CURRENT LITERATURE

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General and History

Bergel, Meny. La lepra como enfermedad metabolica. [Leprosy as a metabolic disease.] Publ. Cent. Estud. Leprol. **15** (1975) 8–44. (In Portuguese)

The author summarizes an extensive series of theoretical and experimental considerations on etiology, pathogenesis, prevention and treatment of leprosy. Upon these considerations, the author finally concludes that leprosy must be located within nutritive-metabolic diseases and not within infectious diseases. The autooxidative disease is described in particular. General considerations are made with regard to the present leprologic experiences, and especially a critical study which was carried out concerning the immunologic manifestations of leprosy. Also, special emphasis is placed on the prevention and treatment of leprosy.—*(Adapted from* author's English summary)

Browne, Stanley G. Research in a "bush hospital" in Africa. Trop. Doct. **6** (1976) 187–189.

Dr. Stanley Browne reminisces about his early experiences in initiating research in a "bush hospital." From these he derives his "Ten Commandments":

1. Train others to do the routine work.
2. Write it down—the fuller and more methodical the better.
3. Learn the normal (usual) and then recognize any departures therefrom.
4. Stand back and stare, i.e., critical evaluation of priorities, etc.
5. The obvious or the urgent may not be the most important.
6. Fill the gaps in your professional preparation.
7. Keep up your reading.
8. Learn from anybody and everybody.
9. Maintain the inquiring mind.
10. Write it up.

So be it.—OKS

Rotberg, A. O complexo "lepra: pejorativo e endemia," grave problema médico-social da América Latina. [The complex "leprosy:—the pejorative, the endemic," a serious Latin-American medico-social problem.] An. Bras. Dermatol. **50** (1975) 87–89. (In Portuguese)

The word "leprosy" has two different connotations. As a synonym for ignominy, defilement, corruption and infamy, it is historically correct and corresponds to the Hebrew Bible's "Tsara-ath," translated as "Lepra" in the Greek Bible. As a medical name, it is illegitimate and derives from the unjustified application of that name to a disease not even known in the time of Moses. According to the utilization of those connotations for "Lepra," countries are divided into four groups:

1. No pejorative, no disease, as Germany and Scandinavia.
2. Pejorative, no disease, as England and France.
3. Disease, no pejorative, as Japan and India.
4. Disease *and* pejorative: the "complex" that affects the Americas and some other countries.

Enlightenment of the public of group four will only be possible when the "complex" is broken and the disease is liberated from its stigmatizing name.—*(Adapted from* author's English summary)

Clinical Sciences

Bergtholdt, Harry T. and Brand, Paul W. Temperature assessment and plantar inflammation. Lepr. Rev. **47** (1976) 211–219.

The rehabilitation of the healed plantar ulcer is difficult to monitor by routine methods. Monitoring of skin temperature has been found to detect the early inflammatory response of the soft tissues to the insult imposed during walking. Methods of doing this are discussed and case histories described. The human hand, though quantitatively inaccurate, can effectively detect temperature contrasts. If routine management follows the recognition of early inflammatory responses, deformity can be prevented.—Authors' Abstract

Browne, Stanley G. Recent advances in the therapy of leprosy. Castellania **4** (1976) 44–46.

While the chemotherapy of leprosy cannot lay claim to anything comparable to the significant recent advances in the fields of microbiology and immunopathology, the past few years have seen the introduction of new remedies, the development of precise methods for evaluating drug efficacy, the demonstration of drug resistance, and the first tentative approaches to immunotherapy.—Author's Summary

Carayon, A., Courbil, J. L. and Giraudeau, P. Évolution actuelle de certains procédés de chirugie palliative de la main lépreuse paralytique. [A study on some surgical procedures in the treatment of the paralytic leprous hand. Present trends.] Med. Trop. (Mars) **36** (1976) 181–191. (In French)

A review of surgical procedures used in the treatment of the leprous paralytic hand. Four points are emphasized: 1) the proximal attachment of the activating transplant; 2) a new pattern for the passage through the carpal canal; 3) a peculiar treatment of the contracture of the interosseous muscles (resection); and 4) the pattern to activate the thumb, with use of two transplants. [The surgical procedures are illustrated in a series of line drawings.]—(*From* Trop. Dis. Bull.)

Carayon, A. and Giraudeau, P. Valeur de la résection de l'épitrochlée dans la décompression et le déroutement de 87 névrites cubitales hanséniennes. [Value of the resection of the epitrochlea for decompression and diversion of a leprous cubital nerve.] Med. Trop. (Mars) **36** (1976) 163–173. (In French)

The translocation of a leprous cubital nerve has good physiopathologic bases and has proved to be a reliable technic. The rerouting may be carried out by a limited anterolateral diversion, by an anterior one. The resection of the epitrochlea which prevents the elongation of the nerve without vascular risk is preferred today. A study of 87 cases is reported.—(*From* Trop. Dis. Bull.)

Dongre, V. V., Ganapati, R. and Chulawala, R. G. A study of mono-neuritic lesions in a leprosy clinic. Lepr. India **48** (1976) 132–141.

An analysis of 11,581 leprosy patients registered at the Acworth Leprosy Hospital clinic showed that 494 cases (4.3%) had primary polyneuritic leprosy, and 143 (1.2%) localized cutaneous anesthetic lesions (or nonvisible anesthetic lesions), accounting for 5.5% who had no evidence of obvious skin lesions.—Authors' Summary

Hashizume, Chozo. Amputation of the ankle region and its indication for intractable plantar ulcer in leprosy patients. Lepro **44** (1976) 142–149. (In Japanese)

A series of 12 leprosy patients with forefoot amputation, talipes equinovarus-type contracture, or a marked degree of destruction of the tissues adjacent to the ankle-joint or of the tarsal region, with an extensive incurable ulcer, were treated surgically by Chopart's amputation combined with resection of the talus and with coaptation of the calcaneus to the tibia. Six months to a little over one year after the operation, the patients showed an average foot contraction of 4 cm and were capable of walking along barefoot within the walls. There was no evidence of ulcers in ten of the cases and they are now quite able to walk long distances with the aid of an artificial limb. With the combined surgical treatment, not only does the patient become able to stand and with bare feet, but

also the stump or the base of the calcaneus may be maintained more physiologically with remarkable firmness than in the case of Syme's amputation which usually provides an uncertain degree of correction for a paralyzed leg. The method described is considered preferable particularly for the treatment of affected legs in leprosy patients who tend to develop ulceration.—(*Adapted from* author's English summary)

McLeod, J. G., Hargrave, J. C., Gye, R. S., Pollard, J. D., Walsh, J. C., Little, J. M. and Booth, G. C. Nerve grafting in leprosy. Lancet **1** (1976) 95–96. (Letter to Editor)

Sir: Dr. Crawford (Lancet **2** [1975] 326) says that nerve grafting should not be done in leprosy because the sensory loss leading to burns, trophic ulcers, cellulitis, osteomyelitis, and bone resorption is due to a generalized peripheral neuropathy rather than a localized lesion of peripheral nerves. In our paper to which he refers (Brain **98** [1975] 203), we do not claim that only one nerve was affected; in fact our patients had generalized diseases of peripheral nerves. We stated that in some nerves we were able to demonstrate clinically and electrophysiologically that disease was localized predominantly to one isolated segment and that by inserting a nerve graft we were able to restore protective sensation to the extremities of some patients. In the patients whom we treated successfully, skin ulcers healed in regions which were reinnervated. We made no statements about osteomyelitis, cellulitis, or bone resorption. Although useful protective sensation was restored after insertion of 9 of the 23 grafts and has persisted for three years postoperatively, we emphasized that the procedure was suitable only for a small proportion of leprosy patients and that our results did not justify its widespread use at present.—Authors' Letter to Editor

Palande, Dinkar D. Some clinical and laboratory signs indicating external compression of a nerve trunk in leprosy: details and rationale. Lepr. Rev. **47** (1976) 35–39.

The details and rationale of clinical signs which when positive indicate the presence of active external compressive and traumatic factors affecting an inflamed nerve trunk in leprosy are described. A new laboratory test suggesting peripheral vascular insufficiency and indicating the need of posterior tibial decompression is also described. The increasing trend towards nerve surgery in leprosy is reviewed and the need for proper selection of cases is stressed.—Author's Abstract

Reichart, Peter. Facial and oral manifestations in leprosy. An evaluation of 70 cases. Oral Surg. **41** (1976) 385–399.

A clinical and radiologic study of early and late manifestations in tuberculoid, dimorphous, and lepromatous leprosy was undertaken in order to determine characteristics, occurrence, and incidence of facial and oral lesions. Dermal, mucosal, neural, skeletal, and dental changes were correlated with the duration of leprosy, duration of treatment, and age of the patient.—Author's Abstract

Sebille, A., Saint-Andre, P., Giraudeau, P. and Rougemont, A. Manifestations cliniques de la multinévrite lépreuse chez l'Africain de l'Ouest. A propos de 90 observations. [Clinical manifestations of leprous polyneuritis in West Africans. Report of 90 cases.] Bull. Soc. Pathol. Exot. **68** (1975) 335–344. (In French)

The authors report the results of the clinical examination of ten main peripheral nerve trunks, together with the corresponding sensory and motor deficits, in each of 90 West African leprosy patients in the Institut Marchoux in Bamako, Mali. They emphasize the importance of enlargement of the nerve trunk at sites of predilection as the most frequent and earliest sign of nerve damage, and refer to the probable importance of compression of the trunk in fibro-muscular canals. Obvious atrophy and weakness of the muscles supplied, and sensory deficit (as demonstrated by testing with a wisp of cotton wool, and pinpoint) were less useful signs, though sensory impairment usually preceded motor weakness. The ulnar nerve was most commonly affected, and the facial least. In the latter no enlargement was detected in the nerves of the superficial cervical plexus. [The small nerves passing over the malar bone are not mentioned.]

The authors claim that the immunologic classification of the disease had no bearing on peripheral nerve damage [a statement at variance with the findings of most authors], and that *erythema nodosum leprosum* had a

transitory effect only on the appearance of the signs of neuropathy.

[A greater precision of the clinical findings would be welcome, together with a correlation of the enlargement and hardness of the nerve trunks with the stage of the disease and the immunologic classification of the form of leprosy concerned. Other sensory modalities (such as temperature sense) might well have been included in the examination.] —S. G. Browne (*From* Trop. Dis. Bull.)

Shukla, R. K., Chaturvedi, S. N., Srivastava, R. K. and Gupta, A. K. Modified Zancolli's operation in claw hand in leprosy. Lepr. India **48** (1976) 48–54.

The operative technics of the modified Zancolli's operation in claw hand are easy. Reeducation is easier in Zancolli's capsulorrhaphy than any other operation. Results of this operation are encouraging. It is particularly required when quick turnover of cases is needed and when adequate facilities for physiotherapy are not available. In cases operated on by Zancolli's capsulorrhaphy, active flexion of the metacarpophalangeal joint is possible. Complications are few, e.g., pulling of capsulorrhaphy and development of flexion contracture.—Authors' Summary

Chemotherapy

Barnetson, R. StC., Pearson, J. M. H. and Rees, R. J. W. Evidence for prevention of borderline leprosy reactions by dapsone. Lancet **II** (1976) 1171-1172.

Sixty-eight patients were included in a prospective study of the treatment of borderline leprosy, 34 were treated with dapsone 5 mg daily, and 34 with 50 mg daily. Reversal reactions developed in 11 of those on 5 mg daily and in 3 of those on 50 mg daily. The statistically significant difference between the two treatment groups indicates that, contrary to previous teaching, dapsone given in higher dosage does not predispose patients to reversal reactions and indeed may prevent them.—Authors' Summary

Desikan, K. V. and Balakrishnan, S. Tissue levels of clofazimine in a case of leprosy. Lepr. Rev. **47** (1976) 107-113.

A quantitative assessment of clofazimine in some of the organs obtained at autopsy is reported. Although 40 days had elapsed since stopping treatment with the drug, significant quantities of the substance were found in the organs of the reticuloendothelial system. The intestinal mucosa also showed a heavy concentration of the drug. Attention is drawn to the heavy accumulation of the drug during prolonged treatment.—Authors' Summary

Huikeshoven, H. C. J., Honhoff, C., Van Eys, G. J. J. M., Anten, J. G. F., Mayer, J. M. A. and Van Helden, H. P. T. Weekly self-medication of leprosy patients monitored by DDS/creatinine ratios in urine. Lepr. Rev. **47** (1976) 201-209.

The self-administration of once-weekly doses of 300 mg dapsone (DDS) by leprosy patients in the Mwanza region of Tanzania was monitored using the urine-test method described by Ellard *et al* in 1974. DDS/creatinine ratios were determined on urine samples voided by 65 supervised leprosy patients on each of seven successive days following the ingestion of 300 mg DDS. The method was then applied to urine samples collected by means of surprise visits to the homes of 158 outpatients two days after the day on which a 300 mg dose of DDS should have been taken. The extent of DDS self-administration by the outpatients was estimated by comparing the results with those obtained from controls given supervised DDS doses and from subjects not taking DDS. Significant amounts of DDS were not detected in the urine samples collected from 30% of the outpatients. Furthermore, the average DDS/creatinine ratios of the urine samples of the other outpatients were significantly lower than those from the supervised controls. The implications of these findings to the treatment of leprosy in the Mwanza region and their relevance to other leprosy control schemes is discussed.—Authors' Abstract

Languillon, J. La clofazimine dans la lèpre (son action sur les formes réactionnelles

et les formes resistantes). [Clofazimine in leprosy (its effect on the reactive and resistant types).] Med. Trop. (Mars) **36** (1976) 127-130. (In French)

The author summarizes his experience with clofazimine [Lamprene (Geigy), B663] in Bamako (Mali) and Dakar (Senegal). In his first series of 15 patients suffering from lepromatous leprosy, untreated, and given clofazimine at a daily dose of 100 mg, he obtained good clinical and bacteriologic results, the Morphologic Index falling to zero in 24 weeks and the Bacterial Index falling by one-half in 12 months. No patient showed signs of reaction during the period of treatment.

His second trial was designed to evaluate the practicability of using clofazimine in a mass treatment scheme, and to compare the results of treatment of patients with lepromatous leprosy given either a weekly dose of 600 mg of clofazimine or a weekly dose of 600 mg of dapsone. No difference was noted in the speed of clinical or bacteriologic improvement between the groups, but among the 13 patients treated (and followed up) with clofazimine, there were only two instances of *erythema nodosum leprosum:* both were considered to be of slight degree and were easily controllable; whereas there were 8 cases of severe reaction among the 13 patients treated (and followed up) with dapsone. The author quotes the experience of Menke, who gave a loading dose of 600 mg of clofazimine daily for seven days, followed by a monthly dose of 1 gm to 23 patients suffering from lepromatous leprosy in Papua New Guinea.

A group of 34 patients suffering from *erythema nodosum leprosum* was treated with clofazimine at doses varying from 200 mg to 600 mg a day, 19 of them being given 300 mg daily. Improvement in the systemic and skin manifestations of the reactive state was noted in about 20 days for the majority, the limits being from 15 to 60 days. The author stopped all other leprostatic treatment when he gave clofazimine in these cases.

Another group of 26 patients treated at Bamako for "reaction" in lepromatous leprosy was given, in addition to clofazimine, either thalidomide (for males) at a dose of 400 mg daily for seven to ten days, or aspirin or a corticosteroid (for females) at a dose of 10 to 15 mg daily for ten days. Excellent results were obtained in this regimen. To 15 patients with lepromatous leprosy, suspected on clinical grounds of harboring sulfone-resistant bacilli, clofazimine was given as follows: 300 mg daily for six months, then 200 mg daily for three months, followed by 100 mg daily. The clinical and bacteriologic results were good, and pigmentation was no problem in the dark-hued African. [It may be that some of the patients in this group were slow responders, and did not harbor dapsone-resistant bacilli.]

The author concludes that clofazimine is the antileprotic of choice in the treatment of patients with lepromatous leprosy, especially those prone to reaction, and could with obvious advantage be used in mass treatment programs in Africa, where the lepromatous/tuberculoid ratio is low. For patients in the throes of the severe reaction of lepromatous leprosy, and those harboring dapsone-resistant bacilli, clofazimine is the drug of choice. [A word of warning should be uttered regarding the toxic effects of prolonged high-dose clofazimine therapy.]—S. G. Browne (*From* Trop. Dis. Bull.)

Levy, Louis. The activity of a thiadiazole on *Mycobacterium leprae* (39475). Proc. Soc. Exp. Biol. Med. **153** (1976) 34-36.

A new broad-spectrum antimicrobial, 2-amino-5-(1-methyl-5-nitro-2-imidazolyl)-1,3,4-thiadiazole, reported inactive against *Mycobacterium tuberculosis,* inhibited multiplication of *M. leprae* in the mouse foot pad when administered orally to the mice. The dose response curve was very steep: 0.2 gm% of the drug exhibited considerable activity, whereas 0.05 gm% was only modestly active in one experiment and inactive in another. This drug appears to be one of the few that is bactericidal for *M. leprae.*—Author's Summary

Levy, Louis and Peters, John H. Susceptibility of *Mycobacterium leprae* to dapsone as a determinant of patient response to acedapsone. Antimicrob. Agents Chemother. **9** (1976) 102-112.

In the course of a clinical trial of acedapsone therapy in 17 patients with lepromatous leprosy, the rate of response to therapy was measured by inoculation of mice with *Mycobacterium leprae* recovered from biopsy

specimens of skin lesions obtained before treatment and at intervals of 4, 12 and 24 weeks after institution of treatment. The susceptibility of each isolate of *M. leprae* to dapsone was measured by passaging organisms that had multiplied in mice to new groups of untreated mice and to mice treated with DDS incorporated in the mouse chow in concentrations of 10^{-5}, 3×10^{-5}, and 10^{-4} gm/100 ml. The rate of response to acedapsone therapy and the susceptibility of patients strains of *M. leprae* to DDS varied widely among patients. All isolates were inhibited from multiplication by treatment of mice with 10^{-4} gm of DDS per 100 ml; all but two isolates were susceptible to 3×10^{-5} gm of DDS per 100 ml; and 17 of 36 isolates, representing nine patient strains, were susceptible to 10^{-5} gm of DDS per 100 ml. Plasma levels of DDS measured in the mice administered these diets show that the minimal inhibitory concentration of DDS for *M. leprae* isolated from untreated patients is about 3 ng/ml. No relationship could be demonstrated between DDS susceptibility of pretreatment isolates of *M. leprae* and the rate at which patients responded to acedapsone therapy. Neither acedapsone treatment of patients nor DDS treatment of mice appeared to select genotypically more resistant *M. leprae.*—Authors' Summary

Plock, H. and Leiker, D. L. A long-term trial with clofazimine in reactive lepromatous leprosy. Lepr. Rev. **47** (1976) 25-34.

A report is given on 17 lepromatous patients, all but one steroid dependent because of repeated, serious reactions, treated with clofazimine in dosages of 100-600 mg daily, for periods up to five years. In 14 patients who completed 2½ years of treatment the average annual decrease of BI in smears and biopsies was 13% and 14% respectively, being somewhat slower than after sulfone treatment (17%). Out of six patients who completed five years of treatment, five became negative, one after four years, four after four and one-half years. In some patients, however, the decrease of the BI was slow and unsatisfactory. No evidence of resistance to Lamprene was found. No correlation was found between slow response and long period of weaning off steroids or with other complications.

The decrease was somewhat slower in patients with long duration of disease and long duration of previous (sulfone) treatment. In this series of patients the overall long-term reaction suppressive effect was somewhat less than in other trials, and not better than in patients treated with 100 mg daily. No correlation was found with duration of disease and bacteriological progress.

In this series an unusually high proportion of the patients complained of abdominal pain, vomiting after medication, and some of diarrhea, to the extent that clofazimine treatment had to be discontinued (7 out of 17 patients). No correlation was found with duration of disease, duration of previous treatment, steroid dependence or sex. The lower frequency of abdominal complaints reported from trials with lower dosages of clofazimine suggest a relationship with dosage. A history in several patients of severe enteritis or dysentery prior to clofazimine treatment suggests that clofazimine acts as an irritant in particular if the intestines have already become irritable by other factors.—Authors' Abstract

Taylor, P. M., Chacko, C. J. G. and Job, C. K. Study of sulfone resistance in leprosy patients in India. Lepr. Rev. **47** (1976) 5-11.

Studies were undertaken to confirm the occurrence of resistant strains of *M. leprae* in leprosy patients who fail to respond to treatment with dapsone. In the first three years, 39 patients who had highly active disease despite a long history of treatment were selected from our outpatient clinic. A suspension of bacilli from an active lesion was injected into the foot pads of a group of normal CBA mice. The mice were then fed varying doses of dapsone in the diet for several months. At harvest, multiplication had occurred in the presence of high doses of dapsone in 12, at low dosage in 7, and only in the control group in 14. There were six failed experiments. This demonstrates that 19 patients harbored *M. leprae* to some extent resistant to dapsone.

Observations on the clinical manifestations and subsequent progress are made and compared with reports from other centers.—Authors' Abstract

Immuno-Pathology

Almeida, J. O. and Kwapinski, J. B. Reatividade de antígenos de actinomicetos com soros de lepra, avaliada por imunofluorescência em suporte de acetato de celulose. [A study of the reactivity of actinomycetes together with lepra sera by means of the immunofluorescent test with cellulose acetate.] Publ. Cent. Estud. Leprol. **14** (1974) 73–90. (In Portuguese)

1. The immunofluorescence reaction using cellulose acetate discs was negative (less than a Turner fluorometer reading of 50) in 276 normal sera from tuberculin negative individuals.

In 24 sera from tuberculoid leprosy patients, 18 were negative and 6 had a fluorescence between 50 and 100. In 420 sera from lepromatous patients, 310 gave a reading greater than 100; 68 with a fluorescence between 50 and 100, and only 42 with less than 50.

2. The reproducibility of the reaction was verified by repeating the test in 30 discs with the same negative serum; of these 30 discs, 3 produced fluorescence greater than 100 and 27 showed readings less than 50. In 30 discs of known positive leprosy serum, 24 fluoresced between 300 and 500, 2 had values of 200, and 4 produced fluorescence greater than 500.

3. Those antigens which inhibited the Rubino reaction produced greater fluorescence than those that did not, either when they are impregnated directly on the discs or when serum was added first.

4. The sera of lepromatous leprosy produced high values of immunofluorescence with antigens of actinomycetales, whether or not inhibiting the Rubino reaction, which were significantly higher than the values obtained with sera from tuberculoid leprosy.

5. No observation was made of any constant relationship between the capacity of antigens to inhibit the Rubino reaction and their precipitation in gel by the antileprosy sera.—(*Adapted from* authors' English summary)

Antia, Noshir H. and Pandya, Narendra J. Qualitative histology and quantitative bacteriology in various tissues of 50 leprosy patients. Lepr. Rev. **47** (1976) 175–183.

Fifty patients (45 males and 5 females) from different parts of the leprosy spectrum and at various stages of the disease and its treatment, were examined both by multiple skin smears, nasal scrapings and also by qualitative histology and quantitative bacteriology of skin, dartos muscle, lymph node, nasal mucosa, muscle and nerve. A total of 797 tissues were studied by histology as well as homogenization.

Our study revealed that the qualitative involvement and quantitative bacillary load in the nerves was highest of all the tissues examined. A high incidence of *M. leprae* in the nerves of tuberculoid patients (40%) as opposed to other tissues—skin (7%), dartos (8%), nasal mucosa (7%), lymph node (7%), voluntary muscle (0%) was also observed. The nerve was also found to be a major and the most important reservoir of *M. leprae*. Scrotal skin biopsy was shown to be a suitable and practical site for diagnosis of leprosy. A smear obtained from the homogenate of the scrotal skin can be a useful investigation when histologic facilities are not available. The findings of histology and homogenization correlate fairly well except in the skin where homogenization (24%) was better than histology (18%) for detection of bacilli. Nasal mucosa had a similar bacillary load while the lymph node showed a higher load. The importance of voluntary or involuntary muscle (dartos) as a reservoir of *M. leprae* was not borne out in our study.—Authors' Abstract

Backe, J. T., Charlesworth, E. N. and Garcia, R. L. IgM deposits in tuberculoid leprosy. Arch. Dermatol. **112** (1976) 557–558. (Letter to Editor)

Deposition of IgM has recently been demonstrated at the dermoepidermal junction in lesions of lepromatous leprosy by means of immunofluorescence microscopy (Bullock *et al,* 1974 and Quismorio *et al,* 1975). We wish to report what we believe to be the first demonstration of IgM in a lesion of tuberculoid leprosy.

Report of a case. A 42-year-old man had two gradually enlarging, annular, slightly scaly plaques with hyperpigmented borders

on his left thigh and right ankle of six months' duration. These lesions were devoid of hair and anesthetic to soft touch, pain, heat, and cold. A biopsy specimen, on routine staining with hematoxylin-eosin, showed a granulomatous infiltrate composed of epithelioid cells with a few giant cells and many lymphocytes. In some areas the infiltrate invaded the epidermis, and invasion of nerves was seen in the dermis. An acid-fast stain demonstrated no bacilli.

Involved skin was also examined with the use of direct immunofluorescence microscopy, and granular deposits of IgM were found in the tips of the dermal papillae in an irregular linear pattern. Examination for IgG, IgA, complement, and fibrinogen gave negative findings.

The patient was placed on a regimen of dapsone therapy (presently 200 mg per week) with a resultant gradual reduction in the size of his lesions over the past six months.

Comment. Further investigation of patients with both lepromatous and tuberculoid leprosy is in progress by our group. These studies use immunofluorescence technics to determine if a specific *in vivo* or *in vitro* immunoglobulin exists in the skin and serum of these patients.—Authors' Letter to Editor

Bjune, G., Barnetson, R. St.C., Ridley, D. S. and Kronvall, G. Lymphocyte transformation test in leprosy; correlation of the response with inflammation of lesions. Clin. Exp. Immunol. **25** (1976) 85–94.

Lymphocyte transformation tests (LTT) using "whole washed" and "sonicated" preparations of *Mycobacterium leprae* as antigen were studied in 81 patients with borderline leprosy. The results were correlated with the histologic and clinical pictures.

There was a good correlation with the histologic spectrum, LTT responses generally being higher in the borderline tuberculoid leprosy patients and lower in the borderline lepromatous. However, considerable variation was noted in each group of the borderline leprosy spectrum, and it was found that this was due in part to the degree of inflammation in the skin. Thus, those with "inflamed" skin lesions had higher responses than those with "silent" lesions, and even those with borderline lepromatous leprosy with inflamed lesions had higher responses than those with borderline tuberculoid leprosy whose lesions were silent. Those who had reversal reactions, where inflammation is very marked, had very high LTT responses which fell with treatment of the reaction with steroids.

It thus appears that the LTT in leprosy is influenced by the occurrence of hypersensitivity reactions as well as by the patient's ability to resist bacillary multiplication.—(*From* Trop. Dis. Bull.)

Chatterjee, Animesh. Melanocytic activity in leprosy lesions with special reference to cellular infiltrate. Lepr. India **48** (1976) 142–148.

To assess the correlation, if any, between the clinical hypopigmentation in leprosy-affected skin and the inflammatory cellular infiltrate in dermis, skin tissue sections from the maculoanesthetic and tuberculoid lesions of 50 cases were studied with DOPA and H & E stains. The results indicated: 1) a proportionate lack of DOPA oxidase activity in the hypopigmented leprosy lesions in commensuration with the relative degree of clinical hypopigmentation; and 2) that the cellular infiltrate is not related to the clinical hypopigmentation or DOPA oxidase activity.—(*Adapted from* author's summary)

Ganapati, R. and Chulawala, R. G. Bacteremia in leprosy and its relation to distribution of *M. leprae* in skin. Lepr. India **48** (1976) 42–47.

Evidence of bacillemia through examination of heparinized blood smears was obtained in 17 of 20 cases (85%) of untreated leprosy cases belonging to the spectrum ranging from BT to LL. Among 17 cases whose blood smears were positive for AFB, the endothelial cells of blood vessels in skin lesions showed AFB in 11 instances (64.7%), and in 7 (41.2%) of these cases biopsies obtained from apparently normal skin also showed bacilli in the blood vessels. The fact that blood smears may show AFB even in patients belonging to types classifiable as BT-BB in the Ridley-Jopling scale (a child of 3½ years showed this feature) emphasizes the importance of investigations to assess thoroughly the extent of bacillation in leprosy patients.—Authors' Summary

Hartman, A. DNCB—reactivity in patients with leprosy in Kenya. Lepr. Rev. **47** (1976) 193–199.

Sensitization followed by graded challenges of dinitrochlorobenzene (DNCB) were performed in 105 leprosy patients (Bantu) in Kenya (22 tuberculoid, 53 borderline and 30 lepromatous). The results were compared with those obtained in a group of 38 relatives (index cases 5 lepromatous leprosy patients) and in a group of healthy controls (no known household contact with leprosy). All patients showed a diminished DNCB reactivity as compared to healthy controls. In the group of relatives of lepromatous leprosy patients no decrease of DNCB reactivity (as compared to local controls) was observed.

The percentage of DNCB reactors in healthy controls in Africa proved to be significantly lower than the percentage of DNCB reactors in healthy controls of Caucasian and Negro ancestry in Holland. The factors possibly influencing these results are discussed.—Author's Abstract

McDougall, A. C. and Salter, D. C. Thermography of the nose and ear in relation to the skin lesions of lepromatous leprosy, tuberculosis, leishmaniasis, and lupus pernio. J. Invest. Dermatol. **68** (1977) 16–22.

The nasal and aural temperature patterns of 100 normal subjects have been investigated by infrared thermography, paying particular attention to possible errors of instrumentation and technic which may arise in such areas of complex morphology.

Although by no means invariable, the pattern of thermograms confirms that certain areas which are relatively cool are often affected in lepromatous leprosy, tuberculosis, leishmaniasis, and lupus pernio. In lepromatous leprosy, low temperature appears to govern the localization of disease in most parts of the body, and the possible reasons for this are discussed. Thermography may have a place in the investigation of other skin diseases in which the distribution of lesions on the body surface is unexplained.—Authors' Abstract

Mehra, N. K., Dasgupta, A. and Vaidya, M. C. An evaluation of the immune state in leprosy. Lepr. India **48** (1976) 231–237.

An evaluation of the immune state in leprosy was done by the application of a system of graft-versus-host reaction. Peripheral blood lymphocytes obtained from patients with different forms of leprosy and from normal healthy individuals were injected intravenously into irradiated mice. The rate of blast transformation of the donor cells was measured by the radioactive thymidine uptake. The number of cells labeled with tritiated-thymidine was much higher in the normal individuals and in patients with tuberculoid leprosy than in the patients with lepromatous leprosy, with the borderline group falling between the two. However, following successful treatment with DDS, an increased responsiveness and active DNA synthesis could be observed in the previously less responsive lepromatous lymphocytes.—(*Adapted from* authors' summary)

Moreno, A. N., Gago, I. S., Romero, A. C. and Molina, M. L. Lepra de Lucio. [Lucio leprosy.] Actas Dermosifiliogr. **67** (1976) 31–36. (In Spanish)

We report one case of Lucio leprosy which represents one type of leprosy reaction. This disease has a very bad prognosis and is an unusual manifestation characterized by nodulation and ulceration. There are practically no subjective sensations. *Mycobacterium leprae* was constantly present in the ulcerations. The histopathology is characterized by vasculitis. The paper includes nice color photographs.—(*Adapted from* authors' English summary)

Rea, T. H., Quismorio, F. P., Harding, B., Nies, K. M., Di Saia, P. J., Levan, N. E. and Friou, G. J. Immunologic responses in patients with lepromatous leprosy. Arch. Dermatol. **112** (1976) 791–800.

Immunologic responses were measured in 46 patients with lepromatous leprosy. These patients were not distinguishable from controls on the basis of responses to soluble intradermal antigens, sensitization to contactants, peripheral blood T and B cell percentages, *in vitro* lymphocyte responses to a mitogen, or the prevalence of autoantibodies. Generalized immunologic abnormalities in patients with lepromatous leprosy are neither predisposing causes nor necessary accompaniments of lepromatous leprosy, but are probably remote sequellae of the illness. By

implication, the generalized immunologic abnormalities reported in other diseases are likely to be remote sequellae of the particular illness.—Authors' Abstract

Saha, K., Mittal, M. and Maheswari, H. B. Passive transfer of immunity in leprosy patients by transfusion of lymphocytes from lepromin positive healthy donors. J. Indian Med. Assoc. **66** (1976) 93–101.

Four hundred million viable lymphocytes from the peripheral blood of healthy tuberculin and lepromin positive individuals were transfused into five patients with leprosy [three lepromatous (LL), one borderline lepromatous (BL) and one borderline tuberculoid (BT)], all in a reactive condition and all negative to lepromin and normal lymphocyte transfer tests. Three transfusions were given at monthly intervals. Reactive episodes followed each transfusion in all cases, but definite bacteriologic and histologic improvement was observed in four of the five patients; clinical improvement was also witnessed, most marked in the BT and BL patients. In repeat immunologic assessment in three patients five months later, the only change observed was that the BL patient developed a positive Fernandez reaction.—T. F. Davey (*From* Trop. Dis. Bull.)

Saint-Andre, P. La stimulation de l'immunité à médiation cellulaire dans la lèpre lépromateuse: état actuel du problème. [A survey of the stimulation of cell-mediated immunity in lepromatous leprosy.] Med. Trop. (Mars) **36** (1976) 80–85. (In French)

Lepromatous leprosy is caused by a deficiency in cell-mediated immunity (CMI) and recent advances in CMI are reviewed by the author. He, then, considers the best tactical approach for antileprosy action and he favors the stimulation of CMI associated with chemotherapy: injections of leucocytes, the use of transfer factor, unspecific stimulations by BCG, various bacterial lysates and Levamisole (original experiments).

The author emphasizes a new antileprosy procedure beginning with rifampicin (900 mg a week for the first two months) then CMI stimulation associated with chemotherapy.—(*From* Trop. Dis. Bull.)

Saint-Andre, P., Louvet, M., Giraudeau, P. and Schlech, B. Effets de la stimulation de l'immunité cellulaire par les lysats et extraits bactériens dans la lèpre lépromateuse. [Results of the stimulation of cell-mediated immunity in lepromatous leprosy by bacterial lysates and extracts.] Med. Trop. (Mars) **36** (1976) 137–145. (In French)

The authors attempted to stimulate cell-mediated immunity in leprosy patients by giving them a series of injections (every other day) of a glycocolic lysate of *Neisseria perflava* (Ducton), an agent that nonspecifically accelerates phagocytosis of carbon particles in the experimental animal.

In three of the seven patients with lepromatous leprosy, treatment was abandoned after 7 to 12 months in the absence of improvement. In two others, however, rapid improvement was noted for 18 months but relapse followed. In the sixth patient, rapid and sustained improvement occurred and the Mitsuda test became positive. The variable and unpredictable results are attributed to differences in the potential for cell-mediated immunity. In three patients with borderline leprosy, improvement in the clinical state and in signs of nerve damage was thought to be due to the treatment given. Moreover, the improvement was maintained for 21 months.

A mixture of bacterial lysates intended to stimulate local rhinopharyngeal defense mechanisms against infection (Stimugène) was given to nine patients suffering from lepromatous leprosy. Sublingual and injectable preparations were used. The results as demonstrated by improvement in lesions in the nasopharynx (rhinitis and epistaxis) and the skin were "astonishing," and the authors consider that they were at least as good as those achieved by standard chemotherapy. The histopathologic and bacteriologic results were thought to be equally satisfactory. The injectable form of the product had a more rapid action than that administered sublingually.

[This novel form of attack deserves further critical evaluation in a larger series of patients, and its long-term effects on the disease and lymphocyte activity should be more precisely determined.]—S. G. Browne (*From* Trop. Dis. Bull.)

Saint-Andre, P., Louvet, M. and Schlech, B. Stimulation de l'immunité à médiation

cellulaire par le BCG dans la lèpre lépromateuse et intérmediaire. [Stimulation of cell-mediated immunity by BCG in lepromatous and borderline leprosy.] Med. Trop. (Mars) **36** (1976) 133–136. (In French)

This interim report continues the previous work of the authors. Their original posology is now modified and they give progressively increasing doses of BCG, intradermally, beginning with 0.1 ml of 1 in 100 dilution. This dose is increased every fortnight, until a maximum of 0.1 ml of a 1 in 10 dilution is attained. The injections were well tolerated, except that necrotic nodules developed at some injection sites in all the patients.

The authors concluded that acceptable degrees of stimulation of cell-mediated immunity had been demonstrated in all patients. In seven suffering from polar lepromatous leprosy, the Mitsuda reaction became positive clinically, but histopathologic examination revealed a predominantly borderline response. In six patients with borderline leprosy, there was rapid clinical and bacteriologic improvement, even of signs of nerve damage in four out of five patients. In two patients with lepromatous leprosy out of a total of ten treated with BCG, *erythema nodosum* of moderate severity occurred.

It is concluded that the clinical improvement noted was more rapid than that observed when dapsone alone is given, and that further investigations are indicated. [See Trop Dis. Bull. **73** (1976), abstract 1815.]—S. G. Browne (*From* Trop. Dis. Bull.)

Shanker, A., Gupta, S. B. and Sharma, J. N. A study of serum and skin zinc in leprosy. Indian J. Dermatol. Venereol. Leprol. **42** (1976) 258–260.

Serum and skin zinc values were determined in 50 cases of leprosy and 50 normal healthy controls (25 male, 25 female) of various age groups. The "Dithizone extraction" method of Vallee and Gibson (1948), as modified by Vallee and Hock (1949), was followed in this study.

The mean value of serum zinc in healthy individuals was 105.78 μg with S.D. 7.47 (range 88–123). The mean value of serum zinc in leprosy patients was 91.20 μg with range 79–104 μg. Serum zinc is significantly reduced in all types of leprosy as compared to healthy controls.

The mean value of skin zinc in healthy individuals was 83.24 μg with range 68.93 μg. The mean value of skin zinc in leprosy patients was 84.90 μg, the range being 72–97 μg. No significant difference was found in skin zinc in leprosy patients and in healthy controls.

Presence or absence of trophic skin ulcerations did not affect serum and skin zinc levels. There is no significant change in values of serum/skin zinc after 90 days of initial therapy in leprosy patients.—(*Adapted from* authors' summary)

Skinsnes, Olaf K. and Matsuo, Eiichi. Hyaluronic acid, β-glucuronidase, vitamin C and the immune defect in leprosy. Int. J. Dermatol. **15** (1976) 286–289.

Observations are made leading to the hypothesis that the bacilli in leprosy are in competition with macrophage enzymes for nutrient acid mucopolysaccharide and that in tuberculoid leprosy this competition is detrimental to the pathogens whereas in lepromatous leprosy the absence of macrophage β-glucuronidase is conducive to bacillary proliferation. The lepromatous defect may reflect a macrophage carbohydrate metabolic defect which is not evident as a general metabolic deficiency disease since β-glucuronidase is present in lepromatous serum and other tissues. Moreover, it is possible that this macrophage defect is also reflected in an inability to adequately break down bacillary components with the resulting formation of insoluble polysaccharide/lipid complexes and the continuing presence of polysaccharide antigens, which in the tuberculoid patients are rapidly metabolized.—(*From* authors' text)

Talwar, G. P., Hanjan, S. N. S., Mehra, V. L. and Kidwai, Z. Lack of interaction of circulating T cells with phytohemagglutinin in bacillary positive untreated lepromatous leprosy patients—identification of subpopulation of lymphocytes by shifts in electrophoretic mobility. J. Immunol. **118** (1977) 242–247.

Incubation of human peripheral blood lymphocytes from normal healthy subjects with phytohemagglutinin (PHA), causes the reduction of the surface charge of a subpopulation of T cells by 1363 ± 242 e.s.u./cm^2. The affected subpopulation was predominantly the high charge-bearing cells identifiable

with early (10 minutes) rosette-forming cells with sheep erythrocytes. Purified lymphocytes obtained from untreated bacillary-positive, lepromatous leprosy patients contained high charge-bearing T lymphocyte subpopulation. However, incubation with PHA did not result in the shift of electrophoretic mobility of these cells, suggesting the absence of interacting sites for the mitogen on the surface of these cells. The absence of mitogen-interacting sites is not an inherent trait of leprosy patients; the surface charge of lymphocytes from dapsone-treated bacillary-negative subjects was reduced upon incubation with PHA. A close correlation was found between the number of cells whose charge alters on incubation with PHA and the transformation index obtained with this mitogen.—Authors' Abstract

Ward, P. A., Goralnick, S. and Bullock, W. E. Defective leukotaxis in patients with lepromatous leprosy. J. Lab. Clin. Med. **87** (1976) 1025–1032.

Serums from patients with lepromatous leprosy show a high incidence of a chemotactic inhibitor. This inhibitor acts directly on leukotactic factors (bacterial chemotactic factor, C3 fragment, and C5 fragment) to render the factors irreversibly inactive. Functionally, the inhibitor acts as a chemotactic factor inactivator. While normal serum shows no inhibitory activity under the conditions employed, inhibitory activity causing >30 percent reduction of the bacterial chemotactic factor was found in the serums from 14 of 19 patients with lepromatous leprosy. Although exceptions were noted, a correlation was found between the presence of the inhibitor and depressed skin reactivity to a series of antigens (lepromin, trichophytin, candida, PPD, and mumps antigen) used for elicitation of delayed-type hypersensitivity reactions. The presence in leprosy serums of this inhibitor may be responsible, at least in part, for some of the defects of cellular inflammatory responses in patients with lepromatous leprosy.—Authors' Summary

Microbiology

Hirata, Tsunehiko and Nakayama, Tetsu. Cytomorphologic study of leprosy bacilli in the host cell. Lepro **44** (1975) 163-176. (In Japanese)

Electron microscopy studies on the cellular organelles of *M. leprae* were done in a comparative cytomorphologic method. Outlines of the main subjects are briefly described:

1. *Peripheral parts of the bacilli.* The peripheral parts of the bacilli were divided into three layers: a) the capsular structure, b) the cell wall, and c) the cytoplasmic membrane. The capsular structure of *M. leprae* was thinner than that of *M. lepraemurium.*

2. *Intracytoplasmic organelles.* In cytoplasm of the bacilli, two kinds of organelles—the intracellular membranous organelles (mesosomes) and the electron-dense or -homogenous granules, were typically found.

3. *Cell division process.* In active bacilli, the mesosomes were generally observed at or near the cell division site, and they seemed to play a significant role in the cell division process.

4. *Other organelles in the lepra cell.* The large electron-dense and -homogenous bodies were found outside the bacilli, and in these bodies the small electron-dense granules were observed. It was assumed that these bodies originated from the bacilli and the "L-form theory" or "life cycle hypothesis" was adopted for explaining their existence and organization. Further investigation should be made in the future on this problem.—(*Adapted from* authors' English summary)

Hirata, Tsunehiko and Nakayama, Tetsu. Cytomorphologic study on *M. leprae* inoculated and grown in the mouse foot pads. Lepro **44** (1975) 177-186. (In Japanese)

Dynamic investigations of *M. leprae* inoculated and grown in mouse foot pads were studied in the cytomorphologic method at the ultrastructural level.

In the experimentally infected mouse foot pads, the large electron-dense and homogenous-bodies were frequently found outside the bacilli, and the small electron-dense

granules were observed in these bodies. These observations might show the pleomorphism of *M. leprae,* and the L-form theory was adopted for explaining the existence of the granules mentioned above. These bodies and/or granules were never found in normal mouse foot pads.—(*Adapted from* authors' English summary)

Kato, L., Adapoe, C. and Ishaque, M. The respiratory metabolism of *M. lepraemurium.* Can. J. Microbiol. **22** (1976) 1293-1299.

The respiratory metabolism of *M. lepraemurium* isolated from Sprague-Dawley rats' lepromata using several substrates was investigated. None of the intermediates of the glycolysis cycle as well as of the tricarboxylic acid cycle except succinate was oxidized by purified whole suspensions of *M. lepraemurium.* Likewise, many sulfur compounds such as cystine, thiourea, thioacetate, thiodiglycol, mercaptosuccinate, and mercaptoethanol were inactive. However, yeast extract and some sulfhydryl compounds, e.g., cysteine, dithioerythritol, dithiothritol, and penicillamine were readily oxidized by murine bacillary suspensions, whereas thioglycolate, thioglucose, and reduced glutathione were oxidized at a slow rate. Succinate was not or was very poorly oxidized by normal cells probably because of impermeability of the cell wall, but the addition of succinate to the cell suspensions frozen for 1 minute at –40° C considerably enhanced oxygen uptake over the endogenous value. The oxidation of succinate was unaffected by inhibitors rotenone, atabrine, and amytal but was markedly inhibited by thenoyltrifluro-acetone, antimycin A, 2-*N*-heptyl-4-hydroxyquinoline-*N*-oxide, and cyanide. The thiol-binding agents, *p*-hydroxymercuribenzoate and *N*-ethylmaleimide were also effective inhibitors of succinate oxidation, but the process was not affected by uncouplers dinitrophenol, dibromophenol, pentachlorophenol, and carbonylcyanide-*m*-chlorophenylhydrazone. The results indicated that succinate oxidation by *M. lepraemurium* was mediated by oxidative enzymes involving an electron transport chain with oxygen as the terminal electron acceptor.—Authors' Abstract

Olitzki, A. L. The effect of dioxyphenylalanine (DOPA), amides and some potential sources of energy on the multiplication of *Mycobacterium leprae.* Boll. Ist. Sieroter. Milan. **55** (1976) 110-119.

The multiplication of two of three *M. leprae* strains on a medium containing substances from digested nonacid-fast microorganisms or even free of them was significantly promoted by D-3.4-dihydroxyphenylalanine (DOPA).

The following organic substances exerted growth-promoting effects on several strains: 0.02-0.10% concentrations of succinate > fumarate > α-ketoglutarate and acetate > glycerol; 0.2% concentrations of citrate and pyruvate > isonicotinamide and benzamide > lecithin; 0.5% concentrations of oleate > cytrate > pyruvate > acetate > fumarate succinate; 5.0% concentrations of butanol and butandiol > propanol > sorbitol > ethanol.

However, these effects were variable and strains of various origins acted differently.

On media containing DOPA, malachite-green (MG) and at least 0.12×10^6 microorganisms/ml the following oxidation-reduction reaction was observed: DOPA was oxidized to a brown compound and malachite-green reduced to an almost colorless product. Consequently, the blue color of the cultures turned from blue to brown. This DOPA-MG reaction and the inability to grow on conventional media were used for the identification of ten cultures (inocula directly from patients) as *M. leprae,* while a DOPA-MG negative patient strain grew on media employed for cultivable mycobacteria and was not identical with *M. leprae,* as proved by the foot pad test in mice.—Author's Summary

Experimental Infections

Brown, I. N. and Draper, P. Growth of *Mycobacterium lepraemurium* in the mouse bone marrow: an ultrastructural study. Infect. Immun. **13** (1976) 1199-1204.

The ultrastructure of the mouse bone marrow during the first eight weeks after intravenous inoculation of animals with 10^9 *M. lepraemurium* is described. The bacteria

were almost exclusively in macrophages, which became converted to epithelioid cells after eight weeks, at which time they were very heavily infected. The nature of the exceptionally rapid increase in numbers of bacteria in the bone marrow compared with other tissues early in the infection is discussed. It is concluded that a short doubling time of bacteria situated in the marrow is a more probable explanation than recruitment from elsewhere in the animal.—Authors' Summary

Brown, I. N. and Krenzien, H.-N. Systemic *Mycobacterium lepraemurium* infection in mice: differences in doubling time in liver, spleen, and bone marrow, and a method for measuring the proportion of viable organisms in an inoculum. Infect. Immun. **13** (1976) 480-486.

Counts of acid-fast bacilli were made on homogenates of whole liver, whole spleen, and two femurs of CBA mice killed at various time intervals after intravenous infection with *Mycobacterium lepraemurium*. The growth curves so obtained showed that the bacillus multiplied faster in bone marrow than in liver or spleen. No evidence of redistribution during the early part of infection was obtained. The time of appearance of significant numbers of bacilli (10^7) in the bone marrow was used to make estimates of viability of *M. lepraemurium* suspensions. Several applications of the technics described are discussed.—Authors' Summary

Collins, Frank M. and Morrison, Norman E. Restoration of delayed hypersensitivity to sheep erythrocytes by thymosin treatment of T-cell depleted mice. Infect. Immun. **13** (1976) 564-568.

Calf thymosin was injected subcutaneously in daily doses of 0.1 to 3 mg for 12 to 15 days into adult thymectomized, irradiated, bone marrow-reconstituted (THXB) mice. Thymosin partially restored the ability of the T-cell depleted host to develop delayed-type hypersensitivity to sheep erythrocytes. The degree of restoration varied from 50% to 75% of control values. Thymosin treatment of normal mice potentiated the foot pad responsiveness to sheep erythrocytes by as much as 50% over that of untreated controls. The optimum dosage of thymosin seemed to be in the 200- to 500-μg range, and multiple injections were essential for a significant response. Twelve daily injections of 100 to 500 μg of thymosin restored T cell reactivity to the THXB mouse, but the responsiveness decayed relatively rapidly once the treatment was stopped. The restoration of immune responsiveness to sheep erythrocytes in T-cell depleted mice provides a convenient means of demonstrating activity in thymosin preparations *in vivo*.—Authors' Summary

Colston, M. J. and Hilson, G. R. F. Growth of *Mycobacterium leprae* and *M. marinum* in congenitally athymic (nude) mice. Nature **262** (1976) 399-401. [Correspondence]

Congenitally athymic (nude) mice were tested for susceptibility to infection with *Mycobacterium leprae* in the hope that they would provide a more convenient model for experimental infections of the lepromatous type. A previous attempt to infect nude mice (Prabhakaran *et al.*, Experientia **31** [1975] 784) had only been maintained for six months, which was regarded as insufficient. Thirty homozygous nude mice were inoculated in the foot pads with *M. leprae*, together with a group of heterozygous phenotypically normal littermates which were used as controls.

Survival of the nude mice was poor, but enhancement of growth in the two longest surviving mice at 266 and 322 days, by comparison with controls, was highly significant. In addition to the foot pad, significant numbers of bacilli were found in the liver ($10^{5.6}$) and spleen ($10^{5.3}$), and scanty bacilli were found in testes, nose, tail and forepaw. In another experiment, enhancement of growth of *M. marinum*, which does not curtail survival of nude mice, was even more convincing. If the problem of survival could be overcome, nude mice might provide a very useful model for leprosy.—D. S. Ridley (*From* Trop. Dis. Bull.)

Desikan, K. V. and Venkataramaniah, H. N. A modified method of harvesting *M. leprae* from foot pads of mice. Lepr. India **48** (1976) 157-162.

A modified technic of harvesting *M. leprae* from the foot pads of mice is described. The method is simple and takes less time than the conventional technics. The yield of bacilli is also better. No difficulties have been encountered in its application in these laboratories.

Seven experiments were conducted using Swiss albino mice inbred in our laboratory. In each experiment, two to five mice were used. Both of the hind foot pads of each mouse were inoculated with 7.5×10^5 *M. leprae*. Each experiment was conducted at a different sitting. The inoculum used in each experiment was different, being a part of the material processed for infecting the mice in other experiments. The soft tissues were collected separately from the right hind foot pad of each mouse by the conventional method described earlier, homogenized and suspended in 2 ml of Hanks balanced saline solution (BSS). The container was kept in ice. Eight circular smears were made on a clean glass slide using 0.005 ml of suspension measured with a micropipette. The material from the left foot pad was collected by the following modified technic. The foot was thoroughly washed with a detergent and rinsed in tap water. It was then cleansed with ethanol. All the digits were snipped and discarded. The remaining part of the foot was cut off just above the ankle joint and transferred to a sterile glass mortar kept in ice. It was minced thoroughly with a pair of scissors. The tip of the scissors was washed down with 1 ml sterile Hanks BSS. The material was homogenized in the fluid by gently triturating with a pestle. The suspension was then transferred with a Pasteur pipette to a sterile test tube kept in ice. The mortar and pestle were rinsed with 1 ml Hanks BSS and the entire fluid with the tissue particles was transferred to the same test tube. The contents of the test tube were thoroughly mixed with the Pasteur pipette and allowed to stand for one minute, at which time all the large particles settled down. The supernatant was transferred into another test tube. Smears for enumeration of bacilli in this fluid were prepared in the same way as for the material collected from the right foot pad. There would thus be eight slides with the smear (in an experiment using four mice), four slides containing material from the right foot pad and four slides containing material from the left foot pad. All of these slides were given code numbers by a person outside the laboratory. The slides were dried on a level platform under a 60 watt electric bulb for 30 minutes. They were stained by the Ziehl-Neelsen technic using the cold method. In each slide four smears were selected for the counting of bacilli. Their diameters were measured using the vernier scale on the stage of the microscope. Twenty random microscopic fields were examined in each smear using the oil-immersion objective. The same combination of ocular and objective was always used for all counts, the area of the microscopic field with this combination being calibrated earlier. The number of bacilli per ml of suspension (N) is calculated by the following formula: $N = \pi r^2 \frac{n}{a} \times 200$, where "r" is the radius of the circular smear, "n" is the average number of bacilli per microscopic field, and "a" is the area of the microscopic field. In order to find the number of bacilli per foot pad the figure has to be multiplied by two since 2 ml of the fluid has been used.—(*Adapted from* authors' article)

Fieldsteel, A. Howard and Levy, Louis. Dapsone chemotherapy of *Mycobacterium leprae* infection of the neonatally thymectomized Lewis rat. Am. J. Trop. Med. Hyg. **25** (1976) 854-859.

In order to learn whether the neonatally thymectomized Lewis rat (NTLR) infected with *Mycobacterium leprae* could serve as a model for chemotherapeutic studies in a situation resembling that found in human lepromatous leprosy, NTLR inoculated with *M. leprae* either locally or intravenously 9 to 16 months earlier were treated for from 1.5 to 8.5 months with dapsone (4,4′-diaminodiphenylsulfone, DDS) incorporated in the rat chow in the concentration providing the minimal inhibitory concentration of the drug for *M. leprae* and in the 100-fold larger concentration. NTLR were killed at intervals; the *M. leprae* were counted and passed to mice. Treatment with the smaller dosage of dapsone neither killed *M. leprae* nor reduced the number of organisms in the bacterial populations, whereas treatment with the larger dosage both killed *M. leprae* and reduced their numbers. The rate at which the organisms were killed (i.e., rendered noninfective for mice) was much the same as that in patients treated with dapsone in comparable dosage. The dead organisms were removed from the rat tissues at a faster rate than encountered in patients. The NTLR may indeed be suitable for chemotherapeutic studies relevant to man. In addition, the more rapid disappearance of dead *M. leprae* from the rat tissues may facilitate the study of treatment regimens designed to eradicate persisting viable organisms.—Authors' Abstract

Fieldsteel, A. Howard and Levy, Louis. Neonatally thymectomized Lewis rats infected with *Mycobacterium leprae:* response to primary infection, secondary challenge, and large inocula. Infect. Immun. **14** (1976) 736-741.

Several experiments were carried out to measure the ability of neonatally thymectomized Lewis rats (NTLR) to limit multiplication of *Mycobacterium leprae.* NTLR inoculated in one hind foot pad with 10^7 viable *M. leprae* and challenged in the other hind foot pad with 5×10^3 organisms simultaneously, or 120 or 180 days later permitted multiplication in both sites. By contrast, immunologically intact rats similarly inoculated did not permit multiplication from either inoculum. NTLR and immunologically normal BALB/c mice were equally susceptible to infection with *M. leprae,* in that multiplication occurred regularly in the foot pads of both species when inoculated with a bacterial suspension diluted to provide five organisms per foot pad. Finally, multiplication occurred when five viable *M. leprae* diluted with 10^7 heat-killed organisms were inoculated into the foot pads of NTLR. Although there was some evidence that NTLR are not completely immunosuppressed, NTLR appear to be capable of detecting much smaller proportions of viable *M. leprae* than can be detected by immunologically normal mice.—Authors' Abstract

Holmes, I. B., Banerjee, D. K. and Hilson, G. R. F. Effect of rifampin, clofazimine, and B1912 on the viability of *Mycobacterium leprae* in established mouse foot pad infection (39276). Proc. Soc. Exp. Biol. Med. **151** (1976) 637-641.

Continuous dietary administration of rifampin to mice with an established *M. leprae* foot pad infection reduced the bacillary solid ratio, with an estimated survival half-life of five to six days. In rifampin-treated immunosuppressed animals the survival half-life of solid bacilli, in the absence of host immunity, was 12-13 days. Clofazimine and B1912 produced a significant effect on solid ratio only after a lag period of apparently 100 days. The rate of action was considerably slower than that of rifampin. Intermittent (once monthly) administration of both drugs produced effects similar to those of continuous administration.—Authors' Summary

Kawaguchi, Y., Matsuoka, M., Kawatsu, K., Homma, J. Y. and Abe, C. Susceptibility to murine leprosy bacilli of nude mice. Jap. J. Exp. Med. **46** (1976) 167-180.

Comparative observations were made on the development of experimental murine leprosy in various inbred strains of mice, including nude mice having congenital thymic aplasia. The susceptibility of these strains of mice to murine leprosy bacilli was evaluated by the development of leproma at the subcutaneous infection site and also by the involvement of visceral organs.

Nude mice developed a much more severe disease than C3H which is the representative of the malignant type. Their high sensitivity was also demonstrated in the case of intraperitoneal infection.

The observations in nude mice and other mouse strains confirmed our concept that experimental mouse leprosy can be classified into three clinical types; benign, intermediate and malignant, and suggested that such mouse strain differences are related with their cell-mediated immunity.—Authors' Summary

Krushat, W. M., Schilling, K. E., Edlavitch, S. A. and Levy, L. Studies of the mouse foot pad technic for cultivation of *Mycobacterium leprae.* 4. Statistical analysis of harvest data. Lepr. Rev. **47** (1976) 275-286.

An analysis of data generated by harvests of *Mycobacterium leprae* from the foot pads of mice is presented. Acid-fast bacteria (AFB) were randomly distributed within the circles of a counting slide in fewer than half of the preparations; the AFB were more likely to be distributed randomly in those preparations containing fewer organisms. The mean coefficient of variation

$$100 \times \frac{\text{standard deviation}}{\text{mean}}$$

of the number of AFB was 29% for the three circles on a counting slide, 60% for the four foot pads normally pooled for a harvest, and 48% for harvests from four replicate pools of four to eight foot pads. The doubling time of *M. leprae* during logarithmic multiplication in mice averaged 10.7 days, confirming an almost identical estimate made in an earlier study by a different technic. Finally, multiplication of *M. leprae* was found to be a little slower in mice inoculated in both hind foot pads than in mice inoculated in only one.

This analysis confirms the precision of data generated by work with Shepard's foot pad technic. Except for the case of foot-by-foot harvests, differences among measurements equivalent in time or numbers of AFB to two doublings of *M. leprae* appear certainly to be meaningful.—Authors' Abstract

Levy, Louis and Merigan, Thomas C. Inhibition of multiplication of *Mycobacterium leprae* by polyinosinic-polycytidylic acid. Antimicrob. Agents Chemother. **11** (1977) 122-125.

Contrary to the results of an earlier study in which polyinosinic-polycytidylic acid [poly(I:C)] administered intraperitoneally to mice had no effect on multiplication of *Mycobacterium leprae* in the mouse foot pad, the local administration of poly(I:C) every 12 hours for 15 doses during logarithmic multiplication was found both to inhibit bacterial multiplication and to produce high tissue levels of interferon (IF). Local administration of poly(I) alone inhibited multiplication of *M. leprae* to almost as great a degree without at the same time producing a measurable IF titer in the foot pad tissues. Mouse IF and "mock" IF both inhibited bacterial multiplication to the same degree, but administration of only the former resulted in a measurable IF titer. Polyadenylic-polyuridylic acid administered locally neither inhibited multiplication nor induced IF; fetal calf serum, administered in the same concentration as found in the preparations of IF and mock IF, was modestly inhibitory, without inducing IF. Thus, the local administration of poly(I:C) appears to have inhibited multiplication of *M. leprae* independently of IF induction. —Authors' Abstract

Mehta, L., Shetty, V. P. and Antia, N. H. Study of early nerve lesions in mice in fected with *M. leprae*. Lepr. India **48** (1976) 31-35.

The present study is of quantitative histology in immunologically intact mice inoculated with *M. leprae*. A total of 12 sciatic nerves were studied. The fibers were grouped as large, medium and small. Initially, there was a loss of small-sized fibers. In the later stages there was involvement of all fiber sizes, and ultimately the Wallerian type of degeneration set in. The process of regeneration is more active than that of human leprosy of the tuberculoid type. This study adds a new dimension to the understanding of the pathogenesis of leprosy.—(*Adapted from* authors' summary)

Ulrich, M., Convit, J., Centeno, M. and Rapetti, M. Immunological characteristics of the armadillo, *Dasypus sabanicola*. Clin. Exp. Immunol. **25** (1976) 170-176.

The immunologic responses of the armadillo are of interest because of its susceptibility to generalized lepromatoid infection with *Mycobacterium leprae*. In this study, specimens of *Dasypus sabanicola* were found to have a typical mammalian distribution of lymphoid cells in thymus, spleen, lymph nodes and blood. Their complement was active in bactericidal, protozoan immobilization and hemolytic systems. Blood lymphocytes responded to phytohemagglutinin and to pokeweed mitogen. Sensitization with ovalbumin in CFA resulted in the production of circulating precipitins; strong Arthus reactions were detectable in the sensitized animals. Responses of cell-mediated immunity to DNCB and to *M. tuberculosis* were very discrete. Heat-killed *M. leprae* elicited granulomatous reactions characterized by microscopic necrosis, but without abundant lymphocytic infiltration; skin tests and lymphocytic transformation were generally negative in the animals injected with *M. leprae*.—(*From* Trop. Dis. Bull.)

Yoshinaga, Toshio. Studies on organ lipoid content of murine leprosy and experimental tuberculosis. I. The alteration in organ lipoid contents of murine leprous mice and rats. Lepro **44** (1975) 129-136. (In Japanese)

Organ lipoid contents of murine leprous mice and rats were compared, respectively, with those of normal cases. The results were as follows: 1) The content of organ triglycerides in murine leprous mice showed a decrease; 2) This decrease was remarkable in the spleen, liver and kidney; 3) The content of organ phospholipids in murine leprous mice generally showed an increase; 4) This increase was remarkable in the spleen, liver and kidney; 5) No clear alteration in the content of organ total cholesterol could be found in any organ of the murine leprous mice; 6) The tendency in the alteration of organ lipoid content by murine leprous rats was

almost similar to that in the previously mentioned mice cases, throughout triglycerides, phospholipids and total cholesterol.—(*Adapted from* author's English summary)

Epidemiology and Prevention

Chatterjee, B. R., Taylor, C. E., Thomas, J. and Naidu, G. N. Acid-fast bacillary positivity in asymptomatic individuals in leprosy endemic villages around Jhalda in West Bengal. Lepr. India **48** (1976) 119-131.

Three general surveys of a village population of 7,000 in a highly endemic area in Purulia District, West Bengal, have included clinical examination and earlobe skin snip examinations. Multiple between-survey follow-up examinations have also been conducted on both bacillary positives and clinical cases. In the general population 5.8% of the individuals showed bacteriologic positivity with a concentration technic for AFB without showing clinical signs of infection. During two years of observation, clinical leprosy was diagnosed in 13.6% of bacillary positives, in 4.8% of nuclear family contacts of clinical cases, and 2.3% of the rest of the general population of the villages.—(*Adapted from* authors' summary)

Koticha, K. K. and Nair, P. R. R. Anti-leprosy measures in Bombay, India: an analysis of ten years of work. Bull. WHO **54** (1976) 67-77.

Leprosy control measures adopted in Bombay consist of health education, case-detection, and treatment, and are carried out mainly by the Ackworth Leprosy Hospital and its subsidiary, the Greater Bombay Leprosy Control Scheme. Although the data collected on different aspects of leprosy during the ten-year period 1963-1972 are hospital-based and retrospective, their analysis provides a useful indicator of the possible situation in the field. Health education is provided by medical social workers, field staff, and physicians, and the significance of this activity in relation to early detection of leprosy is analyzed. It is shown, however, that case-holding is a more urgent priority than case-detection. Trials have confirmed the effectiveness of chemoprophylaxis with dapsone for contacts of infectious index cases in crowded households. Comparison of annual expenditure per outpatient in leprosy clinics with that for inpatients in a leprosy hospital demonstrates greater cost-effectiveness of outpatient treatment. Some practical recommendations are made for leprosy control—Authors' Abstract

Leiker, D. L. and Fischer, P. The incidence of leprosy between 1943 and 1973 in a hyperendemic area, before and after the introduction of leprosy control measures. Lepr. Rev. **47** (1976) 115-125.

A leprosy incidence study in a hyperendemic area (prevalence 7%) is presented, based on whole population surveys at intervals, and covering a period of 30 years (1943-1973). The effect of three measures, introduced at different times, segregation of patients, mass chemotherapy and BCG vaccination, was assessed.

In the period 1943-1952 segregation of a proportion of the infectious patients was the only control measure. It was found that the incidence of leprosy remained nearly stable. Apparently this measure was virtually ineffective. In 1950 sulfone treatment was introduced. All segregated patients were treated. After 1952 an intensive casefinding, mass treatment and caseholding program was implemented. In the period 1958-1960 a very marked decline in the incidence was found. The incidence decreased by 74%, as compared with the preceding three year period.

In 1957 a mass BCG vaccination campaign was carried out. The epidemiological data are not compatible with a spontaneous "natural decline." The decrease has to be ascribed to the control measures. If the mass treatment campaign alone was responsible for the decline in incidence one would expect a proportionally similar decline in the incidence of progressive forms of leprosy and of tuberculoid leprosy. It was found, however, that the decline in incidence of tuberculoid leprosy was much more marked and more sudden immediately following the BCG vaccination campaign. In 1958-1960 the incidence of B + L cases had de-

creased by 41% as compared with the preceding three year period, but the incidence of tuberculoid leprosy had decreased by 86%.

It is concluded that the decline of progressive forms of leprosy and a proportionally similar decline of tuberculoid leprosy was due to the mass treatment campaign, but that the BCG vaccination campaign had contributed additionally and significantly to the decline of tuberculoid leprosy. It is encouraging to learn from this example that with conventional leprosy control measures, provided that they are conscientiously applied, rapid and impressive results can be obtained. The leprosy case load was reduced to such low proportions that general basic health services should be able to cope with the remaining case load.—Authors' Summary

Nebout, Max. Le traitement ambulatoire des lépreux par la méthode de l'auto-traitement. Bilan d'une étude réalisée en République du Tchad de 1966 à 1973. [The ambulatory treatment of leprosy patients by the "self-treatment" method. A study conducted in the Chad Republic from 1966 to 1973.] Med. Trop. (Mars) **36** (1976) 147-152. (In French)

This enthusiastic and reasoned report provides an excellent summary of the author's program of "self-treatment." The accepted methods of control of leprosy in the West African countries that were formerly colonies of France consisted mainly of circuits maintained by motor vehicles and/or cyclists. Because of the small number of doctors (1 to 65,000 inhabitants), the inaccessibility of many of the villages, lack of credits, and relatively poor results of the leprosy program then in operation, a district in the Republic of Chad containing about 700,000 inhabitants was selected for the self-treatment trial.

A total of 18,412 leprosy patients in this population was placed under treatment. Clinical examinations were performed every six months by a competent team of medical auxiliaries headed by a doctor; the bacteriologic status was determined (skin smears being obtained from all patients suffering from infectious or potentially infectious forms of leprosy); adequate records were kept; the opportunity was taken for health education talks. The team visited the centers every three or six months to check the patients gathered by convocation and to distribute packets containing sufficient tablets for a daily dose of dapsone: the dose was 100, 50 or 25 mg, according to body weight. Each team was on the road for 20 days a month, covering an average of 500 km, and seeing about 60 leprosy patients a day.

At the end of seven years of effort along these lines, the prevalence of leprosy has fallen from 32 to 8 per 1,000 and the incidence from 0.8 to 0.1 per 1,000. A total of 24,418 patients have been discharged, disease arrested, and in 50% of the remainder the disease is no longer considered to be active. Useful comparative tables are included. [These impressive results in an area of high prevalence and a high proportion of tuberculoid and spontaneously resolving forms of leprosy, may not be automatically reproducible in other situations, but the principles of "self-treatment" merit further application and evaluation.]—S. G. Browne (*From* Trop. Dis. Bull.)

Other Mycobacterial Diseases and Related Entities

Dreisin, R. B., Scoggin, C. and Davidson, P. T. The pathogenicity of *Mycobacterium fortuitum* and *Mycobacterium chelonei* in man: a report of seven cases. Tubercle **57** (1976) 49-57.

The clinical records of seven patients referred to the National Jewish Hospital and Research Center over a six year period for evaluation of an abnormal chest x-ray and repeated sputum isolates of rapidly growing mycobacteria (Runyon's Group IV) were reviewed to determine the potential pathogenicity of these organisms. *Mycobacterium fortuitum* was isolated from five patients and *Mycobacterium chelonei* from two. Hemoptysis, cough and weight loss were prominent in six. Three had rheumatoid arthritis. Although two demonstrated cutaneous anergy, lymphocyte responsiveness to PHA was normal. PPD-F was not useful in skin testing or in the *in vitro* evaluation of lymphocyte function. Histologic examination of the lungs of two patients demon-

strated caseating granulomata. One patient died of massive pulmonary hemorrhage soon after initiation of therapy. Multi-drug treatment regimens generally resulted in progressive sterilization of the sputum and improvement in the appearance of the chest x-ray.

We conclude that some rapidly growing mycobacteria can cause potentially fatal cavitary lung disease and that intensive antituberculosis therapy may successfully alter its course.—Authors' Summary

Epners, Z. K. Differences in biochemical tests performed on photochromogenic mycobacteria isolated from human sources. Tubercle **57** (1976) 151-159.

The photochromogenic mycobacteria do not all belong to one homogeneous species. With a simple heat-stable esterase (HSE) test it is possible to divide photochromogenic mycobacteria into two groups: HSE-positive—strongly pathogenic strains; and HSE-negative—weakly pathogenic strains. HSE-positive strains are mostly associated with pulmonary disease. HSE-negative strains are seldom associated with pulmonary disease, but are often associated with renal disease. It is rather difficult to draw a clear dividing line between pathogenic and nonpathogenic photochromogenic mycobacteria; and such a distinction probably does not exist in nature.—Author's Summary