepromatous patients treated for at least 4 years were included and subdivided into 4 groups according to the regularity of treatment: those who took 75% or more of the total precribed dose were considered as regularly treated.

There is a correlation between regularity of treatment and bacteriological results: 7.6% of negative bacteriology in the patients with an index of regularity of treatment inferior to 25% while in those regularly treated, 79.6% were negative. The data also show that even in the patients who had 50-75% of the prescribed dose, DDS was effective in a relatively high proportion of cases (64%).

Regularity and period of treatment are two important factors in reducing contagiousness of lepromatous patients.

3. As can be expected, regularity of treatment in sanatoria was considerably better than in static and mobile units. In these, the bacteriological results were poorer and in Thailand 55% of the patients treated for 6 years still remain positive, while in sanatoria, only 21% were positive.

TABLE 1

DURATION OF TREATMENT AND BACTERIOLOGICAL RESULTS

Countries	Period of Treatment																	
	0 to 25%			1 year			2 years			3 years			4 years			5 years & more		
	−	+	Tl.	−	+	Tl.	−	+	Tl.	−	+	Tl.	−	+	Tl.	−	+	Tl.
Katsina	4	29	33	9	20	29	18	19	37	20	15	35	21	10	31	70	14	84
Cameroun	4	8	12	6	9	15	13	7	20	9	4	13	6	6	12	118	24	142
Thailand	80	117	197	10	25	35	13	22	35	20	11	31	47	21	68	153	51	204
W. Nigeria	1	7	8	4	4	8	1	5	6	5	4	9	4	1	5	110	8	118
Total	89	161	250	29	58	87	45	53	98	54	34	88	78	38	116	451	97	548

TABLE 2

REGULARITY OF TREATMENT AND BACTERIOLOGICAL RESULTS

Countries	Regularity of Treatment											
	0 to 25%			25 to 50%			50 to 75%			75% and above		
	—	+	Tl.	—	+	Tl.	—	+	Tl.	—	+	Tl.
Katsina	0	1	1	2	1	3	10	1	11	91	24	115
Cameroon	0	1	1	2	0	2	7	1	8	124	130	154
Thailand	1	10	11	5	17	22	29	24	53	200	72	272
W. Nigeria	0	0	0	0	0	0	1	0	1	114	9	123
Total	1	12	13	9	18	27	47	26	73	529	135	664

PANEL ON EDUCATION AND SOCIAL ASPECTS

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Program of assistence in the leprosy problem

C. C. Neves

The solution of the social problem of leprosy requires the necessary moral courage to face taboos. To set out to engage in this endeavor means a disposition to correct what is established custom.

The control of leprosy cannot be successfully achieved if prophylaxis is attempted by police methods, if the patient is stigmatized as an outcast and if the members of his family begin to suffer privations. The natural reaction of man is to flee from moral and physical suffering. Therefore, the leprosy patient should be attracted to treatment and not chased as though treatment were punishment and isolation condemnation.

Grasping this situation, in less than twenty years, as a citizen and as a deputy, the author has been able to transform the "leprosaries" into sanatoriums, to assist the patient and his family without humiliating them, legislate in favor of the patient's rights and change the mental attitude of the public toward the problem of leprosy.

In her program of work in the field of leprosy, she has always sought to educate the patient and the public, to assist the patient and the members of his family and to protect the patient by legislation. Thus she has endeavored to correct by law what seemed to be mistaken in the law. Intuitively, the author has put into practice recommendations later to be made by international leprology congresses.

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Sanitarian education and social rehabilitation in connection with leprosy

A. Brandão Filho

The author proceeds to a general consideration of the various aspects of the problem of education in sanitarian and social leprology, dwelling in greater detail on what has been done in this field in Brazil. Emphasis is laid on the absolute need for the services of the Sanitarian Instructor and Social Worker in planning and carrying out the various stages of leprosy control. Suggestions are put forward as regards what seems to the author to be the most efficient way of performing the work, chiefly with a view to spreading modern scientific knowledge, not only among the medical and cognate professions, but also among the other liberal and intellectual professions, and thence to the public in general. Finally, a system is proposed for evaluating the work done.

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Educational and social aspects of the leprosy problem with particular reference to the Far East

N. D. Fraser

This paper emphasises the importance of cooperation and coordination. Governments, the Community, Voluntary Organizations and leprosy patients themselves each have a contribution which only they can make to the solution to the problem of leprosy; and no one group can take over the responsibility that belongs to any other. A new pattern of organization and administration of the work is also referred to in which it is pointed out that outpatient clinics need to have access to a Leprosy Center for Clinical Investigation and Surgical Reconstruction; and further that there will be a continuing need for Homes for the disabled in which training can be given in measures of self-help.

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Social assistance to lepers and their families including state maintenance

E. Cruz — J. E. Faggin — M. L. Salomão

The authors think social assistance to the leprosy patient must be close-

ly interrelated with Health Assistance and Mental Hygiene, controlled by the same administrative body and extended, not only to the patient, but also to his relatives, especially his children, from birth on, the responsibilty therefor devolving on the government and on private organizations. The leprosy patient, as soon a sthe disease is diagnosed, raises problems of a traumatic psychical, physical and social nature, involving the family and influencing the professional activity of the individual, whence the need for social support, primarily of the close relatives of the leprosy patient, and of society in relation to those relatives, as a fundamental and decisive influence in the treatment. Reference is made to the conclusions of the V International Leprosy Congress, Havana, on the subject of the program to be developed with regard to Assistance. The scope of state aid is outlined as comprising pensions to be granted in cases of irreparable deformities and inevitable mutilations, disability and old age, incompatible with active employment, and it is urged that whoever is capable of working be encouraged to do so, each to the extent of his strength and abilities, in order to reinvigorate his mental attitude. Finally, the authors report that the social work in generic or specific connection with the grave problem of the leper has been adequately taken care of by the creation of the Rehabilitation Service of the Leprosy Prophylaxis Department of São Paulo (Brazil), by Decree Nº 36675 of May 27, 1960, and that this is a great stride forward in the history of social medicine, a definitive advance the true extent of which will only be measurable by the scale of future achievement.

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Social and educational aspects of leprosy in the United States

J. R. Trautman — E. B. Johnwick — O. W. Hasselblad — C. I. Crowther

The paper begins by outlining questions regarding leprosy to which satisfactory answers cannot be given on the basis of available medical knowledge. There follows a discussion of the universal fear of leprosy with emphasis on the situation in the United States.

Presented next are the principles and criteria on which are based leprosy control measures as they are applied in the continental United States. Included in these measures are recommendations thought by the medical staff of the U.S. Public Health Service Hospital at Carville to be a realistic approach to the problems involved. These principles and criteria include the belief that leprosy is a communicable disease, that members of the immediate household of patients are probably more susceptible to the disease than is the general public and that hospitalization for the patient with leprosy, although of major importance during the early phases of treatment and during periods of exacerbation of the disease, should be accomplished on a voluntary basis.

The paper concludes with the recommendation that leprosy research and training be intensified throughout the world, and the question is raised as to how the United States Public Health Service can be of assistance.

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Assistance to the kin of leprosy patients and to discharged lepers

E. Weaver—G. Gibson

In so vast a country as Brazil, there are regions where a high prevalence of leprosy is all the more serious because of the extreme poverty with which the patients and their offspring are afflicted. The situation is aggravated by the fact that the disease may attack several members of a family at the same time, with the result that the family is left to struggle with overwhelming difficulties, not only in the home, but also as an outcome of the pauperism in the surrounding region, dominated by underdevelopment.

It is in these cases, unfortunately only too frequent, that efficient action is taken by the Assistance to Lepers and Leprosy Control Societies spread all

over the country, which help the sufferers most effectively in three different ways: 1) Home assistance to indigent leper families. 2) Assistance to under-age children of lepers who are isolated or live in out-of-the-way parts of the country, where there is neither nursing care nor medical observation available, nor material and educational assistance, which is provided in the homes or boarding-schools where they are sent to live. 3) Assistance to discharged inmates of leprosaries, so as to enable them to become readjusted to the society of healthy men and women in their community.

Besides these three fields of activity which cover all the relatives of leprosy patients, the Societies engage in various forms of social support and solidarity, such as aid at weddings, festivities and by way of religious assistance to the patient himself, not only when segregated, but also when under treatment at an ambulatorium, and actively collaborate in the sanitary education of the public and the families that enter into contact with the patients.

PANEL ON PHYSICAL MEDICINE AND REHABILITATION
(INCLUDING SURGERY AND VOCATIONAL TRAINING)

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A consideration of tendon transfers to restore thumb adductor power

W. L. White

The loss of adductor power of the thumb in intrinsic palsy results in considerable weakness of pinch and grasp. Attempts to restore thumb adduction by tendon transfers have mostly failed to provide consistent suitable results. One of the probable causes for failure of these transfers is the acute angulation necessary if the transferred tendons are to produce the desired direction of pull. There is a tendency for the transferred tendons to bind and become fixed at the point of angulation.

Several techniques designed to restore thumb adduction will be presented, and evaluated. In one of these, binding is avoided by yoke action.

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Treatment of perforating ulcer of the sole of the foot

L. M. Silveira

The treatment of perforating ulcer of the sole of the foot is based on the pathogenesis of the ailment. There are three conditioning factors: 1) Absence of sensitivity to pain, resulting in a lack of proper protection of the plantar skin; 2) Absence of reflex postural accomodation of the foot, giving rise to a long period of ischemia, with trophic degeneration of the plantar skin; 3) Outward pressure due to dislocation of the metatarsals, so that the soft parts are seriously compressed.

The ideal way of treating perforating ulcer of the sole of the foot would be to restore the sensitivity of the plantar skin. It is easy enough to heal a plantar ulcer, merely by immobilizing the foot in a suitably shaped plaster cast, but recidivation is frequent, because the insensitivity persists and is indeed the most important etiological factor. When the bone is attacked, it should be attended to first, for if not the ulcer will not heal, but develop into the outlet of a fistula originating in the deeper-seated lesions. Bone involvement demands a mutilating operation that is not always successful. Thus resection of the metatarsals is often followed by recidivation, whereas the more radical operations, such as Lisfranc's or Syme's amputation, give better results, inasmuch as a stump is formed that is capable of resisting the inevitable attrition at that part of the body.

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Epineurectomy of the common peroneal nerve in leprosy

N. Oliveira—J. M. Rosas Netto

The good results achieved by Ranade *et al.* with epineurectomy of the com-

mon peroneal nerve in the treatment of drop foot and perforating ulcer of the foot encouraged the authors to ascertain the effects of this operation in such cases at the Pirapitingui Sanatorium.

Investigation was also made of the effects of epineurectomy in reducing the time taken for trophic ulcers of the legs and stumps in Syme's amputation to heal.

The authors emphasize the simplicity of the surgical operation and the slight risk involved, entering into considerations with respect to the technique used and the post-operative results, both immediate and deferred, obtained with this therapy.

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Rehabilitation of the leprosy patient

J. E. FAGGIN

The organization of the Rehabilitation Service of the Leprosy Prophylaxis Department (São Paulo) is described, in accordance with a detailed plan, beginning with a rapid survey of the present status of the problem of rehabilitation in various fields. Reference is made to the fact that the Leprosy Department of the Brazilian state of Minas Gerais is also busy with the problem. Rehabilitation is defined as being based on the international concept in contrast with Professional or Occupational Rehabilitation, which is called Readaptation, as ordained by Decree law N° 7,036 of Nov. 10,1914, modified by Decree-law N° 7,577 of May 7, 1945. It is devided into 4 stages, viz.: Recovery, Reeducation, Readaptation and Reinstatement or Reemployment, each stage being explained so as to show how difficult it is to separate them in practice.

A Rehabilitation Service depends upon teamwork, for which a minimum of well-trained personnel is required as may be seen from an organization chart accompanying the paper. Furthermore, a building with special accomodation is necessary to the efficient operation of a Rehabilitation Service.

An idea is sketched in of the eligibility at the present time of candidates for rehabilitation at the Rehabilitation Service of the Leprosy Prophylaxis Department, the working of which is illustrated by a flow sheet.

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Surgical treatment of paralytic ectropion of leprotic origin

L. E. REGINATO

The author begins with clinical considerations on the subject of paralytic ectropion in connection with leprosy and reviews the clinical and surgical methods used up to date, as an introduction to his own experience with 20 cases in which he treated paralytic ectropion surgically by raising the lower eyelid with a sling of fascia lata attached to the aponeurosis of the temporalis or frontalis muscle or to the subcutaneous tissue in the nasal region, with or without temporal canthoplasty. He concludes that this method does not provide an ideal solution, but rather, a reasonably efficient working device capable of protecting the eyeball. It ensures gentle pressure of the lower eyelid on the surface of the eyeball, rectifying the position of the lachrymal ducts and directing the flow of tears almost normally.

In some cases the operation was associated with that of Kühnt-Symanowski. In others, in addition to raising the lower lid with a strip of fascia lata, he resorted to subtotal section of the levator palpebrae superioris in an attempt to narrow the opening of the levator through lack of antagonism of the orbicularis palpebrarum.

Nevertheless, the author is in favor of experimenting with recent techniques in which the temporalis muscle is used directly in the treatment of palpebral paralysis, *cf.* GILLIES (1957), ANDERSON (1961) and JOHNSON (1963), in the hope of achieving still better results.

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Epineurectomy of the posterior tibial nerve in the treatment of perforating ulcers of the foot of leprotic origin

P. Canton—W. E. Belda—
L. E. Reginato —
J. E. Faggin—E. Cruz
N. G. Almeida — F. C. Mendes

The authors preconize decapsulation of the posterior tibial nerve as a fundamental measure in the treatment of perforating ulcer of the foot. To hasten the cure they recommend decapsulatation of the external popliteal sciatic nerve as well, since it may also be involved.

Four decapsulations were performed on the posterior tibial nerve, the last two being accompanied by decapsulations of the external and internal popliteal branches of the sciatic nerve. Although the first case failed to evolve successfully owing to the condition of extreme malnutrition of the skin on the lower third of the leg, with dehiscence of the stitches and abnormal healing, it served to show how seriously the nerve was involved at this level and in the retromalleolar groove. The other decapsulations, however, resulted —without any other kind of treatment and without absolute rest—in a rapid cure of the perforating ulcer, resumption of sensitivity, improvement of vasomotor conditions and adaptability of the foot for walking purposes. The satisfactory results obtained still persist now that 9 months have elapsed since the second decapsulation and 6 months since the third and fourth decapsulations.

The nerve was approached through a J-shaped incision in the interior retromalleolar sulcus, half-way from the tendo achillis, 15-16 cm. long, as far as the calcaneal canal, starting fairly high up the lower third of the leg. When the aponeurotic sheath had been slit open, the nerve was freed from adhesions to the bone surface; decapsulation was then performed, and the interfascicular adhesions of the nerve removed. When the surgical wound was closed, the aponeurotic incison was left unsutured.

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Decompression and epineurolysis in the prevention and treatment of sensitive and motor disorders of the hand

W. Beida — J. E. Faggin
L. E. Reginato — M. M. M. Napoli
— T. Arakaki — C. M. Grisolia

The authors, admitting the existence of conditions of nervous involvement at the level of the carpal canal, similar to those occurring at the epitrochlea, examined the ulnar and median nerves of eighteen leprosy patients suffering from sensitive and motor disorders of the hands. Two cases were excluded on the grounds of insufficient data. Nineteen operations were perfomed on sixteen patients, and the techniques used and surgical findings are fully described.

In seven cases, there was simultaneous involvement of the ulnar at the epitrochlea and the carpus and of the median at the carpus. In nine cases there was simultaneous involvement of the ulnar at the epitrochlea and median at the carpus. In two cases involvement was confined to the ulnar at the epitrochlea and in only one case was the median solely involved at the carpus. In short, the median was found to be involved in seventeen out of nineteen cases investigated. The authors believe that further research is necessary with regard to the involvement of the ulnar at the level of the carpal canal. The data obtained leads them to consider as obligatory procedure in surgical treatment of sensitive and motor disorders of the hand in leprosy; investigation; decompression and epineurolysis of the median at the level of the carpal canal.

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Attempt at correction of amyotrophic deformities of the back of the hand by a new method of skin grafts

P. Homem de Mello — L. E. Reginato

This paper begins with a critical historical survey of the methods used in plastic restoration of the shape of the back of the hand, deformed by leprotic amyotrophy of the interossei. Concluding that the methods proposed in the past failed to solve the problem satisfactorily, the authors proceed to a description of the trial of a new metrod: free autodermic grafting. The patient treated was formerly afflicted with the tuberculoid form of leprosy, but had been definitely discharged as cured 15 years previously; the principal stigma left by the disease consisted of deep excavations in the intermetacarpal spaces. So the intermetacarpal loculi, pierced by incisions disguised in the folds between the fingers, were filled with slips of skin of suitable shape and thickness, kept in position by transfixing with nylon sutures. Immobilization was maintained for 20 days by means of ordinary wooden splints. The donor area on the right side of the abdomen was made good with the patient's own skin after removal of the transplant. A year later, the cosmetic results had become stabilized at a fairly satisfactory level.

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Clawhand and its surgical treatment

R. Borsani

Twenty cases of clawhand due to invasion of the median and ulnar nerves by *Mycobacterium leprae* were all operated upon with the same technique so as to be able to evaluate the results. The procedure followed was that described in Argentina by Eduardo Zancolli, consisting in capsuloplasty of the metacarpo-phalangeal articulations, and essentially the method is based on shortening the capsulas of those joints on the palmar plane. It is believed that the good results obtained are due to lengthy postoperative immobilization, which is maintained for fifty days with the metacarpophalangeal articulation bent almost at right angles. These bent almost at right angles. These good results must be attributed to the fact that strict immobilization promotes permanent, definitive fibrosis of the volar plane of the joint, thus avoiding ever-extension of the first phalanx. Functional recovery is rapid as soon as the plaster cast is removed, and postoperative stiffness is not a hazard. The technique is easy to perform and, if practiced early enough, ensures permanent correction of the deformity.

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Perforating ulcer of the elbow and its treatment

J. O. Benimali — J. T. de las Aguas

Perforating ulcers are very frequently the trophic sequelae of leprosy and, in addition to occurring preferentially on both the instep and sole of the foot, develop fairly often at the elbow.

Seven lepromatous patients with perforating ulcer of the elbow were studied, three of them positive and four negative for some years. In all of them, sensitivity had been seriously impaired in the elbow area and the skin was ill-nourished, dry, hyperpigmented and atrophied. Of the seven patients under observation, six had only one perforating ulcer and one had two.

As regards the pathogenesis of the ulcers, they should be attributed a continuous series of microtraumatisms to which the elbows are more exposed owing to the frequent movements of the joint and because it is an area where the skin is stretched directly over the bony surface of the olecranon. Another reason for the injury is the universal habit of resting the elbows on the table.

In four of the patients, the lesion was on the left elbow, in three on the right. In three patients, X-rays revealed an exostosis of the olecranon. It was decided to resort to surgery, since topical

treatment proved unsuccessful. In some cases it was enough to extirpate the edge and the bottom of the ulcer, leaving it to heal by second intention. In two cases, there was a serous bursa at the bottom of the ulcer which was also extirpated, and in the cases of exostosis of the olecranon, it was considered advisable to remove this excrescence too.

Six out of the seven cases were male patients, and this predominance is believed to be due to the fact that men are more exposed to traumatisms.

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The surgical rehabilitation of lepers at the Fontilles Sanatorium (Spain)

F. Contreras Duenas—
F. Contreras Rubio

The total number of operations for the surgical rehabilitation of lepers at the Fontilles Sanatorium in the last two decades amounts to 615, plus 204 eye cases, which sums up to 819. In graph nº 1 of this paper, which excludes ophthalmological operations, it may be seen that the increase has been more rapid in the last five years, showing a more active interest in the rehabilitation of these patients through surgery, in accordance with the latest trends, rising to a peak of 108 operations in 1962.

The clear tendency of leprosy to attack the acra may readily be discerned in the fact that the majority of rehabilitation operations dealt with perforating ulcers, 390 in all, breaking down into 298 in the sole of the foot, 74 in the instep, 11 in the hand and 7 at the elbow. Trophic ulcers of the extremities, above all the lower extremities, also claim a large number of operations, 61, and together with perforating ulcers, they are the sole reason why many lepers, cured but suffering from trophic disfigurements, are unable to resume their place in society. Despite the advances in modern operative technique, the two sequelae, etiologically similar, often afford problems that are hard to solve owing to the intense trophic involvement, which frequently implies the necessity of final operations of a radical type, such as extensive osteotomies and amputations. The Brand techniques applied to the rehabilitation of the frequent cases of mesioulnar paralysis have transformed useless infirms into able individuals again.

In the field of rehabilitation, the role of plastic surgery is also of undeniable importance, for rhinoplasties, eylid grafts, face lifts, and operations to reduce hypertrophy of the auricles or correct facial paralysis, etc. have a tremendously encouraging moral effect on the patient, giving him self-confidence and assurance with which to face reintegration in the community.

There is of course still much to be done in the way of rehabilitating many of the infirm and, by the recovery of these functionally impaired ex-patients, casting off the burden of ancient prejudice that used to and still does attach to the affliction; the worst publicity used to be spread by just such cured but mutilated lepers, bacteriologically negative but functionally useless, whereas nowadays, thanks to a service of rehabilitation, they can return to the community they live in and fill the position to which they are justly entitled.

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Procedure recommended in cases of laryngostenosis of leprotic origin

R. F. Sacheri

In the first place the author states that he has only encountered this form of throat disorder in advanced lepromatous cases. In general, leprotic laryngostenosis is due to lepromatous infiltration of the mucosa in the vestibule of the larynx or the glottis when the lesions are in full activity. The symptoms may also appear during the involutional healing of throat lesions, when adhesions may form, blocking the opening of the larynx.

In obstructive laryngopathies, he believes it to be indispensable to proceed

to early tracheotomy, so as to forestall possible asphyxiating developments and ensure the intake of air to the lungs. Surgery should not, however, be resorted to in cases of laryngostenosis so long as open lesions persist, since there is always the danger of a relapse. Anterior median thyrotomy opens up a wide field of access to the area of stenosis, allowing the adhesions to be detached, but electrocoagulation should be used with discretion so as to avoid damaging the anatomical structure of the larynx and interfering with the vocal process.

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Rehabilitation of lepers in Venezuela

J. J. ARVELO — J. CONVIT — C. SISIRUCÁ

In this paper, the basic concepts of rehabilitation are outlined as a preliminary to a discussion of the advisability of integrating this service in the public health programs applicable to a community on the grounds that a sanitarian program is incomplete if no provision is made for rehabilitation. The rehabilitation of lepers involves special problems and for various reasons it is difficult to put into practice. Hence it is deemed to be unwise to attempt execution of programs designed exclusively for leprosy patients, and fundamental, on the contrary, to bring them within the range of general rehabilitation programs. Thus considered, rehabilitation becomes a Public Health problem, and this is exemplified by the way in which the Division of Sanitarian Dermatology is developing its program in Venezuela.

Comments are made on the progress achieved as regards dissemination of the basic concepts of rehabilitation, training of personnel, introduction of the idea of teamwork for purposes of rehabilitation among the Regional Dermatology Services, nation-wide investigation of disablement and steps to prevent this state of affairs. Emphasis is laid upon the importance of the establishment of a first Regional Service of Physical Medicine and Rehabilitation, as an integral part of a Regional Public Health Service, and the features and mechanism of this agency are discussed. In conclusion, a description is given of the framework of the program adopted by the Division of Sanitarian Dermatology of Venezuela insofar as the rehabilitation of leprosy patients is concernet.

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Experimental inoculation of human leprosy in laboratory animals

J. CONVIT — P. LAPENTA — A. ILUKEVITCH — T. IMAEDA

In a previously prepared paper presented for publication in the International Journal of Leprosy and now in press, the authors have reported the results obtained in laboratory animals inoculated with material from cases of human leprosy. The present report condenses the net experience gained during the four years that this work has been carried on.

Experimental inoculations with human material were made in 65 groups of animals. In 27 groups the material used was from LL cases. Borderline material was used in 21; material from the indeterminate type was used in 6 and tuberculoid, specially from reactional stages, in 11 groups. Control groups were injected with material sterilized at 120°C. A total of 2,502 animals were inoculated. Of these, about 60% were hamsters and the rest white and black mice, rats, guinea pigs, rabbits and swine. The inoculum was prepared in two ways, either by triturating the material in normal saline as soon as removed from the patient to obtain a suspension to be injected in its fresh state, or by treating material, similarly triturated, with trypsin to obtain a nearly pure suspension of bacilli to be injected as soon as prepared. The animals were inoculated intradermally; sites chosen were the ear, footpad, testicles, peritoneum or cheek pouches (hamster). All animals that died were autopsied with careful attention to the akin and the viscera.

The examinations included microscopy of smears prepared with the Ziehl-Neelsen stain, as well as histopathological and electron microscopic studies. Cultures were attempted in the Löwenstein-Jensen medium. The observations were the following: In three groups, inoculated with borderline material, lesions appeared after 8-10 months. Material from these lesions was used in subsequent passages in which the period of inoculation was shortened to 3 or 4 months and even less. Ten passages have been made to date. Smears from the lesions showed an abundance of acid-fast bacilli, as did also the histiocytes composing the granuloma. The electron microscope gave evidence of lesions that recalled the human leprous granuloma.

Our repeated attempts to cultivate the bacilli originating in borderline lesions were negative. In the 27 groups inoculated with LL material only one animal, a hamster, produced lesions with acid-fast bacilli. When these were inoculated into the Löwenstein-Jensen medium a culture was obtained of an acid-fast, "non-photochromogenic" bacillus.

An antigen was prepared from the lesions produced in the hamster with material of borderline origin. The reactions produced in lepromatous patients in tests with that antigen are subject to discussion.

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Rehabilitation of invalids in leprosy control

A. Z. Saenz

The author comes out in favor of integrating rehabilitation programs in a leprosy control organization, on the grounds that without them assistance and sanitarian programs are impaired or stultified by a lack of accurate indications to enable the social problems engendered by the disease to be met.

Allusion is made to the decisions of the Experts Committee of WHO, meeting towards the end of November 1960 at the Schieffelin Leprosy Research Sanatorium in Karigari, Southern India, where subsequently the author, on a grant from the WHO Panamerican Sanitary Bureau, gained experience in the most up to-date practices in the field under the direction of Prof. Paul W. Brand, of Vellore, India, and Dr. C. K. Job, superintendent of the Karigari Sanatorium.

A brief outline is given of the leprosy control organizations in the countries of America (Argentina, Brazil, French Guiana, Mexico, Surinam and Venezuela), Spain in Europe, Nigeria in Africa, India in Asia and the American state of Hawaii, and emphasis is laid on the attention paid there to rehabilitation of invalids.

In closing, the author asserts that the public, no less than the medical profession, should be made aware of the fact that leprosy is a curable disease and that the deformities and disabilities arising thereform can and should be controlled, prevented and set right to a very large extent by educational, physiotherapeutical and or surgical means, in accordance with the classification of the patients into four groups: 1. With deformities that are easily redressed; 2. Severely deformed; 3. Totally disabled 4. With neither deformity nor disfigurement; as suggested by associate professor of orthopedic surgery Dr. A. A. J. Selvapandian, of the Christian Medical College and Hospital of Vellore, India.

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Leprosy disability statistics in Nigeria, Cameroon and Thailand

V. M. Dominguez—L. M. Bechelli

This paper deals with the data collected in North Nigeria (Katsina), Cameroon and Thaïland (Khon Kaen) by the WHO Leprosy Advisory Team in random sample surveys, and may be summed up as follows:

Frequency of disabilities: In random sampling surveys, the frequency was 23.40% in N. Nigeria, 35.0% in Cameroon and 41.5% in Thailand. Disabilities were considered in accordance with the recommendations of the second

WHO Expert Committee on Leprosy. This means that in Katsina Emirate there will be about 10,000 disabled patients and presumably more than 100,000 in the Northern Region of Nigeria. In Cameroon there will be nearly 30,000 disabled patients. These data show the importance of leprosy from the social and public health points of view.

Type of disabilities: (data collected from both within and outside of the sample survey): In Northern Nigeria, 37.8% of the patients had some type of disability or deformity in the hands; 30.4% in the feet, and 15.7% on the face. In Cameroon, 43.4% of disabilities were in the hands, 47.9% in the feet and 14.8% on the face. In Thailand, 52.2% were in the hands, 55.1% in the feet and 34% on the face.

Disabilities in relation to the form of leprosy (L.I.T.) (data collected from both inside and outside the sample survey): Disabilities are more frequent in lepromatous patients and less common in tuberculoid patients.

Disabilities according to sex: In Northern Nigeria and Thailand, disabilities were more prevalent in males than in females; in Cameroon, disabilities were slightly more prevalent in males (37.8%) than in females (32.5%) but the difference is statistically not significant.

Disabilities according to age: There was a strong correlation between frequency of disabilities and age-groups. The frequency increases in older age-groups. This is understandable by reason of the more advanced stage of the disease and higher proportion of lepromatous patients amongst old people.

Disabilities and ethnic groups: In N. Nigeria, disabilities were slightly more frequent in Hausa (33%) than in Fulani (26%).

The data show the importance of disabilities in leprosy and the need for a rehabilitation programme in leprosy campaigns. Simple physiotherapy methods should be used in mobile and static units. However, special rehabilitation services should only be created when the means, fundamental equipment and necessary personnel have already been provided for the development of basic activities in leprosy control, for the most effective prevention of deformities is achieved with the prevention of the disease.

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Medical and surgical treatment of perforating ulcers of the feet of leprotic origin

R. Manzi—A. Marzetti

In planning the treatment to be adopted, various factors must be taken into account, e. g. the social psychological type, general clinical type, etiopathogeny of the ulcer, structural condition of the foot, present ability to walk, future ability to do so after the changes have been made, and steps to be taken to prevent recurrence of the lesion.

Analysis of these factors: a) Social and psychological, e.g. possible insanity. *b*) General clinical: cardiovascular or renal disorders, diabetes, amyloidosis; age of patient. *c*) Regional problems: ulcers of the leg and foot, edemas, pyodermitis, difformities, paresis, paralysis, etc. *d*) Concomitant alterations: osteopathies, arthropathies, etc. *e*) Static and dynamic architecture of the foot, before and after treatment. *f*) Lesion: type of ulcer—indolent, exuberant, etc.; depth of ulcer, fistulas, bone abscesses, osteoarticular alterations, etc. *g*) Medical and surgical treatment indicated. *h*) Prevention of recurrence; orthosis and prosthesis.

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Pathology and clinical investigation of ulcers in the feet of leprosy patients

A. Marzetti—R. Manzi

Etiopathogeny: Actuating elements: 1. Neural alterations, similar to those observed in neurology (syringomyelitis, polimyelitis, etc.). 2. Disorders: vascular, arterial, venous, capillary, lymphatic, specific lesions of the arterial wall, functional (occlusions, spasms, arteriovenous communications, etc.) 3. Traumaitisms: *a*) By abnormal pressure (bedsores, perforating ulcers); *b*)

Pathological fractures. 4. Complex lesions; intervention of specifific lepromatous infiltrates, pyogenic infections, traumatisms, vascular and metabolic alterations (diabetes, amyloidosis, etc.).

Symptomatology: General clinical examination: cardiovascular, renal, diabetes, anasarca, etc. Regional examination of the limb: skin, cellular, muscle, osteoarticular. Local examination: painful spots, scars, abscesses, etc. Instrumental explorations: with blunt probe, to look for fistulas. Sole of the foot: determination of shape of the foot and pressure areas. Simple radiography of bones, and fistulography, to determine course and origin of the sore (bone, articular, synovial or phagedenic ulcer).

Radiological clinical pictures: 1. Abnormal pressure or perforating ulcers. 2. Pathological fractures: complex, with osteomyelitis, abscesses and fistulas. 3. Synovial, articular and tendinous fistulas. 4. Complex alterations: severe deformation of the foot, with fistulous osteomyelitis, ischemic necrosis, and alterations of the general state of health (septic conditions, amyloidosis, etc.).

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Surgical treatment of ulnar neuritis in leprosy

A. M. Marroqui

1. Attention is drawn to the importance of surgical treatment in cases of leprotic neuritis of the ulnar nerve and the satisfactory results obtained, with marked sensitive and functional recovery of the infected limb. 2. A description is given of the multiple nervous and neuromuscular anomalies in the distribution of ulnar innervation, which make it hard to interpret the symptomatology observed. 3. The histopatological findings in fragments of nerves obtained *in vivo* in the course of the operation are shown to be quite similar to those observed in cutaneous tissues. 4. The surgical technique employed is described. It is thought advisable to carry the epineurectomy as far as possible up the nerve and that decapsulation should be followed by lengthy longitudinal incisions and resection of the nerve fascicles that are seen macroscopically or under electric stimulus to be thoroughly degenerated. It is also wise to proceed to the resection of the epitrochlear ganglions, together with the surrounding fibrotic tissues, during the operation. 5. Epineurectomy can be performed during the acute leprotic flare. Anesthesia of the brachial plexus has proved effective, assisted on certain occasions with local infiltration of 2% novocain. 6. The results obtained suggest the advisability of immediate postoperative mobilization. 7. Six operated cases are presented and the results obtained illustrated with colored slides.

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Reconstruction of the face in leprosy

N. H. Antia

The stigma of leprosy is a visible deformity that persists even after cure of the infection. Surgical correction is essential for social and economic rehabilitation of patients. The deformities are fairly stereotyped, affecting the face, hands and feet.

This paper is based on work with 300 inpatients at the Kondhwa Leprosy Hospital near Poona. Emphasis has been laid on elucidating the cause of facial deformities and devising operations for their correction. Wherever possible, the procedures evolved have been simplified and standardized so that they can be put into practice under the conditions usually available for leprosy surgery.

Deformities of the face are the result of lepromatous infiltration of skin, subcutaneous tissue and mucous membranes, except for lagophthalmos, which is the result of nerve paralysis. They include: (1) depressed nose, (2) lagophthalmos, (3) loss of eyebrows, (4) leonine facies, (5) sagging face, (6) ear deformities, (7) destruction of the palate.

Depressed nose: The primary lesion, mucous membrane ulceration, is followed by exposure necrosis of the cartilaginous and bony framework. The alar cartilages, protected by skin on both sides, are rarely destroyed. Post-nasal epithelial inlay, as now employed, is the operation of

choice in most cases. In the absence of dental aid a skin graft is carried on a mold anchored by wires to the teeth. Later support is provided by a retrograde bone graft taken from the olecranon. This is essential when the fingers are absorbed. The oronasal fistula is closed. This can be undertaken under local anesthesia in an ambulant patient.

Lagophthalmos: This is caused by selective paralysis of the zygomatic branch of the facial nerve. It is one of the commonest causes of loss of sight from "exposure keratitis." Lower lid ectropion, besides being unsightly, produces conjunctivitis and constant watering of the eye. The previous operations of tarsorrhaphy and static sling, besides being unsightly, cannot protect the eye completely, and result in recurrent ectropion. By transposing an innervated slip of the adjacent nonparalyzed temporalis muscle and with fascial extension—the "temporalis musculo-fascial sling operation"—the eye can be opened and closed at will. A normal appearance results and there is no risk of recurrence of ectropion.

Eyebrows: In an area of endemic leprosy loss of eyebrows is a stigma of the disease. The methods of replacing them are: (1) temporal artery island scalp flap, (2) transposition scalp flap without artery pedicle, (3) free graft of postmastoid hair-bearing skin. The last is the simplest and safest procedure, but its success depends on adequate "defatting" of the graft.

Leonine facies: Shaving and dermabrasion helps.

Sagging face: Face lift results in psychological rejuvenation. The technic has to be varied and requires further study.

Ear deformities: The ears need trimming.

Palate: Perforation and destruction need repair by local flaps or by skin tube pedicle.

Deformities of the face in leprosy lend themselves readily to surgical correction and hence plastic surgery can play a great part in the world-wide rehabilitation of the patient. This work can be carried out in most leprosaria with the facilities at their disposal and without the aid of complicated dental and accessory help. These operations have been performed under local or block anesthesia in the lack of facilities for general anesthesia. Post-operative nursing care has been left to patients themselves in the absence of a nurse. This paper is based on the experience of 300 operations.

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Transplant of posterior tibial muscle to the foot in leprosy*

R. SANCHEZ BEAUJON

(presented by J. J. Arvelo)

Paralysis of the external popliteal nerve leads to muscular imbalance in the foot, which in most cases leaves the important muscular forces in the posterior part still active, i.e., the group represented by the muscles which integrate the Achilles tendon and the long common flexor of the digits, and in the internal part, the posterior tibial muscle, which is inserted in the scaphoid tubercle. This results in an equinovarus deformity.

For effective treatment one needs to make a distinction in this deformity between subjects whose paralysis occurs during or after the period of growth. In the first case there is osseous structural deformity, and the foot gets fixed in the deformity and cannot be corrected by passive manipulations. In the second case the deformity is more of a functional nature, and by passive manipulations the foot can be returned to normal position. Therefore in order to carry out in the first group the procedure we shall describe, surgical intervention in the bones, permitting correction of the deformity, is required. In the second group intervention in the bones is not needed.

The procedure to which we refer is contraindicated when osseous destruction occurs as a result of repeated plantar ulcers that have modified the osseous structures, since the surgical intervention reactivates the infectious processes, which not only cause loss of the benefits of the procedure but also compromise the existence of the foot and even of the leg. In the degenerative processes of Charcot type there may be an acceleration leading to disintegration of the joints. The author describes the operative procedure.

*Translation from the Spanish by J. R. Innes.

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Multiplication and behavior of Hansen bacillus in tissue culture

J. P. Deville

Cultures of human amniotic cells have been inoculated with Hansen's bacilli obtained from lepromas. These bacilli are rapidly taken up by phagocytes. Multiplication of acid-fast bacilli is observed after 4 weeks. The acid-fast bacilli do not grow on the usual bacteriologic media. Some cells are packed with bacilli, but the number of bacilli undergoing noticeable multiplication seems small. Transfer from these cultures to fresh amniotic cells has not resulted in new growth of acid-fast bacilli. On one occasion inoculation of trypsinized lepromas in cultures resulted in marked growth of bacilli from 10 cells. After 51 days of growth at 36°, 50% of the cells contained bacilli. Numerous cells contained many bacilli. It has even been possible to see a small colony consisting of a cluster of globi. Therefore, an important multiplication of Hansen's bacilli has been obtained. Inoculation on bacteriologic media has resulted in no growth.

When cells from Kaposi's lesions are inoculated with Hansen's bacilli from lepromas, noticeable multiplication of bacilli has been observed after 123 days. Sixty-four per cent of the cells contained bacilli, many of which showed high numbers. Cultures more than 6 months old are still under observation and some transfers have been successful. In old cultures bacilli seem to undergo degeneration. This is particularly notable for isolated bacilli. Much less degeneration occurs on subcultures.

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Dimorphous leprosy*

Felix Contreras

In a strict sense dimorphous is not the same as borderline, which when translated into Castilian is "limitante" or "fronterizo." In Spain we have not seen cases that could be considered indubitably as dimorphous, nor as limitantes or fronterizos. Our pathologists trained in leprology have never met with undoubted forms of tuberculoid and lepromatous granulomata coinciding in time and space with these borderline forms. In our environment, in which the great majority of patients are treated and controlled, mutation between the two polar types is most rare. Perhaps this is the reason for the infrequency of cases coming under discussion.

We have met with some patients who clinically make us suspect dimorphous leprosy, but histologically they turn out as clearly lepromatous or reactional tuberculoid. At the same time, patients clinically lepromatous or reactional tuberculoid, do present some difficulty in their histologic classification in some of their lesions.

We believe that in order to classify a patient as dimorphous, histologic proof is indispensable showing specific tuberculoid and lepromatous characters in the same lesion or in different lesions but simultaneously. In this respect we understand that the band of Unna, the character of the conjunctiva, histochemical changes, and the nerve lesions, are histologic characteristics with little specificity, since they represent quantitative changes difficult to evaluate in doubtful cases. The presence of giant cells and cellular vacuolization are characteristics that do not deserve to be taken into account, because they can be brought about easily by error. Specific histologic characteristics then are only the presence of epithelioid cells and of Virchow cells. It is possible that error in histologic diagnosis takes place in interpreting as epithelioid cells histiocytic cells in hyperplasia, which are noted in reactivation of lepromata, or in general in young lepromata.

Histologically difficult cases should be studied carefully with all useful techniques, and therefore frozen sections should be made to study lipids and ferments, and silver impregnations, and paraffin sections for routine staining. With this plan of action, from the histologic point of view, lesions can always be grouped as either lepromatous or reactional tuberculoid leprosy.

To admit that dimorphous leprosy exists depends entirely on the importance we give to reactional tuberculoid leprosy. In effect, cases which are doubtful clinically are histologically reactional tuberculoid. Nevertheless, on occasion, histologic diagnosis of reactional tuberculoid leprosy does not fit perfectly into the clinical picture. These cases, as we see

*Translation from the Spanish by J. R. Innes.

it, are those that make up the dimorphous group. The proposal made by various authors in the symposium in Brazil does not seem acceptable; they considered two varieties under reactional tuberculoid, viz., a typical one of cases which clinically and histologically can be grouped in it, and an atypical one (which by our way of thinking would be dimorphous leprosy) made up of cases that are histologically reactional tuberculoid, but clinically difficult to classify precisely.

The forms that we are coming to consider as atypical reactional tuberculoid are rare among us and in our judgment do not represent a sure transition toward the lepromatous type. Rather we are dealing with an instability phase, more or less lasting, which only on rare occasions can transform into lepromatous leprosy.

In the Fontilles Sanatorium we have seen 1,046 patients In all of them we have studied completely the four aspects, clinical, bacteriologic, immunologic and anatomopathologic. In most and at various times we have followed the evolutive process in all its aspects. Of the 1,046 patients, 79 were classified as indeterminate leprosy and 69 as tuberculoid leprosy. Of the 898 lepromatous patients, only in 6 were there any doubts whether they were dimorphous or not. Of the 69 tuberculoid, 27 were reactional tuberculoid and of these 27, 9 were atypical or in periods of instability which could make us think of dimorphous leprosy. In conformity with these data, doubt if we were dealing with dimorphous leprosy occurred in 0.66% of the lepromatous and 13.04% of the tuberculoid cases.

In the Spanish campaign among 3,751 classified patients, 594 were indeterminate, 1,063 tuberculoid, and 2,094 lepromatous. We cannot be precise about the frequency of reactional tuberculoid nor of dimorphous.

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Indeterminate leprosy*

FELIX CONTRERAS

As its name indicates, this is the form in which leprosy must begin. Sometimes it is of fleeting duration, lasting only until there is a definite change to one or other polar type making one think, mistakenly, that the disease has begun by one of these types. At other times the duration is longer. It can even remain immutable as indeterminate leprosy during the whole course of the disease, or regress to cure.

Our concept of it has not changed since 1953 and we continue to include in the indeterminate group those relatively unstable benign cases, almost always negative for bacilli, which have flat skin lesions. Sometimes these skin lesions are lightly erythematous but almost always hypochromic. The lepromin reaction is usually negative, though in some cases it is positive. There are evident changes in sensitivity and changes in reflexes due to impairment of conductivity of nerve fibers (histamine reaction). When it remains immutable for a sufficient time, more or less extensive forms of neuritis can appear, and we even should accept the possibility that pure neural forms exist within this group, which will be very difficult to diagnose. We should consider as cases of indeterminate leprosy only those in which, besides the features previously pointed out, an absolutely nonspecific histology is established. As soon as some sign of specificity is noted, e.g., histologically at least some epithelioid cells of Virchow, the decision is plain; such cases should be classified as tuberculoid or lepromatous, without admitting the names "pretuberculoid" or "prelepromatous." Nor should be considered as indeterminate leprosy those residual nonspecific lesions preceding the cure of both polar forms, since clearly they have a very different biological meaning and their characteristics are very different.

The proportion in which we have found the indeterminate form has been as follows: 79 of 1046 classified in the Sanatorium of Fontilles (7.5%) and 594 of 3751 among the total classified by different services in Spain (about 15.9%). The diagnosis of indeterminate leprosy is to be made clinically in simple macular cases, especially when there are hypochromic or lightly erythematous nodules. It can be made also in some purely neural cases with little symptomatology. An intensely positive bacilloscopy raises the possibility of the lepromatous variety. Immunologic reactions are without value in these cases. Diagnosis of cases in this group should be confirmed by pathologicoanatomic methods, even though patho-

*Translation from the Spanish by J. R. Innes.

logic anatomy cannot prove the specificity of leprosy. Even when the clinical, bacteriologic and immunologic data are known, only the histologic picture will permit exclusion of the possibility that one of the two succeeding polar types is concerned.

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Judgment on indeterminate leprosy*

J. R. Puchol

This is a macular form of leprosy which generally precedes one of the other forms and which can develop toward them, remain as such, or regress toward cure. It is therefore a form generally initial, unstable and benign.

We have studied 1,603 biopsies classed as follows: lepromatous, 828 cases, or 50.8%; tuberculoid, 509 cases or 31.2%; indeterminate, 281 cases or 17.2%; reactional tuberculoid (borderline), 12 cases or 8%.

We found hypochromic or erythematous macular lesions of irregular distribution. They generally had well-defined borders, sometimes not very precise, with upsets of sensitivity. There could be involvement of nerve trunks, usually in cases of long duration.

Histologically there were nonspecific inflammatory infiltrates. These were banal and predominantly lymphocytic, chiefly around the vessels and at times the sweat glands. At times there was perineuritis in the nerves of the deep dermis. There were no epithelioid or Virchow cells. When this happens the case should be classified in the corresponding polar type. Bacteriologically the cases were mostly negative or weakly positive.

The most important data for correct classification are: a) Clinical. Strictly macular lesions, i.e., without infiltration in the lesions. b) Histologic. A single inflammatory structure. The finding of small groups of cells of epithelioid type or of Virchow cells implies exclusion from the group.

The bacteriologic and immunologic data in this form of leprosy are chiefly of prognostic value, since they indicate a tendency or possibility of evolution.

*Translation from the Spanish by J. R. Innes.

Purely neuritic cases, in which histologic data are rarely available and which only sometimes are indeterminate, should be classified according to the rules proposed by the Ibero-American group in the Madrid Congress.

The onset is usually slow and insidious with raré symptoms or none at all, rarely in the form of an eruption. Evolution is variable: (a) cases of spontaneous involution, (b) persistent cases, (c) cases which transform into lepromatous, (d) cases which transform into tuberculoid, (e) cases which transform into borderline. Transformation into lepromatous or tuberculoid can be slow or by successive attacks. Transformation into borderline comes about as a consequence of a special outbreak of soft plaques, which are very erythematous, and edematous and succulent, and the general condition is good. The attacks are repeated and at the beginning regress without leaving marks. After several attacks a final lepromatous type is apt to establish itself.

The residual macular lesions should not be classified in the indeterminate group, but keep their popular primitive label as "residual." The macular atypical lesions, such as have been noted especially by Davey, Browne, and Ross Innes, are certainly transition phases of indeterminate forms to one of the polar types. These intermediary forms of macular leprosy correspond to the older "prelepromatous" or "pretuberculoid," which generally we classify in the polar types.

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Borderline leprosy*

J. R. Puchol

We seem to be dealing with an unstable form of the disease, corresponding to a stage or phase of transition from one polar type to another, caught in an intermediary evolutive stage, nearer to one than the other pole, and therefore with variable characteristics.

Possibly important geographic differences influence the frequency, which is distinct in different countries. In Spain the number of cases seems very small. If, as we think, reactional tuberculoid

*Translation from the Spanish by J. R. Innes.

leprosy is at least one of the forms of borderline, our classified cases provide 0.8% of all patients seen in a total of 1,630 cases.

In our opinion the cases classified up to now as reactional tuberculoid leprosy correspond to a form of borderline. We have studied 12 well-controlled cases and some isolated biopsies of patients in the Far East, received through Prof. Gay Prieto. They were diagnosed there as borderline, and we have cataloged some as lepromatous, and others as reactional tuberculoid. Clinically there were outbreaks in the form of plaques, generally large, erythematous and sometimes almost violaceous, with much infiltration and edema. The localization was arbitrary, but very often on the face and extremities. The edema was intense in the hands, feet, and pavilions of the ears, especially in the lobules, where it can simulate lepromata. At times there were circular plaques with diffuse external border and internal border very sharp in contrast. The general state is apt to be insignificantly affected. There can be neuritis, generally not very intense at the beginning.

The bacteriology is positive, more so in the lesions than in the nasal mucosa. The lepromin reaction is generally negative. The histology is that of a granuloma, with contradictory characteristics between the polar types as often said. This granuloma is deformed by the exudative features characteristic of a reactional attack. In our opinion, no one of the histologic characteristics described, such as persistence or not of the band of Unna, existence or not of small globi, greater or less vacuolization of the cells, presence of giant cells, etc., always evaluated quantitatively, is constant. Consequently we are dealing with a "depersonalized" histologic picture. We have never seen the two polar granulomata coexist in one patient, neither in the same biopsy, nor in biopsies from different skin territories.

In this form of leprosy the histology does not form a solid basis for classificative diagnosis. In our opinion the fundamental cause of discrepancies among leprologists as to the borderline form lies in a desire to find a defined morphological picture, which makes it possible to give character and expression to some clinically awkward points pertaining to the disease.

It appears to us very difficult to obtain strictly histologic differentiation between a lepra reaction of a quiescent tuberculoid, reactional tuberculoid, and borderline leprosy. If a polar form can change into another, there will be intermediate degrees in the exudative reactional episodes, which will produce variable pictures, with quantitative differences in certain limits. This could explain the divergent judgments of different leprologists.

If we consider that the bacteriologic and immunologic data, which almost always incline us toward the lepromatous form, are not decisive from the point of view of classification, it will be understood that the basis of diagnosis must be essentially clinical, and reliance will be placed on the general characteristics of the attack. Naturally, when the histology demonstrates an evidently polar structure in spite of the clinical appearance, the classification will be the polar type corresponding.

So understood, borderline leprosy comprises unstable cases in evolution, transforming between polar types, with reactional tuberculoid at one extreme and possibly the phenomena of reactional reversion of Wade at the opposite (pseudo-exacerbation of Souza Lima?). In our opinion it is not possible to speak of borderline macular forms (see our report on indeterminate leprosy).

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Indeterminate and borderline leprosy

DHARMENDRA, C. G. S. IYER, K. RAMANUJAM and G. RAMU

A study is reported of 11 indeterminate and 22 borderline cases. Classification of these cases in the two categories was purely on clinico-bacteriologic grounds. The study included also immunologic and histopathologic investigations.

Indeterminate leprosy: The age of the patients varied from 8 to 27 years, and the duration of the disease, according to the history, from 10 months to 11 years. Clinically all cases presented multiple, widely and bilaterally distributed lesions. In all cases the lesions were flat, and in most instances poorly defined. Surfaces of the lesions were smooth in some and dry in others. All cases showed loss or impairment of fine touch in some

at least of the patches. The peripheral nerve trunks were thickened in all, but there was no thickening of cutaneous nerves in association with the patches.

Bacteriologically all the cases but one were positive for lepra bacilli, from an occasional to a few bacilli in skin smears taken by the "slit and scrape" method. Smears from apparently normal skin were negative.

The lepromin test, using Dharmendra antigen, was mildly "positive" (1+) in one case, "doubtful" in 5 and "negative" in the remaining 5 cases. Histopathologically roughly half of the cases showed only chronic non-specific inflammation. In the others small groups of epithelioid cells were found in relation to appendages and nerves. Bacilli were found in sections singly and in small groups predominantly in nerves.

Borderline leprosy: The age of the patients varied from 8 to 55 years. The duration of leprosy ranged from 3 months to 13 years, and the duration of the presenting clinical condition (infiltration, etc.) from 1 week to 3 years. The onset in most cases was abrupt. In the majority of cases it followed administration of DDS for varying periods. According to history, some originated from erythematous thick lesions and others from hypopigmented flat lesions. Clinically the lesions were multiple and widely distributed, bilateral and sometimes symmetrical. All the cases had infiltrated, erythematous, and mostly succulent lesions; a small number in addition had hypopigmented flat lesions. In a majority of cases the edge of the lesions was sloping. In some there were both well demarcated and sloping-edged lesions. Some of the thickened lesions showed an apparently normal looking center. Sensory changes, varying from impairment to loss of fine touch, were seen in at least some of the lesions of all the cases; in addition there was thickening of cutaneous nerves in relation to patches in about half the cases.

Bacteriologically all the cases were mildly to moderately positive. Smears from the unaffected normal skin away from the patches were negative. The lepromin test, using Dharmendra antigen, gave "negative" results in 6 cases, "doubtful" in 2 and "mildly" positive (1+) in 7.

Histopathologically the histologic features encountered in these cases can be grouped broadly in the following 3 categories: 1) The "tuberculoid" type, with some atypical features, such as a variable admixture of polymorphonuclears and intercellular and intracellular vacuolation. 2) In some cases exudates were generally larger and both focal and continuous. .The predominate cell was a polygonal element with ample granular or vacuolated cytoplasm, a clear vesicular nucleus, and cell outline that varied from oval to elongated. As in the previous group, inflammatory cells were found admixed in variable numbers. The subepidermal zone was not infrequently spared. 3) In the remaining cases the histologic picture was a combination in various proportions of these two types.

In all these categories nerves were affected and the involvement took the form of infiltration, fragmentation, total replacement or prominence of the mesenchymal investment of the nerves. All cases showed acid-fast bacilli predominantly within the nerves and frequently in the cells also, singly and in small groups. In a few cases larger groups resembling globi were also seen.

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Chemical aspects of the chemotherapy of leprosy*

QUINTINO MINGÓIA

The author describes the antileprosy medicaments introduced in the last 20 years in the field of chemotherapy or antibiotic therapy, dividing them according to their origin and chemical constitution into the followng groups: (1) sulfones, (2) thioureas, (3) thiosemicarbazones, (4) thiolesters and thioamides, (5) antibacterial sulfamides, (6) nonsulfurated compounds, (7) antibiotics. He brings evidence of the superiority of the sulfurated synthetic compounds in their different forms (sulfones, thioureas, sulfamides) and the importance of associated treatments. He supports the study of new chemotherapeutic agents, some of them recently employed in the chemotherapeutic treatment of tuberculosis, which show new chemical characteristics (geometric isometry, polynitrogenated heterocyclic molecules, thiouronic-S, etc.).

*Translation from the Portuguese by J. R. Innes.

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National campaign against leprosy in Brazil, 1963*

F. Plasencia Filho

The fight against the leprosy endemic in Brazil, in the way instituted by SNL and carried out by CNCL, showed in seven years of progressive activities, some of them unforeseen, that it was superior in various ways to the prophylactic system based mainly on the tripod of leprosarium, dispensary, and home for the protection of children.

Some advantages observed were: (1) It was more humane, practical, economic, and receptive. (2) There was a reduction in unadjusted mental states, prejudices, and taboos and a lack of stigmatizing. (3) It made possible the control of a greater number of leprosy foci and contacts. (4) It created in fact a leprologic conscience outside the teams of specialists. (5) It obtained in an appreciable proportion of cases an early diagnosis and an early treatment.

It showed the possibility of eradication of this particularly incapacitating disease, and showed that those responsible for collective public health favor the use of resources which are indispensable to attain the objective visualized by SNL.

The advice and opportunity to carry out the program of CNCL by means of projects well planned and adjusted to the local and regional features of the endemic, avoiding being involved in a very rigid stage, had the result that US has taken on, as soon as possible, the whole responsibility for leprosy control in the various fields of action.

*Translation from the Portuguese by J. R. Innes.

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Lepromin reaction in an endemic area of leprosy. Evaluation of the anergic level*

J. C. de Souza Carvalho, W. de Moura Hildegrand, E. A. Serodio

The authors, who have worked in the national campaign against leprosy (SNL) since 1958, have been verifying the low percentage of positive Mitsuda reactions among contacts in the Araras region in the state of São Paulo. Impressed by the high anergic band in the region, i.e., the negative lepromin reactions, they decided to carry out a general test of the population of the municipality of Araras, which has 39,398 inhabitants.

Because of the impossibility of making inoculations of lepromin (Mitsuda-Hayashi antigen) in the whole population, we chose seasonal population groups of all social strata in urban and rural zones. So we have carried out 1,365 inoculations of lepromin, reaching school, gymnasia, and military training groups, makers of high quality goods (Nestle), haciendas, sugar factories (São João factory), and old people's homes, etc.

The 1,365 inoculations of lepromin involved reading the results on 1,088 individuals. The reading was made at 48 hours (Fernández reaction) and at the 4th week (Mitsuda reaction). The standard used for reading was that of the National Leprosy Service as set forth by Orestes Diniz.

For example: positive reaction = nodule 5 mm. or more; doubtful reaction = nodule less than 5 mm.; negative reaction = absence of any inflammatory phenomena.

Results of lepromin reaction readings

Positive	222	21.3%
Negative	486	44.7%
Doubtful	370	34.0%
Total	1,088	100.0%

Conclusion: The negative anergic zone in the Araras municipality is 44.7%. The increase of the doubtful reactions which have reached the anergic level in 78.7% of the population in that region, indicates the gravity of the problem.

Immunologic investigation of this nature must be made previously to the installation of specialized dispensaries or field teams. Considering that those numbers reflect the lack or resistance of a population in relation to *M. leprae*, they are more significant than the indices of prevalence and incidence.

*Translation from the Portuguese by J. Ross Innes.

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Infantile nodular tuberculoid leprosy and BCG*

G. MANGEON

The author presents three cases of infantile nodular tuberculoid leprosy in patients of ages 1 to 2 years and 10 months. Two were given BCG at birth in a single dose. All three were in contact with the clinical form of lepromatous leprosy shortly after birth. The author thinks there was a latent period of a few months, and also that there was penetration of the Hansen bacillus, in the anti-allergic period, before premunition by BCG. He thinks that BCG should be used in the premunition of leprosy because it is one of the two probable agents in changing the Mitsuda test, in which it is shown that one dose may be sufficient.

*Translation from the Portuguese by J. R. Innes.

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Psychosocial repercussion in children with leprosy*

C. ESTRADA SILOS

"*We do not know the child . . .*" This lack of knowledge reaches its supreme point when it is in the doctor before whom a little leprosy patient appears, and he is given attention as a patient, forgetting that it is the *child* who should be considered above everything. The child is the human being whose psychic state is found in the most delicate and susceptible state of all.

In Mexico a team labors in the Centro Dermatológico "Pascua." Social workers, Sisters of Charity, receive the patient in their medico-social department, and from the very beginning establish human relations with the child and his relatives.

The object of this paper is to follow the aspects of the child leprosy patient from the psychosocial point of view. We studied 100 child leprosy patients cared for medically and socially in the Pascua Center between 1951 and 1962. Clinically lepromatous patients predominated at 49%; tuberculoid cases made up 27%, and indeterminate 24%. In 44%, the source of infection as antecedent case was the parents. All these were given sulfone treatment in dosage of 25 and 50 mgm. per day, with favorable results except in diffuse lepromatous cases. At the present time 65% continue treatment and 8% are without medical supervision because they have been lost to observation.

From the social point of view, remembering the principles expounded and considering the patient first of all as a human person with all his problems, we find that all these children continue their normal life and hence are able to pursue their studies and occupy their place in society. Of the children 90% are of school and pre-school age, about 5 to 14 years of age, and of the children 35 are illiterate.

Concerning social class and all pertaining thereto, we have adopted a special classification and have formed two groups, normal-social and weak-social; the latter classification has three grades, 1, 2 and 3. Among the 100 children studied we found: normal-social, 25%; weak-social, 75%; weak-social 1, 28%, weak-social 2, 17%, and weak-social 3, 30%.

It has been said among us that leprosy sometimes has been an opportunity to go forward. At the present time we have 52 normal-social children; 27% may be able to progress further and be useful to themselves and to society.

*Translation from the Spanish by J. R. Innes.

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Borderline and indeterminate leprosy

V. R. KHANOLKAR

The "indeterminate" phase of leprosy is a stage in which the disease has not yet disclosed the type or variety into which it will evolve. Clinically this phase is marked by the appearance of weal-like papules, or pale pink macules with an irregular wrinkled surface. There is often a spontaneous and permanent recovery in about three-quarters of infected persons, but in the remainder the disease may progress to dimorphous, tuberculoid or lepromatous leprosy, depending upon the natural susceptibility and racial proclivity of the persons affected. There is very little clinical or histopathologic indication of the probable course the

disease will follow. Occasionally the "indeterminate" phase may be bypassed and the silent phase may blossom out into either a lepromatous or the tuberculoid type.

Histologically the skin biopsy shows foci of chronic inflammatory exudate, mainly around the finest nerves in the dermis. The exudate consists of lymphocytes, histiocytes, plasma cells and occasionally polymorphonuclear leucocytes. It is possible to demonstrate small numbers of acid-fast bacilli by a concentration technique in some cases. In some of the histological sections acid-fast bacilli are seen either in the reticular tissue of the dermis or in the finest cutaneous nerve twigs. The lepromin test at this stage of the disease is variable, ranging from negative to faintly or strongly positive.

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Contribution to the study of borderline and indeterminate leprosy

R. D. Azulay

Classification of the clinical forms of leprosy should be linked closely to degree of resistance, and hence to heredity. To be rational, any classification must be based on the concept of polarity. The interpolar zone, owing to the instability of resistance therein, admits of divergence of opinion. This band covers the forms: reactional tuberculoid, borderline and indeterminate.

Borderline leprosy: A study was made of 35 cases from clinical, immunologic, bacterioscopic and histopathologic angles. The frequency of borderline leprosy varies with the interest, and the extent of resources available for diagnosis; it is probably far more frequent than is suspected. The highest frequency, in comparison with other forms of leprosy in the statistics presented up to date, is 6.4%.

Considering the matter from a clinical point of view, the author draws attention to: hollowed or Swiss cheese lesions; infiltrated lesions peculiar to the TR form; edema of the extremities; hypochromic and erythematous patches with uncertain edges; infiltration of the ear lobes on one or both sides; the great number of lesions less symmetrical than in L; lesser nerve involvement than in L; frequent absence of general symptoms and fever; finally, negative data, e.g., absence of ocular involvement, gynecomastia, madarosis, orchitis, adenopathy and visceral disorders. Histologically, the author stresses the concomitance of the two structures, L and T, either in a single lesion or in different lesions, required to make a reliable diagnosis of B, and also insists on the fact that the T and L structures are by no means typical; on the contrary, they are decapitated and upset. Out of 25 cases, the diagnosis of B was made from the first biopsy in 19 cases.

Examination for bacilli led to 100% positive results in the sections, in contrast with sloughing (positivity: 75% in the skin and 73% in the nasal mucus). Negative results were noted in 86% in the early and 59% in the late lepromin reactions. The author draws attention to the frequency of the fluctuating or oscillatory phenomenon in the lepromin reaction (22% of late reactions fluctuated). The onset was slow in most of the author's borderline cases, in contrast with the findings of certain other authors. Furthermore it seemed to the author that the cases started with the I form. The evolution of the case generally followed a chronic course; more rarely it was acute. Specific treatment brings about a rapid improvement in patients as a result of the disappearance of the T fraction (not really lepromatization), which, in fact, may regress somewhat more rapidly than lepromatous cases.

Indeterminate leprosy: The author confirms the initial views of Brazilian leprologists with regard to this form of leprosy. I leprosy cases are identifiable by hypochromic patches, often with loss of sensitivity and a change in the histamine and pilocarpine reactions. Bacterioscopy is frequently negative and, when positive, few bacilli are to be found. The lepromin reaction may be positive, negative or oscillating. The frequency, as compared with the other forms of leprosy, increases with the efficiency. In Candeias there were 26.1% I cases compared with the other forms of leprosy, but an intensive census brought this figure up to 57.5%. The importance of the I form lies in the early diagnosis of leprosy. I cases may remain as such for many years and even undergo involution or transmute to B, L, or T. Periodically repeated bacterioscopic examinations and

lepromin tests serve to forecast (though not categorically) the possible evolution of I cases. The points at issue, as regards the independence of the I form, are concerned with the conception of maculo-anesthetic, neuritic and macular dimorphous forms. Maculo-anesthetic cases should be considered as I; when biopsy reveals tuberculoid granuloma, they should be reclassified as macular T. Pure neuritic cases may be distributed over the three forms of leprosy (L, T, or I), according to the clinical and bacterioscopic characteristics observed. In its initial stage macular dimorphous leprosy corresponds exactly to the I form.

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Antileprosy campaign in Mexico Training of staff*

José Barba Rubio

The activities, and the philosophic and humanistic spirit of the program for control of chronic diseases of the skin, established in 1960 by the Ministry of Health, are emphasized.

In this program the Mexican School of Dermatoleprology reveals its philosophic and social ideas: (1) prophylaxis is based on early diagnosis and opportune treatment; (2) the campaign should be based on persuasion and conviction and never on drastic systems; (3) it should be made attractive by personal skill following the training of doctors and nurses in dermatology and leprology, and not exclusively in dermatology; (4) besides the dermatologic centers of the campaign, the number of mobile teams should be increased, which would tour ranches and small communities in the endemic zones, giving dermatologic consultations and not using the word leprosy, discovering leprosy cases and controlling them as well as their contacts.

The training should be given in groups of not more than 20 doctors and nurses separately, theoretically and practically, giving a complete scientific education in dermatology, leprology, epidemiology, hygiene, sanitary practice, social anthropology, psychology, statistics and biostatistics. This theoretic and practical teaching of not less than three months' duration should be complemented with one or two months of field work before effective official activities are begun.

*Translation from the Spanish by J. R. Innes.

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Five-year progress in leprosy control in Korea

Joon Lew

This is a progress report of "Epidemiological studies of leprosy in Korea" reported at the 7th International Congress of Leprology. About 20,000 institutionalized and 8,000 outpatients were examined and analyzed as to bacteriology, appearance, deformity and physical capability, and classified for social rehabilitation in 5 categories of bacteriologically negative and positive cases.

To accommodate each category of patients, 5 hospitals for positive cases, 4 special hospitals for far-advanced, crippled cases, 2 special hospitals for corrective surgery, 20 leprosy outpatient clinics, 8 mobile clinics and one pilot project area are in operation. Programs for social rehabilitation in the resettlement project, for negative, arrested and physically capable cases, are carried out actively. A total of 7,658 cases have been resettled in 57 villages. Health education and propaganda campaigns are carried on actively through leprosy training courses in medical and nursing school curricula, lectures to college- and high school-level students, and extensive propaganda for the general public.

Many specialists for leprosy control and corrective surgery are sent abroad. Special leprosy training courses are given to more than 2,000 public health doctors and 1,500 public health nurses. A leprosy journal and a bimonthly magazine for the general public are published. A birth control campaign during the positive stage is carried on. Children are separated from parents with active leprosy, and preventive measures with BCG and DDS are conducted. The compulsory segregation law has been abolished. The sample random survey was made twice, and a nationwide survey of military conscripts is being carried out.

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Leprosy in the Netherlands

E. H. HERMANS

Before the second world war the leprosy problem in the Netherlands was of but little importance, because there were few sufferers from the disease. These were mainly ex-soldiers from the former Dutch East Indies. After the war the situation changed. Within a short time some hundreds of leprosy patients came to the Netherlands from Indonesia, especially Dutch people of mixed parentage and Amboyneses, who needed treatment and for whom provision had to be made. At the beginning this work met great difficulties, but after a special organization to aid leprosy patients was founded, with the help of the Government, matters improved greatly.

A central administration, together with a medical service and an office for social help, were established and a special health-resort was opened for patients of this kind. In some hospitals patients could be admitted without difficulty. In this way we succeeded in curing a considerable percentage of patients, and with the help of the authorities succeeded in rehabilitating them so that they could resume their place in society. Although no compulsory measures were taken and a considerable percentage of the sufferers from leprosy could live entirely free from control, no new infections originating from these people from Indonesia were seen.

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Reconstructive surgery in leprosy

ROBERT R. SCHENCK

Anesthesia, paralysis and deformity in leprosy have as etiology the reactional response in nerves following infection with the causative organism, *M. leprae*. To a varying degree reconstructive surgery can help almost all leprosy patients with deformity. Both social and economic factors present a strong case for including reconstructive surgery as an integral part of the total public health measures advocated in treatment and control of leprosy in countries with a relatively high prevalence. Surgical results will encourage all patients and the medical approach will have greater effectiveness.

Basic principles of reconstructive surgery in leprosy include adequate use of physical therapy pre- and post-operatively, use of proper surgical materials and technics, substitution of non-paralyzed muscles as motor power to replace paralyzed muscles, and use of free tendon grafts, if necessary, between muscles being transposed and the desired site of insertion. Selected surgical procedures in leprosy patients are described, with emphasis on operations designed to replace the action of intrinsic hand muscles in the fingers and thumb. Surgery is useful in treating anterior tibial and hand extensor paralyses, neurotrophic joints, and skin contractures. Prevention of deformity as a program of education can be carried out during the rehabilitation period. Reconstructive surgery offers hope in leprosy.

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The histoid variety of lepromatous leprosy

H. W. WADE, JOSE G. TOLENTINO

The "histoid" variety of lepromatous leprosy is so named because the typical lesions resemble a tissue-forming process rather than a granuloma. The condition is commonly mistaken for fibrosis.

The essential clinical feature is nodule formation, notably subcutaneous but also cutaneous. The nodules are well vascularized, but, being primarily expansible, they contain no nerve branches. Variations of appearance are many.

Histologically the variations from the typical are legion, particularly those involved in activity of the process. Besides (a) the tissue-like character of the lesions, essential features include: (b) a primarily expansible rather than infiltrative manner of growth of the nodules, although certain of the skin lesions are in effect infiltrative, and secondary restricted infiltrative additions often complicate the picture of the nodules; (c) the typical *absence of globus formation;* (d) the spindle-shape nature of the characteristic cells (not of epithelioid type); (e) the common occurrence of undifferentiated large round macrophages (histiocytes) in the more active areas; (f) the frequent occurrence of areas of

breakdown in subcutaneous nodules (local reactional "abscess" formation), usually without polymorphonuclear leucocytes.

Extraneous to the histoid areas in sections of cutaneous lesions, inactive foamy-cell areas (relics of the previously-existing ordinary lepromatous process) may be found; and, also extraneous, there may be more or less active areas of co-existing lepromatous infiltrates.

Bacteriologically, the striking features are: (a) the extraordinary abundance of the bacilli in most lesions, especially in the more active areas; and (b) the large size of the bacilli (conspicuously in contrast with those of any ordinary lepromatous foci that may be present).

In the spindle-shaped cells the bacilli are characteristically in groups or larger packets conforming to the shape of the cells in which they are located, and in the large macrophages of the more active areas they tend to produce solid round masses which obscure the containing cells. These features constitute the "histoid habitus," in striking contrast with what occurs in ordinary lepromatous lesions.

Finally, but important, is the occurrence of definite tuberculoid foci of true epithelioid cells located in ("contaminating") histoid lesions, not infrequent in the subcutaneous nodules but rare in the cutaneous lesions.

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Meaning of antibody titer in leprosy, determined by complement fixation with antigens prepared from tubercle bacilli

Jose Oliveira de Almeida

Antibody titrations, by an isofixation method, with antigens prepared from tubercle bacilli, were carried out in 405 lepromatous patients, who were bled each 4 months for a period of 3 years.

Correlation was found between the presence of Hansen bacilli and the level of antibodies, although serologic curves presented in most cases a marked fluctuation, not related to the clinical findings. It was observed, also, that in a group of 373 freshly withdrawn sera, 228 reacted with complement, in the absence of antigen. This anticomplementary effect could be computed in the determination of specific titers in active sera, since heated sera did not present such an effect. When the ratios between titers of active and inactive sera were calculated, values higher than 5 were obtained in 20% of them; in the group with no avidity for complement, only 14.5% had ratios higher than 5. The irregularity of the serological pattern could be due to antigens released from lesions, with the formation of circulating antigen-antibody complexes, which react with complement. The presence of these immune-complexes could be a major cause for renal conditions and other immune-diseases, such as leprotic reactions in which circulating polysaccharides have been detected in higher concentration.

Antibody formation could be enhanced by leprous granulomata, in conditions comparable to those produced by Freund's adjuvant, as was pointed out by the following trial. Sixty lepromatous patients and one equivalent group of healthy soldiers were inoculated with formalized typhoid vaccine. Antibody response was evaluated and agglutinin titers were higher for leprosy patients, their difference from the controls being statistically significant for H (P. 001) and for O (P. 01). These data support the point of view that lepromatous leprosy is an hyperergic status of the infection.

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Mycobacterium leprae in mouse footpads

Charles C. Shepard

M. leprae multiplies with regularity when inoculated in the mouse footpad. Since the beginning of the work in 1957, *M. leprae* has been isolated from 92 clinical specimens. These were from patients infected in many parts of the world. Isolation has been successful from nearly 100 per cent of untreated lepromatous cases. The minimal infectious dose is about 100 organisms. A convenient dose to inoculate is 5,000 bacilli; after this dose multiplication to a level of about 2 million bacilli occurs in about six months. The infection may then be passed to new groups of mice, and by this means about 30 strains of *M. leprae* are being kept in continuous passage. The oldest strains are now in tenth

passage and have been kept in continuous passage for nearly 6 years. It is important to note that no changes have been seen in the properties of the organism as a result of passage; acquisition of new properties would have raised the possibility of a contaminant. In collaboration with R. S. Guinto, it has recently been shown by means of Mitsuda reactions in adult lepromatous and tuberculoid patients that the bacilli grown in footpads are immunologically identical with leprosy bacilli in standard lepromin. Tests of drugs are being carried out in collaboration with Y. T. Chang, and 11 drugs have been tested so far.