CURRENT LITERATURE

This department carries selected abstracts of articles published in current medical journals dealing with leprosy and other mycobacterial diseases.

General and Historical

Freilich, A. R. *Tzaraat*—"biblical leprosy." J. Am. Acad. Dermatol. **6** (1982) 131–134.

Tzaraat refers to a group of skin diseases that, according to the Old Testament, renders one ritually unclean. Analysis of the text reveals that there are four categories of lesions discussed. Each category has a primary lesion as well as specific secondary changes. The primary lesions include depigmented lesions on previously healthy skin, lesions on previously abnormal skin, lesions on areas of diffuse alopecia, and lesions of localized alopecia. It is unlikely that these diseases have a modern-day counterpart.—Author's Summary

Chemotherapy

Anderson, R. The immunopharmacology of antileprosy agents. Lepr. Rev. **54** (1983) 139–144.

Inadvertent immunological manipulation occurs during antimicrobial therapy of individuals with leprosy with possible development of adverse immunological reactions in some cases. This is due to the formation of immune complexes and loss of antigen-induced immunosuppression and occurs as a consequence of the antimicrobial activity of the drugs. Rifampin, dapsone and clofazimine may precipitate ENL and reversal immunity reactions by this mechanism. Dapsone-associated reactions may be intensified by the ability of the drug per se to potentiate PMN migration and T lymphocyte proliferation. Clofazimine, however, is immunosuppressive and may be useful in the control and prevention of such reactions while continuing to provide antimicrobial chemotherapy.—Author's Conclusions

Chemotherapy of non-lepromatous leprosy. Bull. WHO **61** (1983) 413–416.

The WHO Expert Committee on Leprosy, in its fifth report in 1977, recommended that patients with nonlepromatous leprosy should be treated with dapsone until their disease becomes inactive, and thereafter for a period of 1½ years. In most leprosy control schemes, however, the duration of treatment of nonlepromatous patients is significantly longer than this, and few such patients are released from treatment in less than five years. This is partly because the attainment of inactivity may be difficult to establish, leading over-cautious staff to prolong treatment unnecessarily.

There is no doubt that long-term monotherapy with dapsone is difficult for many patients to sustain; many do not complete the full course of therapy; many become irregular in their attendance at clinics, and others take their tablets irregularly even when they collect them regularly. In addition, because patients with nonlepromatous leprosy comprise 50%–80% of all leprosy patients, their prolonged treatment diverts scarce resources from the treatment of infectious lepromatous cases.

The WHO Study Group on Chemotherapy of Leprosy for Control Programmes, which met in Geneva in October 1981, expressed alarm at the increasing prevalence of acquired (secondary) dapsone-resistant disease among lepromatous patients, and the evidence of its transmission as revealed by the appearance of primary dapsone resistance among lepromatous patients, prov-

en by the mouse foot pad technique. Clearly, primary dapsone resistance will also occur among nonlepromatous patients. Although not readily proved, primary resistance to dapsone may be suspected in nonlepromatous patients who show little or no response to dapsone monotherapy. During this time, these patients may develop significant nerve damage, or new anesthetic skin lesions at important sites such as the hands, feet, or face. The Study Group considered it essential to treat nonlepromatous patients with a combination of drugs effective in patients infected with either dapsone-susceptible or dapsone-resistant *Mycobacterium leprae*. The regimen recommended was rifampin in six doses of 600 mg, given monthly under supervision, plus dapsone, 100 mg daily (unsupervised) for six months.

Previous studies of dapsone monotherapy of nonlepromatous patients have shown variable relapse rates. The great majority of relapses occur within the first four years after stopping treatment. The results obtained in two short-term trials of rifampin, with or without dapsone, in the treatment of nonlepromatous leprosy raised the possibility that courses of chemotherapy of shorter duration could result in an acceptably low cumulative relapse rate. Such chemotherapy should improve the patients' morale, encourage them to complete the course with good compliance, and, by reducing the work load of staff, enable health service personnel to concentrate on treating lepromatous patients. An accurate assessment of the proportion of nonlepromatous patients who can be cured within a relatively limited period of combined dapsone/rifampin treatment is therefore urgently required.

The Steering Committee of the Scientific Working Group on the Therapy of Leprosy has thus outlined a standard protocol for studies to identify a well-tolerated regimen of short duration that produces an acceptably low rate of relapse among nonlepromatous patients. The scheme envisages two phases to the trials: a six-month course of treatment, and a period of follow-up without treatment, during which relapse rates would be measured. The protocol gives details of selection of patients, examination during and after treatment, and the treatment regimens to be used.—(*From* the article)

Guelpa-Lauras, C. C., Constant-Desportes, M., Millan, J., Grosset, J., Giroir, A. M. and Perani, E. Résistance de *Mycobacterium leprae* aux sulfones (DDS) et à la rifampicine au cours de récidives de lèpre lépromateuse à la Martinique et à la Guadeloupe depuis février 1980. [Resistance of *Mycobacterium leprae* to sulfone (DDS) and rifampin during recurrences of lepromatous leprosy in Martinique and Guadeloupe since February 1980.] Acta Leprol. **86-87** (1982) 77–80. (in French)

The authors report a preliminary study showing the resistance of multibacillary leprosy patients to dapsone (DDS) and/or rifampin (RMP). Between February 1980 and October 1980, biopsies were made on multibacillary patients, whose disease had been known for 12–44 years, and inoculated into mice. Ten of these biopsies showed bacterial growth in mice and in only one case were the bacilli totally sensitive to DDS and RMP. The others were resistant to DDS: 2 had minimal resistance (growth at 0.001% w/w dietary dapsone), 1 had partial resistance (growth at 0.001% dapsone), and 6 had full resistance (growth at 0.01% dapsone). Three patients were resistant to DDS and RMP: 1 case with total resistance to RMP and full resistance to DDS, 1 case with an almost complete resistance to RMP and a minimal resistance to DDS, and 1 with a partial resistance to RMP and full resistance to DDS. This partial resistance seems real since the bacilli from the mice treated with RMP grew again in one mouse out of four in the presence of rifampin.

The authors conclude that the annual incidence of DDS resistance is at least 1.9% and they recommend the association of three antileprosy drugs (rifampin, DDS, and clofazimine or ethionamide or prothionamide) to prevent the development of resistance to the classical DDS and/or RMP therapeutic regimen.—(*Translated from* the article)

Pattyn, S. R., Carayon, A. and Van Droogenbroeck, J. Dose élevée unique de rifampicine dans la lèpre. Un avertissement. [Unique and high dose of rifampin in leprosy treatment. A warning.] Med. Afrique Noire **28** (1981) 777–778. (in French)

Since the publication of Levy, *et al.* (1976)

on the quick bactericidal activity of rifampin against *Mycobacterium leprae*, the administration of single high doses (1200 or 1500 mg) of this product in addition to the classical dapsone therapy has received great interest (Languillon, 1977). The hope with this treatment is to make the patient rapidly noncontagious and prevent the selection of dapsone-resistant *M. leprae*. The report shows what consequences such a treatment may induce. In May 1978, a patient treated for 18 years with dapsone came to the leprosy institute of Dakar (Senegal). He received 1200 mg of rifampin and returned to his home to continue his dapsone treatment. One year later, he returned to the institute with lesions which were still active. A biopsy performed and inoculated into the mouse foot pad showed an intermediate resistance to dapsone and no resistance to rifampin.—(*Translated from* the article)

Pearson, J. M. H. Dapsone-resistant leprosy. Lepr. Rev. **54** (1983) 85S–89S.

It is likely that in 1983 over 10% of patients with lepromatous leprosy will develop dapsone resistance; the primary resistance rate of new cases is probably about 25%. Patients with active dapsone-resistant leprosy who are still receiving only dapsone monotherapy may well form a larger source of infection than all other infectious cases. Supervisable and cost-effective drug regimens designed to prevent the emergence of dapsone resistance and to control the infectivity of dapsone-resistant cases deserve urgent consideration.—Author's Summary

Saint-André, P., Ferracci, C., Baquillon, G., Ridel, P. R. and Boucher, P. Traitement des érythèmes noueux lépromateux par le chloramphenicol—comparison avec la thalidomide. [Treatment of erythema nodosum leprosum with chloramphenicol—a comparison with thalidomide.] Acta Leprol. **84** (1981) 57–62. (in French)

The particularly quick action of thalidomide on ENL is almost always noticed except when there is a viral or microbial infection which induced the ENL and whose persistance reactivates it.

Chloramphenicol is less quickly active than thalidomide, but it is regularly efficient in 80% of the cases. Consequently, although thalidomide is the best therapeutic agent, chloramphenicol is an efficient substitute for ENL treatment in women of child-bearing age. It is easy to obtain when thalidomide may be difficult to get.

Finally, any microbial infection must be treated to obtain a total efficiency of thalidomide.—(*Translated from* Authors' Comments)

Saint-André, P., Ferracci, C., Ridel, P. R., Baquillon, G. and Boucher, P. Utilisation d'un immunomodulant, l'isoprinosine, dans la lèpre multibacillaire. Etude préliminaire. [Utilization of an immunomodulant (isoprinosine) in multibacillary leprosy. Preliminary study.] Acta Leprol. **86-87** (1982) 113–129. (in French)

In a preliminary comparative study with multibacillary patients, the authors employed isoprinosine, an immunomodulant drug, in an attempt to boost their deficient immunity. They report the remarkable activity of this drug, not only on some parameters of cell-mediated immunity measured with the macrophage inhibition test, but also on the clinical aspects of the lesions as well as on the Bacteriological Index. They discuss the possible mechanisms of its action and suggest its practical uses in therapy.—(*Translated from* Authors' Summary)

Shanghai Zhunyi Hospital, *et al.* Therapeutic study in leprosy. VI. Observation of the therapeutic effect of isobutylpiperazinylrifamycin. Chin. J. Dermatol. **16** (1983) 19–23. (in Chinese)

Nineteen multibacillary (LL or BL type) leprosy patients were treated with isobutylpiperazinylrifamycin (R-76-1) 150 mg daily for 6–18 months with a definite therapeutic effect as shown by the clinical assessments, skin smears and histologic studies. The improvement was more marked during the first six-month period than the second and third six-month periods with unknown reason. Mouse foot pad inoculations with serial skin biopsy specimens had been obtained from ten patients of this group. According to the THELEP protocol for drug resistance study, seven patients were fully resistant to dapsone and the other one was resistant to thiacetazone and thiambutosine. The estimated time of complete loss infectivity to mouse

foot pad after treatment ranged from 3.5–21 days and the median value was 7.25 days. Therefore, R-76-1 in small dosage had a rapid bactericidal effect against *Mycobacterium leprae* as well as to dapsone- or thioureas-resistant strains. Since the ENL episodes and adverse side effects induced by R-76-1 were not so serious as rifampin, it seems that R-76-1 is quite safe in the treatment of leprosy. Further clinical trials comparing the effect of R-76-1 with rifampin will be conducted in near future.—Authors' Abstract

Shepard, C. C., Van Landingham, R. M. and Walker, L. L. Recent studies of antileprosy drugs. Lepr. Rev. **54** (1983) 23S–30S.

As a part of the program of the WHO Therapy of Leprosy (THELEP) Scientific Working Group, a number of compounds with potential activity against *Mycobacterium leprae* were prepared in other laboratories. We report here the results of studies of their activity against *M. leprae* with the use of the kinetic method in mice. A modified protocol is described that facilitates comparison of drugs in the same experiment. Two analogues of cycloserine, glycylhydroxamic acid and beta-analylhydroxamic acid were inactive in a dosage of 0.1% in the diet. Isoetam, (D-2,2′-(ethylendiimino)-di-1-butanol)di-isoniazid methane sulphonate was also inactive at this dosage. Three compounds related to dapsone, 4-nitro-N′-phenylsulphonamide, 4-amino-N′-phenylsulphonamide, and 4,4′-diaminobenzene sulphonic acid phenyl ester, had little or no activity at dosages of 0.01% in the diet in experiments with strains shown to have normal susceptibility to dapsone. Two thiosemicarbazones, pyridinal-4-thiosemicarbazone and pyridinal-2-thiosemicarbazone, were inactive in dosages of 0.01%; the latter was inactive at 0.01% in an experiment where thiacetazone was shown to have bactericidal-type activity at a dosage of 0.1% and marginal activity at 0.01%. Brodimoprim, a dihydrofolate reductase inhibitor, which is related to trimethoprim but has a longer half-life, was inactive in a dosage of 0.1%; it had no synergistic effect with 0.01% dapsone against a dapsone-susceptible strain. It was also inactive against a dapsone-resistant strain, alone or in combination with dapsone. The cyanimino analogues of ethionamide and prothionamide were inactive in a dosage of 0.1% against an ethionamide-susceptible strain. Experiments with a series of compounds related to chaulmoogric acid were unsuccessful because the compounds were too toxic. Experiments with a series of compounds related to clofazimine were unsuccessful because their pharmacokinetics were unfavorable for study at dosages where clofazimine itself was active. The limitations imposed by the mouse foot pad system are discussed and related to those in other experimental systems.—Authors' Summary

Terencio de las Aguas, J. Poliquimioterapia en la lepra. [Polychemotherapy in leprosy.] Rev. Fontilles **14** (1983) 27–35. (in Spanish)

The importance of polychemotherapy in multibacillary leprosy (LL and BL), in patients without any previous therapy, as well as in those already diagnosed and under monotherapy, but most of all in the resistant patients, is presented. Sulfones, clofazimine, and rifampin are selected as first line drugs and prothionamide-ethionamide as second line drugs. The therapy plans with the association of two and three drugs and the convenience of continuing indefinitely with at least one of the drugs are presented, insisting on the advantages of the clofazimine-sulfones and rifampin-sulfones combinations. The necessity of immunotherapy for the recovery of cellular immunity against the bacillus is advocated as the only means of preventing relapses and drug resistance.—(*Adapted from* Author's Summary)

Clinical Sciences

Acharya, B. P. Clinical observation on iridocyclitis in leprosy patients. Indian J. Opthalmol. **33** (1982) 65–68.

A total of 7258 patients with iridocyclitis were seen from 1968 to July 1981 and recorded from coal field hospitals and Safdar-

jang Hospital, New Delhi, India; 715 patients with iridocyclitis following leprosy are discussed in detail. Blindness in 91 patients on account of leprosy was seen. Out of these 715 cases, acute iridocyclitis was seen in 168 patients and 547 cases were of chronic iridocyclitis.—Author's Summary

Alfieri, N., Fleury, R. N., Opromolla, D. V. A., Ura, S. and de Campos, I. Oral lesions in borderline and reactional tuberculoid leprosy. Oral Sur. **55** (1983) 52–57.

Thirty patients, 15 with borderline and 15 with reactional tuberculoid leprosy, were submitted to clinical and histopathologic studies of the buccal mucosa for detection of specific lesions. Five reactional tuberculoid and eight borderline patients presented specific conditions characterized by chronic granulomatous lesions with bacilli, chronic granulomatous lesions without bacilli, and nonspecific chronic inflammatory lesions with bacilli. The infiltrate had small extension, low bacterial levels and the mucosa, with the exception of one case, did not show ulceration. These results suggest that in the reactional tuberculoid and borderline patients the buccal mucosa is not an important source of bacilli elimination.—Authors' Abstract

Boerrigter, G. Grid system and body diagram for leprosy. Lepr. Rev. **54** (1983) 115–118.

Based to some extent on systems used for the charting of burns, multiple injuries and melanomas, a grid system and body diagram is described for the accurate charting of sites of skin smears in leprosy. It may, however, also be used for the recording of birthmarks, scars, "doubtful" skin lesions and sites from which biopsies have been taken, either in drug trials or for routine purposes. It is suggested that the combined use of a body diagram and a written record of the relevant grid space, using figures 1–10 and letters A–L, will increase the accuracy with which such sites are recorded. It could also be of value if data are to be analyzed by computer.—Author's Summary

Bonvoisin, B., Martin, J. M., Bouvier, M., Bocquet, B., Boulliat, J. and Duivon, J. P. Les manifestations articulaires de la lèpre. [Articular manifestations in leprosy.] Sem. Hop. Paris **59** (1983) 302–305. (in French)

Articular manifestations occur in approximately 1% of cases of leprosy, sometimes at onset. They consist of a highly inflammatory polyarthritis, fairly similar to that seen in rheumatoid polyarthritis. They often herald a reactive leprous exacerbation and are dependent upon immunologic disturbances in brittle leprosy (mainly lepromatous). Joint pain should be differentiated from neurologic pain resulting from peripheral neuropathy which is often concomitant. Leprosy should be considered among the causes of polyarthritis, especially in immigrants, but also in residents who have travelled to areas where leprosy is endemic.—Authors' Summary

Brandt, F. and Kalthoff, P. G. The incidence of lagophthalmus and posterior synechiae of the iris during chemotherapy of leprosy (morbus Hansen). Tropenmed. Parasit. **34** (1983) 75–78.

In the Green Pastures Leprosy Hospital in Pikhara, Nepal, 340 outpatients with leprosy were examined to evaluate the incidence of lagophthalmus and posterior synechiae of the iris. Patients who had already received chemotherapeutical treatment during the first five years following the onset of the disease developed fewer cases of lagophthalmus in both types of leprosy than patients who remained untreated for longer than five years. A comparable positive influence of early chemotherapy on the incidence of posterior synechiae of the iris could not be proven. The possible causes were discussed.—Authors' Summary

Caver, C. V. Rapid screening for leprosy. Hawaii Med. J. **41** (1982) 412–414.

Hawaii requires physicians applying for licensure to demonstrate a rudimentary knowledge of leprosy, and thus encourages detection, early initiation of treatment, and reduction of morbidity and disabilities. Most physicians pass this test, then relegate it to the back of their minds to be brought out only in rare instances. When the chance of finding a new case presents itself, the physician may find his knowledge of the disease

sadly lacking. This usually results in referral to a dermatologist or leprologist. Often, family members and other close contacts must be referred for examination. A rapid and simple procedure for screening these persons is outlined herein.—Author's Abstract

Chawhan, R. N., Sirdeshpande, S. H., Zawar, P. B., Sengupta, S. R. and Yemul, V. L. Alpha-1-antitrypsin in lepra reaction. J. Assoc. Physicians India **30** (1982) 75–77.

Estimation of alpha-1-antitrypsin (AAT) levels in the sera of 50 cases of lepra reaction and in 50 age- and sex-matched healthy individuals was carried out to determine its value in patients of lepra reaction. The AAT levels were found to be elevated in the cases under study. The mean level of AAT in healthy individuals was 285 ± 66.05 mg%; whereas in patients with type I reaction it was 332 ± 18.8 mg%, and in type II reaction the AAT value was 450 ± 73.7 mg%. The rise of AAT in patients with type II reaction was found to be statistically significant.—Authors' Summary

Goracci, G. and Colangelo, G. Considerazioni sulle manifestazioni oro-facciali della lepra nei casi osservati in Somalia. [Remarks on the orofacial symptoms of leprosy observed in Somalia.] Minerva Stomatol. **32** (1983) 1–5. (in Italian)

After a description of the major features of leprosy in the light of modern knowledge, orofacial aspects of the disease are described in detail with examples of cases observed in Somalia.—Authors' Summary

Ravettini, B. A., Capece, A. C. and Achenbach, R. E. Lepra lepromatosa en la infancia. (A propósito de las tres últimas observaciones.) [Lepromatous leprosy in children. (An account of the last three observations.)] Rev. Argent. Dermatol. **64** (1983) 133–142. (in Spanish)

Three cases of lepromatous leprosy in 11–12-year-old children are discussed. In light of the current literature the following aspects are analyzed: transmission mechanism, age, sex, clinical manifestations, bacteriology, histopathology and immunology. They presented different characteristics; one of them with reactive erythema nodosum. No prepuberal exacerbation was observed. The rare frequency of this form of leprosy during this period of life is pointed out.—Authors' Summary

Selliah, K. and Ayasamy, A. An unusual presentation of lepromatous leprosy. Med. J. Malaysia **37** (1982) 213–214.

The patient was a 60-year-old male referred by a dental surgeon with a diagnosis of squamous cell carcinoma of the cheek of six-months duration. Examination showed a nodule of 1 cm × 1 cm on the right cheek. Intraorally, the patient was edentulous and had an extensive granular ulcerative lesion involving the right lower mandibular alveolus, the buccal mucosa of the right retromolar region, and extending posteriorly to involve the pharynx. The lesion involved the right floor of the mouth, the right ventral surface of the tongue, and the posterior aspect of the right hard and soft palate. The entire ulcerated and granular area was red and covered with a slough, and was firm to palpation and slightly tender. The clinical appearance of the lesion was very suggestive of a squamous cell carcinoma. The submandibular glands on the right were enlarged and slightly tender. He had a peripheral neuropathy of both feet and a trophic ulcer on the middle of his left sole. A biopsy specimen was reported to be tuberculoid leprosy. The clinical impression of squamous cell carcinoma was so strong that a further two biopsies were performed and sent to two different pathologists. In both instances the pathologic diagnosis was compatible with tuberculoid leprosy. The patient had a past history of tuberculoid leprosy in 1947, and was hospitalized from 1947 to 1952. Since 1952 he had been followed as an out-patient for his tuberculoid leprosy. The patient was started on rifampin 600 mg daily and dapsone 100 mg daily and within two months the oral lesion had completely healed, leaving an atrophic scar. It was felt that, although the patient had been on treatment for tuberculoid leprosy since 1947, the occurrence of his oral lesion while still on therapy was probably the result of inadequate therapy and poor compliance.—(*Adapted from* the article)

Simone, C. and Racanelli, A. Osteosclerosis in leprosy. Ital. J. Orthop. Traumatol. **8** (1982) 211–219.

The literature contains little reference to the phenomenon of osteosclerosis in leprosy. The aim of the authors' investigations was to determine: a) the incidence of osteosclerosis as part of the radiographic picture in the distal extremities of the limbs, b) the pathological substratum, and c) the possible clinical significance.

The research was carried out on 233 leprosy patients at the Colonia Hanseniana di Gioia del Colle (Bari), Italy. The authors examined 260 radiographs of the hands and 1310 radiographs of the feet. A number of biopsy samples of bone were taken from four patients and examined by means of microradiography, using ultraviolet fluorescent light and also by historadiography.

The basic radiographic features indicative of osteosclerosis were: a) reactive osteosclerosis, b) sclerosing periostosis, and c) massive osteosclerosis. The authors observed a preponderance of osteosclerosis in the bones of the first digital ray, both in the phalanges and metatarsals or metacarpals. The sesamoid bones were affected more commonly in those of the first digit than those of the fifth.

The radiographic findings were confirmed microscopically. It is difficult to assess the possible clinical significance because of the transient nature of the osteosclerosis in the evolution of the lepromatous lesions with time.—Authors' Summary

Stevens, M. H. and Nielsen, D. R. Otolaryngologic manifestations of Hansen's disease. Otolaryngol. Head Neck Surg. **90** (1982) 544–547.

A Mexican migrant farm worker whose condition was previously undiagnosed was examined at the University of Utah Medical Center, Salt Lake City, Utah, U.S.A. He had an unusual peripheral neuropathy, ulcerative and nodular skin lesions, and multiple head and neck complaints. Results of the history, physical examination, and multiple biopsies led to the diagnosis of lepromatous leprosy. Although an uncommon disease in the United States, leprosy remains a common cause of head and neck pathologic conditions in many parts of the world and must be considered in the appropriate clinical setting.—Authors' Abstract

Subramaniam, K., Marks, S. C. and Seang Hoo Nah. The rate of loss of maxillary anterior alveolar bone height in patients with leprosy. Lepr. Rev. **54** (1983) 119–127.

Alveolar bone loss and periodontal status were measured radiographically and clinically in 22 patients with leprosy after a four-year interval. The average reduction in alveolar bone height in the anterior maxilla ranged from 0.09 to 0.13 mm per year, being lowest in patients with lepromatous disease. These results are similar to previous measurements of attachment loss, a comparable parameter, in Norwegian patients without leprosy who exhibit good oral hygiene and much better than Sri Lankan patients with poor oral hygiene similar to that found in these patients with leprosy. These data suggest that previous observations of increased alveolar bone loss in patients with lepromatous disease are the result of bone lost before treatment and that reduced bone loss in the presence of abundant dental plaque and poor oral hygiene may be related to immune dysfunctions in patients with leprosy.—Authors' Summary

Immuno-Pathology

Antia, N. H. and Nedugayil, K. Persistence of *Mycobacterium leprae* in the peripheral nerve. Indian J. Med. Res. **77** (1983) 420–422.

Thirty-two nerves were biopsied from leprosy patients undergoing surgery, who had been treated with dapsone (DDS) for a minimum period of four years. The homogenate of these nerves was inoculated into the mouse foot pad of non-immunosuppressed mice to assess the viability of *Mycobacterium leprae*. Only three lepromatous

patients showed a positive foot pad count.—Authors' Abstract

Bach, M. A., Hoffenbach, A., Lagrange, P. H., Wallach, D. and Cottenot, F. Mechanisms of T-cell unresponsiveness in leprosy. Ann. Immunol. (Paris) **134D** (1983) 75–84.

We analyzed the mechanisms of T cell unresponsiveness to *Mycobacterium leprae* antigens and to unrelated antigens or T cell mitogens in human leprosy and in an experimental model of murine infection by *M. lepraemurium* (Mlm). In human leprosy, monoclonal antibodies OKT3, OKT4 and OKT8 were used to enumerate T cell subpopulations within peripheral blood. Increased percentages of $OKT8^+$ cytotoxic/suppressor cells were observed in untreated, non-reactional lepromatous patients. Conversely, lepromatous patients suffering from erythema nodosum leprosum, an Arthus-like phenomenon, exhibited a transient drop in the percentage of $OKT8^+$ cells with a correlative increase in the proliferative response to T cell mitogens. We studied the proliferative response to *M. leprae* of $OKT4^+$ and $OKT8^+$ cells isolated by a negative selection procedure using antibody-induced cytotoxicity plus complement. None of these subpopulations proliferated when incubated with *M. leprae*. In some patients, control treatment of mononuclear cells with complement alone induced the reappearance of a strong proliferative response to *M. leprae*, suggesting the existence of an active suppressor mechanism through soluble factors of an unknown nature.

In Mlm-induced murine leprosy, a progressive decrease was observed in the proliferative response to concanavalin A (ConA), and an early decrease in Interleukin 2 activity in supernatants from ConA-stimulated spleen cells. Splenic T cells from Mlm-infected mice transferred into naive recipients accelerated the local Mlm growth in these recipients, suggesting that suppressor T cells may play a pathogenic role in the progression of Mlm infection.—Authors' Summary

Birdi, T. J., Mistry, N. F., Mahadevan, P. R. and Antia, N. H. Alterations in the membrane of macrophages from leprosy patients. Infect. Immun. **41** (1983) 121–127.

Macrophage cultures pulsed with viable *Mycobacterium leprae* were assessed for erythrocyte rosetting in three groups of individuals, i.e., normal subjects, and tuberculoid and lepromatous patients. Of these, only the lepromatous group showed a reduction in rosetting ability after infection with *M. leprae*. The specificity of such a reduction pattern was confirmed by using various mycobacteria to infect the macrophages. A threshold effect was noted in all three groups. Although a reduction was obtained in the amount of rosetting of macrophages from lepromatous patients with 10^4 acid-fast bacilli per culture, tuberculoid and normal macrophages resisted such an effect with as large a dose as 20×10^6–30×10^6 and 30×10^6 bacilli per culture, respectively. The *M. leprae*-caused alterations in macrophages from lepromatous patients were reversible by treatment with trypsin and colchicine. Cytochalasin B and Tween 80 were unable to alter the pattern. Treatment of cells with neuraminidase was inconclusive since it enhanced rosetting values of both control and infected cultures. These manipulations were significant in elucidating the target point of the host (macrophage) and parasite (*M. leprae*) interaction and in delineation of the external and internal effects upon the macrophages. Both *M. leprae* and macrophages were participants in Fc reduction, as treatment of the former with rifampin and of the latter with cycloheximide significantly augmented the rosetting ability. In conclusion, it appears that *M. leprae*, upon entering a lepromatous macrophage, initiates the production of a protein which acts via the microtubules to alter membrane topography. It is possible that the altered membrane prevents effective macrophage-lymphocyte interaction. This could be one of the mechanisms by which cell-mediated immunity is suppressed in lepromatous leprosy.—Authors' Summary

Cho, S.-N., Yanagihara, D. L., Hunter, S. W., Gelber, R. H. and Brennan, P. J. Serological specificity of phenolic glycolipid I from *Mycobacterium leprae* and use in

serodiagnosis of leprosy. Infect. Immun. **41** (1983) 1077–1083.

The serological activities of the specific phenolic glycolipid I from *Mycobacterium leprae*, its dissected parts, and related glycolipids from other mycobacteria were examined by enzyme-linked immunosorbent assay against hyperimmune anti-*M. leprae* rabbit antiserum and sera from patients with leprosy and other mycobacterial diseases. High anti-phenolic glycolipid I immunoglobulin M antibodies were found in 23 of 24 (96%) lepromatous leprosy patients on short-term chemotherapy and in 8 of 13 tuberculoid leprosy patients (62%). Sera from patients with tuberculosis or atypical mycobacterial infections were devoid of anti-phenolic glycolipid I activity. The structurally related phenolic glycolipids from *M. kansasii* and *M. bovis* and the aglycone segments of the *M. leprae* product showed no significant activity. Thus, the trisaccharide determinant of phenolic glycolipid I is specific in its structure, serological activity, and, to a lesser extent, the antibody class it evokes.—Authors' Abstract

Deo, M. G. "Pro-eu-karyote" graft acceptance: A mechanism for intracellular parasitism—a new hypothesis for pathogenesis of leprosy. Med. Hypotheses **8** (1982) 287–295.

The capacity to recognize "self" and "non-self," that is present even in unicellular organisms, plays a key role in biological evolution and maintenance of species. As soon as lymphocytes made their appearance in phylogeny, they became an integral part of the process of rejection of foreign grafts. A number of vertebrates also possess a well-defined system of tissue histocompatibility antigens that determines the degree of foreignness in grafted cells. It is well established that donor cells could only survive if they are accepted as "self" by the recipient. This concept is now extended to interaction of prokaryotes (microbes, protozoa, etc.) with mammalian cells. It is hypothesized that intracellular parasites survive and multiply only in those cells which recognize them (parasites) as "self." Once a parasite enters the susceptible cell, a situation similar to a cellular graft in a unicellular organism is created and the host immune system might be of little help, particularly if the affected cells were cells other than macrophages. The basic mechanism of defense in such a situation may reside in a "self," "non-self" recognition system. Those who recognize the parasite as "non-self" would be able to kill it. The mechanisms of "self"–"non-self" recognition, as well as that of killing of "non-self" prokaryotes, need further elucidation. Clinico-pathological features of leprosy, including the Mitsuda reaction, which is the local response of the body to surface (transplantation/recognition) antigens of *Mycobacterium leprae*, have many features that support this notion.—Author's Abstract

Furukawa, F., Ozaki, M., Imamura, S., Yoshida, H., Pinrat, A. and Hamashima, Y. Associations of circulating immune complexes, clinical activity, and bacterial index in Japanese patients with leprosy. Arch. Dermatol. Res. **274** (1982) 185–188.

Although many investigators found the presence of circulating immune complexes (CIC) in patients with leprosy, there are few reports with regard to the correlations among the CIC level, clinical activity, and bacterial index. Based on our findings that the CIC level detected by Clq solid phase assay (ClqSPA) in lepromatous leprosy correlates significantly with clinical and bacteriologic features, ClqSPA seems to be one of the most suitable and reliable methods of studying the mechanisms of an immune-complex-mediated pathology in leprosy.—(*Adapted from* the article)

Gaulier, A., Prat, J. J., Wallach, D., Palangie, A., LeSec, G. and Cottenot, F. Demonstration of T lymphocytes in leprous granuloma using the acid α naphtyl acetate esterase activity. An attempt at quantitative analysis. Pathol. Res. Pract. **176** (1983) 103–114.

In 9 leprosy patients (1 TT, 1 BT, 4 BL and 3 LLp), esterase positive lymphocytes (T lymphocytes) were studied in frozen sections of skin biopsies by α naphtyl acetate esterase pH 5.8 method (ANAE). Four patients had never been treated previously and

five patients exhibited clinical and bacteriological evidence of relapse for inadequate therapy at first biopsy. There was an increase in ANAE (+) lymphocyte density in granulomas when second biopsies were done after efficient treatment, evaluated by bacillary index for the eight bacilliferous patients, and clinical improvement. The significance of T cells in granulomas is discussed.—Authors' Summary

Harboe, M. and Closs, O. Immunological aspects of leprosy. In: *Immunology 80, Progress in Immunology.* Fougereau, M. and Dausset, J., eds. London: Academic Press, Ltd., 1980, 1231–1243.

Leprosy may to a great extent be considered as an immunological disease. The causative organism, *Mycobacterium leprae,* is virtually nontoxic and may occur in great numbers in the skin with almost no clinical symptoms. Most symptoms of the disease are due to immune reactions against the bacilli. Complications, such as nerve damage which is responsible for the deformities so often associated with the disease, are directly due to immune reactions. The case is the same for erythema nodosum leprosum which is a classical example of an immune complex disease in man. It has become increasingly apparent that leprosy offers unique opportunities for studies of the relationship between host and parasite during a chronic infection, particularly development of clinical symptoms due to immune reactions against antigenic substances liberated from micro-organisms. Leprosy is thus developing as a "model disease" which provides essential information on the importance of immune reactions in several chronic infectious diseases.

In this position paper, we present our view on the current state of knowledge on essential immunological features of leprosy. We have deliberately focused attention on areas where current concepts may need to be challenged and where the available information is incomplete, thus pointing to areas in need of further work.—(*Adapted from* the article)

Haregewoin, A., Godal, T., Mustafa, A. S., Belehu, A. and Yemaneberham, T. T-cell conditioned media reverse T-cell unresponsiveness in lepromatous leprosy. Nature **303** (1983) 342–344.

In some subjects the infective agent of leprosy, *Mycobacterium leprae,* causes disseminated (lepromatous) disease. Such subjects have a major role in the transmission of the disease and show deficient T cell responses both *in vivo* and *in vitro* to *M. leprae,* but not to other antigens. Numerous studies have recently shown that T cells with functional capabilities after initial triggering with antigen can be maintained in a state of continuous proliferation *in vitro* when cultured in medium containing Interleukin 2 (IL-2). Here we have studied the effect of IL-2 rich T cell conditioned medium on lepromatous peripheral blood mononuclear cells. Our results show that although lepromatous T cells fail to produce IL-2 after exposure to *M. leprae* they can respond by proliferation to *M. leprae* in the presence of T cell conditioned medium, suggesting that the unresponsiveness in lepromatous leprosy results from a deficiency in the production of IL-2 or related factors and not a lack of *M. leprae*-reactive T cells.—Authors' Summary

Iliadi-Alexandrou, M. E., Patramani, I., Benetsanos, P., Parissis, N. and Pavlatou, M. CH50 and C3 component of complement in Hansen's disease. Int. J. Dermatol. **21** (1982) 515–520.

Although a variety of complement values have been reported in leprosy, we found no difference in the CH50 and C3 in the sera of 30 normal persons and 233 lepromatous patients. No statistically significant difference was observed in CH50 and C3 values between healthy controls and lepromatous patients taken as a whole or separated into the different types of the disease spectrum ($p > 0.1$). A statistical difference in C3 titers was found between healthy controls and borderline patients ($p < 0.05 > 0.01$) but the sample number is too small to be valid. An important number of sera tested had low and an equally important number had high complement values. Sera with high and low values are important because high values are found in acute inflammatory reactions and low values demonstrate complement activation. Discrepancies in reported results

are probably due not only to differences in the methods used, storage, and limited number of sera tested, but mainly to the stage of the disease and the drugs administered.—Authors' Abstract

Ivanyi, J., Sinha, S., Aston, R., Cussell, D., Keen, M. and Sengupta, U. Definition of species specific and cross-reactive antigenic determinants of *Mycobacterium leprae* using monoclonal antibodies. Clin. Exp. Immunol. **52** (1983) 528–536.

Four soluble antigens of *Mycobacterium leprae* have been identified using 12 murine monoclonal antibodies. Their specificity, taxonomic distribution and molecular nature were analyzed by radioimmunoassays and by immunoblotting from polyacrylamide electrophoresis gels. A protein antigen MY1 (12K) reacted with one antibody (ML06) without demonstrable crossreactivity for any of the other 20 tested species of mycobacteria. Another four antibodies which identified antigen MY2 revealed only a marginal degree of crossreactivity with three other species of mycobacteria. Two antigens shared by several other mycobacteria species were: MY3 represented by five protein bands (35–70K) and a subtilisin resistant molecule MY4 (40–50K) with two distinct determinants and presumably of polysaccharide nature. The described monoclonal antibodies may represent novel valuable diagnostic reagents as well as tools for the purification of antigens which could be explored towards prophylactic or therapeutic immunization against leprosy.—Authors' Summary

Modlin, R. L., Gebhard, J. F., Taylor, C. R., and Rea, T. H. *In situ* characterization of T lymphocyte subsets in the reactional states of leprosy. Clin. Exp. Immunol. **53** (1983) 17–24.

Using monoclonal antibodies and the immunoperoxidase technique, the numbers and distribution of T lymphocyte subsets in the tissues of reactional states of leprosy (6 reversal reaction, 9 erythema nodosum leprosum (ENL) and 2 Lucio's reaction) were determined and compared with those found in stable, nonreactional patients (6 tuberculoid, 2 borderline lepromatous and 7 lepromatous). The pattern of segregation of the suppressor/cytotoxic phenotype at the periphery of the granuloma was found in both nonreactional tuberculoid lesions and reversal reactions, but was better developed in the former. In ENL and Lucio's reaction, as well as in nonreactional lepromatous tissue, the helper/inducer and suppressor/cytotoxic phenotypes were both admixed with the aggregated histiocytes. However, the helper/suppressor ratio in ENL (2.1 ± 0.4) was significantly larger than that in nonreactional lepromatous tissue (0.7 ± 0.4, $p < 0.001$). The immature thymocyte antigen OKT6 was found on scattered large nonlymphoid cells, most commonly in tuberculoid and reversal reaction tissues, less commonly in ENL, but only irregularly in nonreactional lepromatous tissue. The peripheral pattern of the suppressor/cytotoxic phenotype may be an immunohistological reflection of a cell-mediated immune response common to both nonreactional tuberculoid and reversal reaction patients. The reversal of the helper/suppressor ratio in ENL as compared to nonreactional lepromatous disease suggests some role for cell-mediated immunity in the pathogenesis of ENL. The OKT6 positive cell is of unknown origin and function.—Authors' Summary

Morito, T., Kano, K. and Milgrom, F. Studies on the Paul-Bunnell antigen-antibody system. III. Detection of a Paul-Bunnell-related antigen in syphilis and leprosy. Int. Arch. Allergy Appl. Immunol. **71** (1983) 117–121.

By means of double-diffusion precipitation tests in agarose gel with selected infectious mononucleosis (IM) sera, an antigen was detected in sera of patients with syphilis and leprosy. Of 378 syphilis sera tested 39 (10.3%) and of 36 leprosy sera 7 (19.4%) gave positive results. Sera of patients with various other diseases were negative. This antigen was demonstrable in sera of patients with both early and late syphilis and was shown to be unrelated to cardiolipin. Absorption studies of the IM sera with bovine and sheep erythrocytes and guinea pig tissues revealed that this antigen was identical with or closely related to the previously described B antigen of the Paul-Bunnell (P-B)

antigenic complex and distinct from heterophile antigens of Hanganutziu-Deicher (H-D) and of Forssman specificity. However, 2 of 89 syphilis sera without the P-B antigen were shown to contain antigen(s) of H-D specificity. None of the syphilis or the leprosy sera contained P-B antibodies, but H-D antibodies were found in 13% of syphilis sera.—Authors' Abstract

Ridley, M. J., Marianayagam, Y. and Spector, W. G. Experimental granulomas induced by mycobacterial immune complexes in rats. J. Pathol. **136** (1982) 59–72.

After BCG were complexed with homologous anti-BCG serum IgM was found to be firmly bound to the organisms. Preparations were made at antigen/antibody equivalence and at twofold and fourfold antibody excess. They were injected subcutaneously into rats. At equivalence the mixtures provoked rapidly developing necrotic destructive lesions containing many bacilli. Injection of mixtures at antibody excess caused the rapid formation of epithelioid cell granulomas without necrosis and containing few bacilli.

Compared with the injection of BCG alone, injection of comparable numbers of IgM-complexed bacilli at equivalence led to more rapid necrosis but also more rapid resolution of the granulomas which followed. Delayed type skin reactions to PPD took longer to develop after injection of complexed BCG, usually as long as four weeks. The delay varied directly with the degree of antibody excess. This failure to detect cell-mediated immunity was reflected in the histology of the draining lymph nodes which differed strikingly from that seen after injection of BCG alone. In animals injected with bacilli in excess antibody, epithelioid cell granulomas formed and viable bacilli were apparently eliminated before skin reactions to PPD developed. It is concluded that circulating immunoglobulin, perhaps IgM in particular, is likely to play a significant role in the pathogenesis of tuberculosis and similar diseases and that the relative ratio of antigen to antibody within the lesions may be crucial in influencing the balance between tissue destruction and healing.—Authors' Summary

Ridley, M. J. and Ridley, D. S. The immunopathology of erythema nodosum leprosum: The role of extravascular complexes. Lepr. Rev. **54** (1983) 95–107.

Skin biopsies of 20 patients with erythema nodosum leprosum were studied histologically, by acid-fast, silver and immunological methods for the demonstration of bacterial antigen, and by immuno-peroxidase for a variety of immunological factors. The results were compared with those in ten nonreacting lepromatous patients.

At the center of the ENL lesions there was always disintegration of macrophages and release of bacterial antigen, comprising cell walls and particulate or diffuse components of *Mycobacterium leprae*. These products were found to combine first with IgM, later with IgG, which together with complement components of the classical pathway were present at the same sites. These complexes were found both extracellularly and in neutrophils and macrophages, and were constant features of acute stage lesions. C-reactive protein and B-lipoprotein were present in varying amounts and were associated partly with connective tissue. It is thought that CRP, and the related SAP, may be factors in the disruption or repair of elastic and collagen, which are conspicuous in some ENL lesions. The results support the view that ENL is an immune complex phenomenon, possibly self-perpetuating, occurring at the site of breakdown of small lepromatous granulomas. The immune complexes are extravascular and in this respect ENL differs from the classical "serum sickness" described by Arthus.—Authors' Summary

Salgame, P. R., Mahadevan, P. R. and Antia, N. H. Mechanism of immunosuppression in leprosy: Presence of suppressor factor(s) from macrophages of lepromatous patients. Infect. Immun. **40** (1983) 1119–1126.

Human peripheral blood mononuclear cell proliferation induced by *Mycobacterium leprae* could be inhibited by the suppressor factor in the lysate of the macrophages of lepromatous leprosy patients. Macrophages from normal subjects and tuberculoid patients did not show produc-

tion of a suppressor factor. Inhibition occurred only when the factor was present in the initial stages of lymphocyte culture. The factor is heat stable and nondialyzable. Proliferation induced by some mycobacteria and concanavalin A could also be blocked by the factor. Interestingly, blastogenic response by a few other antigens and phytohemagglutinin could not be inhibited by the suppressor factor. Mononuclear cells pretreated with such lysate from lepromatous macrophages for 24 hr could induce suppressive activity in the cells *in vitro* in an autologous system. Treatment of these cells with carbonyl iron after the induction phase, to remove phagocytic cells, did not abolish their suppressive activity. The lepromatous macrophage lysate also generated suppressive activity in a T lymphocyte-enriched population of normal subjects. These studies are interpreted to indicate that immunosuppression in lepromatous patients is produced by both macrophages and T lymphocytes. The exact phase in which either of these cells acts as a suppressor may be different. Specific suppression by macrophages to *M. leprae* can be an early event, and nonspecific suppression by T lymphocytes may be a later event in the course of lepromatous leprosy.—Authors' Abstract

Spector, W. G., Marianayagam, Y. and Ridley, M. J. The role of antibody in primary and reinfection BCG granulomas of rat skin. J. Pathol. **136** (1982) 41–57.

Primary subcutaneous infection of rats with BCG leads to a three-stage local reaction. There is first a short-lived simple granuloma corresponding with high levels of cell-mediated immunity (CMI). This is followed by an explosive phase of necrosis and local mycobacterial multiplication corresponding with low levels of CMI and high levels of circulating anti-BCG antibody. Finally the lesion resolves via an epithelioid cell granuloma as bacteria fall in number and CMI returns.

Reinfection with BCG produces quite different lesions when initiated at different stages of the primary infection. Reinfection during the short first stage causes a self-healing epithelioid granuloma. Reinfection during the long second stage produces a florid necrotic, bacilli-laden lesion. Reinfection during the third stage produces only a vestigial, transient granuloma.

It is suggested that the evolution of tuberculous lesions depends on the interplay of CMI, bacillary load, and circulating antibody. A large antigenic load in the presence of high antibody titers causes necrosis and bacillary multiplication; whereas reduced bacterial numbers plus antibody and high CMI lead to compact granulomas and healing. The first situation may be analogous to immune complex disease in antigen excess and the second to complexes in antibody excess.

An analogy is drawn between the reinfection experiments and natural infection after BCG vaccination in humans. It is postulated that BCG vaccination in man may be followed by a phase in which antibody is high relative to CMI. If because of high prevalence rates, natural infection with large doses of bacilli was more likely to occur at this time, the results might help to explain the failure of BCG prophylaxis in India and comparable countries, as opposed to its success in the United Kingdom.—Authors' Summary

Williams, G. T. Isolated epithelioid cells from disaggregated BCG granulomas—an ultrastructural study. J. Pathol. **136** (1982) 1–13.

Non-caseating epithelioid granulomas have been induced in rats by the subcutaneous injection of BCG vaccine, and their cellular disaggregation to yield isolated epithelioid cells has been achieved using collagenase. Ultrastructurally, epithelioid cells in both intact granulomas and disaggregated cell suspensions showed a spectrum of appearances ranging from cells with conspicuous, rough-surfaced, endoplasmic reticulum ("plasmacytoid epithelioid cells") to cells containing numerous cytoplasmic, membrane-bound vesicles ("vesicular epithelioid cells"). Numerous intermediate forms were present. Endocytosed material was inconspicuous.

Investigation of disaggregated 4, 10, and 28 day lesions showed that the proportion of vesicular epithelioid cells increased with maturation of the granulomas. Nevertheless a full spectrum of epithelioid cell morphology was present as early as four days.

It is suggested that mononuclear phagocyte cells entering the granuloma transform into vesicular epithelioid cells via an intermediate plasmacytoid stage. The successful isolation of viable epithelioid cells from granulomas may allow the function of these cells to be evaluated further.—Author's Summary

Williams, G. T. Isolated epithelioid cells from disaggregated BCG granulomas—some functional studies. J. Pathol. **136** (1982) 15–25.

Isolated epithelioid cells from disaggregated rat BCG granulomas show a morphological spectrum from "plasmacytoid" to "vesicular" forms on electron microscopy. Functional studies on these isolated cells showed that all epithelioid cells exhibited poor trypsin-resistant glass adherence and poor phagocytosis of latex, zymosan, antibody-coated and complement-coated erythrocytes when compared with macrophages, especially at the vesicular end of the spectrum. A high proportion of all epithelioid cell types was found to have Fc surface receptors, but C3 receptors were reduced on vesicular cells compared with the plasmacytoid variety. The findings indicate that the progressive transformation of mononuclear phagocytes into vesicular epithelioid cells through plasmacytoid intermediates is accompanied by a concomitant modification of cell function. The significance of these changes is discussed.—Author's Summary

Young, D. B. and Buchanan, T. M. A serological test for leprosy with a glycolipid specific for *Mycobacterium leprae*. Nature **221** (1983) 1057–1059.

A phenolic glycolipid from *Mycobacterium leprae* was purified and used as antigen in an enzyme-linked immunosorbent assay. Antibodies directed against the lipid were seen in serums from leprosy patients but not in serums from uninfected controls or patients infected with other mycobacteria, including *M. tuberculosis*. The antibody response distinguished between the *M. leprae* lipid and the structurally related phenolic glycolipid from *M. kansasii*. This assay has considerable potential as a specific serodiagnostic test for leprosy infection.—Authors' Abstract

Microbiology

Abou-Zeid, C., Voiland, A., Michel, G. and Cocito, C. Structure of the wall polysaccharide isolated from a group of corynebacteria. Eur. J. Biochem. **128** (1982) 363–370.

Leprosy-derived corynebacteria (LDC) is a group of "diphtheroid" bacteria isolated from leprosy patients. Their cell wall was previously shown to contain, in addition to a peptidoglycan of the meso-diaminopimelic type and to mycolic acids of the corynomycolic type, a polysaccharide fraction. The present work relates the preparation and analysis of the wall polysaccharides of three LDC strains and two reference organisms *Mycobacterium smegmatis* and *Corynebacterium hoffmannii*. These polymers were obtained by mild alkali hydrolysis of purified cell walls, and were purified to homogeneity by column chromatography on DEAE-cellulose and Sephadex G-75 columns. By this procedure, two fractions containing, respectively, neutral polysaccharides and polysaccharide-peptidoglycan complexes, were obtained. The former, which was composed of arabinose and galactose in *M. smegmatis*, contained, in addition, mannose in LDC cells, and mannose plus glucose in *C. hoffmannii*. The presence of arabinose, galactose and mannose in a constant ratio in the wall polysaccharide preparations of three LDC isolates suggests that arabinogalactomannan is the polysaccharide component of the envelope of this group of corynebacteria. A structural analysis was accomplished by methylation analysis and periodate oxidation. On the basis of the analytical data, a model for the primary structure of the polymer has been proposed, which is similar to that available for the arabinogalactan of *M. tuberculosis*. According to the proposed model, the main chain of LDC polysaccharide is made of

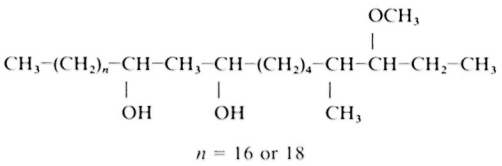
galactopyranose, galactofuranose and arabinofuranose. The latter is present in both the branching points and the lateral chains of the polymer. Mannose in the pyranose form, and arabinose in the furanose form, are located at the extremities. In conclusion, the inference that arabinogalactan is the wall polysaccharide of microorganisms belonging to genera *Corynebacterium, Mycobacterium, Nocardia* (CMN group) is not generally valid, since the corresponding polymers in some corynebacteria have additional monosaccharide components.—Authors' Abstract

Gueur, M. C., Harboe, M., Fontaine, F., Delville, J. and Cocito, C. Comparison of the cytoplasmic antigens of leprosy-derived corynebacteria and some mycobacteria. Scand. J. Immunol. **17** (1983) 497–506.

The immunological relationship between leprosy-derived corynebacteria (LDC) and reference mycobacteria was analyzed by crossed immunoelectrophoresis with intermediate gel. For this purpose, three reference systems (LDC15/anti-LDC15, LDC18/anti-LDC8, and LDC8/anti-LDC8) were developed. They showed 15–20 distinct antigenic components in LDC cytoplasm. Extensive crossreactivity was observed among different LDC isolates, affecting 3–17 components. Moreover, several components were shown to crossreact with mycobacteria when anti-Bacillus Calmette-Guérin (BCG), anti-*Mycobacterium leprae*, other antisera and lepromatous leprosy sera were incorporated in the intermediate gel. The major crossreactive component, antigen M, was present in all LDC isolates and crossreacted with antigen 7 of *M. leprae* and antigen 60 of *M. bovis* BCG. The thermostability of these antigens and the specificity of the crossreacting antigens were assessed. The data underline the degree of immunochemical homogeneity within the LDC group of microorganisms and relatedness with *M. leprae* and other mycobacteria.—Authors' Abstract

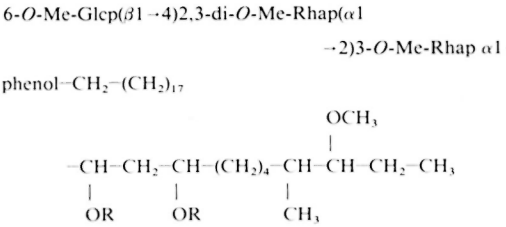
Hunter, S. W. and Brennan, P. J. Further specific extracellular phenolic glycolipid antigens and a related diacylphthiocerol from *Mycobacterium leprae*. J. Biol. Chem. **258** (1983) 7556–7562.

Mycobacterium leprae in infected armadillo tissue produces extracellular phthiocerol-containing lipids in amounts well in excess of the bacterial mass. The principal component (1.38 mg in 1 g of liver, wet weight, containing 3.7×10^{10} *M. leprae* bacilli) consists of a mixture of two phthiocerol homologs, 3-methoxyl-4-methyl-9,11-dihydroxyoctacosane and 3-methoxyl-4-methyl-9,11-dihydroxytriacontane,



n = 16 or 18

in which the hydroxyl functions are acylated by a mixture of three "mycocerosic acids": 2,4,6,8-tetramethylhexacosanoate, 2,4,6,8-tetramethyloctacosanoate, and 2,4,6,8-tetramethyltriacontanoate. The structures were established by saponification of the native lipid, direct probe electron impact- or chemical ionization-mass spectrometry of the phthiocerol or its permethylated derivative, and gas-liquid chromatography-electron impact-mass spectrometry of the methyl esters of the fatty acids. In addition to the previously reported *M. leprae*-specific triglycosylphenolicdiacyl phthiocerol, the extracellular products contain small amounts (about 60 μg/g of infected liver, wet weight) of two other phenolic glycolipids, one of which (Phenolic Glycolipid-III) has been structurally elucidated,



assuming certain enantiomeric configurations for the sugar substituents; the *R*-acyl functions are identical with those in the diacylphthiocerol. Phenolic Glycolipid-III reacts in enzyme-linked immunosorbent assays with sera from patients with leprosy and with rabbit antisera raised against whole

M. leprae. The phthiocerol-containing lipids may be synonymous with the electron transparent capsules of *M. leprae*, and their unreactive state may confer on them the role of passive protectors of the bacillus.—Authors' Abstract

Katoch, V. M., Wayne, L. G. and Diaz, G. A. Serological approaches for the characterization of catalase in tissue-derived mycobacteria. Ann. Microbiol. (Paris) **133B** (1982) 407–414.

Cell-free extracts of *Mycobacterium lepraemurium* from mouse liver and *M. leprae* from armadillo liver were analyzed for the presence of any mycobacterial catalase by using the specific inhibitor 3-amino-1,2,4-triazole and seroprecipitation titrations. These studies clearly demonstrated the presence of a "T" type of mycobacterial catalase in *M. lepraemurium* and placed it, in terms of immunological distance, in a position between *M. tuberculosis* and *M. avium*. The results did not reveal any detectable "T" catalase activity in the *M. leprae* preparations. The "M" type catalase activity which was observed did not bind to antisera against "M" catalase of *M. kansasii*, but was bound to the extent of 80% to antisera against normal armadillo liver catalase. The significance of the component of the "M" catalase in *M. leprae* preparations which did not react against antibodies to normal liver remains to be determined.—Authors' Summary

Kusaka, T. and Izumi, S. Gas chromatography of constitutive fatty acids in *Mycobacterium leprae*. Microbiol. Immunol. **27** (1983) 409–414.

A constitutive saturated and mono-unsaturated fatty acid pattern of *Mycobacterium leprae*, isolated from the liver of a nine-banded armadillo with experimental leprosy, was analyzed gas chromatographically and compared with that of cultured *M. lepraemurium*, *M. avium*, *M. bovis*, strain BCG and *M. smegmatis*. In comparing the fatty acid pattern thus obtained and the known structure of mycolic acids in these mycobacteria, an experiential rule that each species of mycobacteria has a relatively high content of normal (straight-chained) saturated fatty acid having two more carbons than those of the α-branch in this species' mycolic acids, coincided well for all mycobacteria tested. In particular, *M. leprae* was found to contain a relatively high content of behenic acid (n-$C_{22:0}$) and the carbon-number of the α-branch in this species' mycolic acids is 20, as we previously reported. These data suggested the possibility of simple detection of *M. leprae* by gas chromatography, and results sustaining this possibility were obtained.—Authors' Abstract

Pattyn, S. R. Bacteriology of *Mycobacterium leprae*. Lepr. Rev. **54** (1983) 17S–22S.

A review is presented on the morphologic features, chemical characteristics, growth capacity, drug sensitivity, metabolic activity and antigen structure of *Mycobacterium leprae*. Since the availability of large numbers of *M. leprae* from armadillo tissue, knowledge, particularly on the chemical characteristics, has increased. It may be expected that knowledge on the metabolic activities will increase, leading perhaps, one day, to the long-awaited *in vitro* cultivation of the organism.—Author's Summary

Wheeler, P. R. Catabolic pathways for glucose, glycerol and 6-phosphogluconate in *Mycobacterium leprae* grown in armadillo tissues. J. Gen. Microbiol. **129** (1983) 1481–1495.

With radioisotopes, it was shown that suspensions of *Mycobacterium leprae* oxidized glycerol, 6-phosphogluconate, glucose, glucose 6-phosphate, and at a low rate, gluconate, to CO_2. The incubation period in these experiments was usually 20 hr, but after 140 hr up to five times more glucose and gluconate had been converted to CO_2. Studies with differentially labelled glucose indicated that glycolysis and the hexose monophosphate pathway were used for glucose dissimilation.

Key enzymes of glycolysis, the hexose monophosphate pathway and glycerol catabolism were detected in cell-free extracts from purified *M. leprae*, but phosphoketolase, Entner-Doudoroff pathway activity and gluconate kinase were absent. All these enzymes were present also in host tissue, but

biochemical evidence is presented which indicates that all enzymes detected in extracts from *M. leprae* were authentic bacterial enzymes. Additionally, they could all be detected in extracts of *M. leprae* prepared by treatment with NaOH in which host enzymes adsorbed to *M. leprae* are inactivated.—Author's Abstract

Experimental Infections

Adu, H. O., Curtis, J. and Turk, J. L. The resistance of C57BL/6 mice to subcutaneous infection with *Mycobacterium lepraemurium* is dependent on both T cells and other cells of bone marrow origin. Cell. Immunol. **78** (1983) 249–256.

Thymectomized or sham-thymectomized C57BL/6 mice were irradiated and reconstituted with either C57BL/6 bone marrow cells or bone marrow cells from H-2 matched BALB/B mice. The ability to limit organism multiplication at the site of infection in response to a moderate dose of *Mycobacterium lepraemurium* is shown to be T cell mediated and not dependent on the type of bone marrow cells used for reconstitution. Dissemination of the organisms on the other hand appeared to be dependent on both T cells and cells of bone marrow origin.—Authors' Abstract

Kawaguchi, Y., Matsuoka, M. and Kawatsu, K. Susceptibility to *M. lepraemurium* of CBA, DBA and C3H mice. Jpn. J. Lepr. **51** (1982) 57–64.

Susceptibility to subcutaneous inoculation with *Mycobacterium lepraemurium*, strain Hawaiian-B, of four mouse strains (CBA/J, CBA/N, DBA and C3H/Bi) was examined, concerning the relation between the clinical features of subcutaneous leproma at the inoculation site and the evolution of visceral lesions. Hawaiian-B strain has been maintained only by passages from C57BL/6 to C57BL/6 mice in our laboratory since 1956. Mice of C3H, C3H/He, BALB/c, KK, DDD and C57BL/6 strains were also examined by the same manner mentioned above as controls.

Subcutaneous lesions developed, a large and soft, typically malignant type leproma, at the inoculation site in CBA/J, CBA/N, DBA and C3H/Bi mice, and extensive involvement was observed in their viscera, as observed in C3H mice. Taking the characteristics of the above strains of mice into consideration, CBA/J strain mice are much more suitable to use in mouse leprosy experiments as a representative of the typically malignant.—Authors' Abstract

Løvik, M. and Closs, O. Induction of delayed type hypersensitivity against ultrasonicated *Mycobacterium lepraemurium* bacilli without simultaneous local reactivity against live bacilli or protective immunity. Clin. Exp. Immunol. **53** (1983) 319–327.

Delayed-type hypersensitivity (DTH) was induced in C3H mice by subcutaneous immunization with *Mycobacterium lepraemurium* (Mlm) antigens in Freund's complete (FCA) or Freund's incomplete (FIA) adjuvant. The total ultrasonicate (MlmSon-P) of Mlm bacilli as well as the water soluble fraction (MlmSon-S) of this ultrasonicate was found effective. MlmSon-S was used as the test antigen. Specific DTH also developed after immunization with heat-killed Mlm bacilli in FIA, but not with heat-killed bacilli in saline. Some mice were pre-treated with cyclophosphamide (CY) or splenectomized to augment the effect of immunization. In no instance was DTH to MlmSon-S accompanied by detectable local reactivity to live Mlm bacilli measured as swelling of the infected foot pad or by reduced multiplication or dissemination of the bacilli during the first 11 weeks after inoculation. As determined by testing in the infected foot pad eight weeks after inoculation, Mlm infection did not induce DTH to MlmSon-S in non-immunized mice, and Mlm infection was found to neither augment nor suppress established DTH to MlmSon-S. The experiments thus demonstrated a clear dissociation between DTH to MlmSon-S and local reactivity to live Mlm bacilli, as well as between DTH to

MlmSon-S and protective immunity to Mlm infection.—Authors' Summary

Schiefer, H. B. and Middleton, D. M. Experimental transmission of a feline mycobacterial skin disease (feline leprosy). Vet. Pathol. **20** (1983) 460–471.

Non-culturable, acid-fast bacteria from two spontaneous cases of so-called feline leprosy were transmitted to rats and cats and further passaged in rats or cats. Two to six months after infection, cats developed cutaneous lesions that were indistinguishable from spontaneous cases, including the occurrence of nasal granulomata in one cat. When injected into rats, the mycobacteria caused a generalized mycobacteriosis and the granulomatous reaction was composed chiefly of macrophages without polymorphonuclear granulocytes. Infection of cats with *Mycobacterium lepraemurium* did not produce any lesions. The feline disease may be a suitable model for the study of human leprosy (Hansen's Disease).—Authors' Abstract

Shepard, C. C., Van Landingham, R. M., Walker, L. L. and Shunzhang Ye. Comparison of the immunogenicity of vaccines prepared from viable *Mycobacterium bovis* BCG, heat-killed *Mycobacterium leprae*, and a mixture of the two for normal and *M. leprae*-tolerant mice. Infect. Immun. **40** (1983) 1096–1103.

Intradermal vaccines consisting of viable *Mycobacterium bovis* BCG, heat-killed *M. leprae*, or mixtures of the two were titrated in mice in doses of $10^{5.2}$, $10^{5.8}$, $10^{6.4}$, $10^{7.0}$, and $10^{7.6}$ acid-fast bacilli. The immune response was measured by sensitization (48–72 hr foot pad enlargement on challenge with $10^{7.0}$ heat-killed *M. leprae*) and by protection against infection with a viable *M. leprae* challenge. There was increasing response with increasing dose of vaccine, and overall the responses to the three vaccines were similar. At the lowest dose, however, the combination of BCG and *M. leprae* gave superior protection. The local reaction to the vaccines in the lower dose range was less severe with the *M. leprae* vaccine. In another experiment, the three vaccines were compared in normal mice and in mice that had been rendered tolerant by intravenous injection of *M. leprae*. The tolerant mice developed no measurable sensitization on vaccination with *M. leprae*, but they developed partial but distinct sensitization on vaccination with BCG, alone or in combination with *M. leprae*. The tolerant mice developed little or no protection with any of the vaccines, however.—Authors' Abstract

Tomioka, H. and Saito, H. Effect of phorbol myristate acetate, a tumor-promoting agent, on the growth of *Mycobacterium lepraemurium* in the mouse footpad. Microbiol. Immunol. **27** (1983) 395–407.

Phorbol myristate acetate (PMA), a potent inflammatory agent with tumor-promoting activity, was examined for its effect on the growth of *Mycobacterium lepraemurium* (Mlm) in the left hind foot pad of mice. When the animals were infected with 10^4 Mlm and received multiple injections of 3 μg of PMA in the infection site weekly during the first two months and biweekly thereafter, the growth of the bacilli was markedly enhanced. PMA injection in the infection site resulted in severe foot pad swelling accompanied by inflammatory signs, such as redness, edema, induration, and sometimes ulcer. Acetic acid, as potent an inflammatory and hyperplastic agent as PMA but without any appreciable tumor-promoting action, did not stimulate Mlm growth when it was injected biweekly in the site of infection with Mlm at a dose of 30 μmol per injection. When mice were infected with 10^8 Mlm, proper elimination of bacilli from the infection site was observed during the first three months. In this case, multiple injections of PMA in the infection site resulted in the enhancement of the elimination of Mlm by host defense mechanisms, although PMA caused as severe inflammation as that observed when Mlm infection was produced with a small inoculum (10^4 Mlm). In both cases, dexamethasone was synergistic with, but indomethacin and L-1-tosylamide-2-phenylethylchloromethyl ketone were antagonistic to, the effect of PMA.—Authors' Abstract

Epidemiology and Prevention

Banerjee, B. and Hazra, J. Geo-ecology of leprosy with special reference to West Bengal. Geogr. Med. **12** (1982) 26–58.

Although the etiological conditions for leprosy have not been clearly understood yet, the study gives us the whole spectrum of approach for future researchers, so as to focus their emphasis to correlate this disease with the trace elements of soils. Such studies should be encouraged since they provide the key to the control of leprosy. But, at present, the regional concentration of leprosy is less marked and large number of cases go unnoticed in the central plains of Bengal, especially around the Calcutta metropolitan district. If such cases are not isolated and treated there is an immense probability that leprosy in West Bengal will be a much greater menace to society than it is today.—(*From the* Authors' Conclusion)

Collier, P. J. A study of case-holding in leprosy patients in Asia, based on duration of treatment, 1976–1980. Lepr. Rev. **54** (1983) 89–94.

From 14 different centers treating leprosy patients in Asia, a study was made of the periods of time for which patients attended during the years 1976–1980. They were divided broadly into "local" and "non-local," the former being essentially from allocated, nearby leprosy control areas (but also to a lesser extent from the vicinity of the base or hospital, if this was not in fact in the control area). The latter were from "all other areas" and included visitors (rich and poor), vagrants and patients with no fixed address. Within the first year after starting treatment, 32.4% of "local" and 62.9% of "non-local" patients were lost, and two years later they had not returned and no information had been received of their removal from the area, or death. Data are further presented on the percentage rate of loss for five years, and at the end of this period 66% of "local" and 88% of "non-local" patients had been lost. The possibility is discussed that in the case of "non-local" patients these figures may be less disconcerting than they appear, since many may have reported back to some other leprosy control unit in their area of origin or to another part of the country. The figures for loss of "local" patients are, however, considered to be serious and possible reasons are discussed. The collection of these figures on case-holding and their presentation to the staff concerned had an almost immediately beneficial effect in raising standards of work. Possibly the most important factor in achieving this was an even greater attention to personal contact with each patient.—Author's Summary

Dharmalingam, R. and Shanmugan, P. The complexities of health education in leprosy. Int. J. Health Educ. **24** (1982) 176–182.

This experience has brought to light the need to provide adequate training to workers before they engage in health education and community organization. In the particular project, evaluation of the training itself was revealing. So far, the non-medical supervisors had been doing a "mechanical" job during their fieldwork, i.e., checking on cases already detected by the leprosy workers and determining whether they were undergoing treatment or not. They had no idea as to ways of involving leaders and patients or initiating a process of health education at different levels with the aim of making case detection "a voluntary people's program" and leprosy a disease that would no longer be considered as a matter for social contempt. The involvement of satisfied patients was also of value. While the individual approach helped to give confidence to patients, group discussions proved effective in disseminating information and creating a feeling of group responsibility. Above all, the experience was very positive in that it helped the non-medical supervisors to develop new skills in community organization and the planning of health education activities with the people themselves. They were able to appreciate that their role includes a responsibility in health education and the provision of support to leprosy workers in their routine work of surveillance. Furthermore, all groups were able to see the difference between a leprosy control program with

a health education component and one which lacks such an asset.

Control and eradication programs in general can only be effective when people's behavior is in harmony with the objectives. For this purpose, a clear understanding of the different aspects of a disease is required both by the lay people and by the front-line workers who provide the service. To those who are actually dealing with patients and the community, it is even more important to understand the socio-psychological factors operating at the individual, family and community levels.

The knowledge, attitudes and practices study revealed several deterrents to prompt treatment: lack of awareness of the seriousness of the problem; escape mechanism; and fear of being labelled a leprosy case with the stigma attached to the disease. As the disease advances, the patient becomes anxious to get treated but at that stage the community does not give him the sympathy and support needed. These findings point to the fact that health education of the individual alone is inadequate. Strong group support is a major asset in the control of leprosy. It is up to the community and the family to take responsibility in encouraging those who are close to them to seek medical help. To achieve such support, leprosy workers and their supervisors need to receive the kind of professional preparation that will provide them with the skills necessary to convince the community that early diagnosis and continued treatment are important and meaningful.—(*From the* Authors' Conclusion)

McDougall, A. C. and Cologlu, A. S. Lepromatous leprosy in man; depth of the cellular infiltrate and bacillary mass in relation to the possibility of transmission of leprosy by biting arthropods. Ann. Trop. Med. Parasitol. **77** (1983) 187–193.

In order to further define the possible role of arthropods in the transmission of leprosy, the depth of the cellular infiltrate and bacillary mass in the skin of patients with untreated lepromatous leprosy was measured, and this was related to the depth of penetration of the mouthparts of some species of arthropods of medical importance. The results confirmed that large numbers of bacilli are readily available to the biting apparatus of several species of arthropods, but not to that of the scabies mite, which has only a superficial attachment and depth of penetration. The data do not indicate that leprosy transmission in man (or animals) occurs through biting arthropods, but they do lend support to this possibility, if only in a mechanical sense.—Authors' Abstract

Romero, A. Politicas y estrategias para los programas de control de lepra. [Policy and strategy for leprosy control programs.] Bol. Of. Sanit. Panam. **93** (1982) 220–232. (in Spanish)

This article provides an analysis of current policy in leprosy control programs in Latin America, and describes the achievements that have been accomplished as a result of recent epidemiological and therapeutic advances. The importance of being familiar with the leprosy problem in all its aspects and the availability of resources for selecting the most appropriate measures for an effective control program are discussed. A program based on the identification of patients and their followup, as well as on the knowledge of the disease's clinical, bacteriological, and epidemiological characteristics is put forward. Also, other important factors to be considered in preparing a leprosy control program in Latin America are pointed out, such as: rehabilitation; support services; personnel training; health education in the field of leprosy; organization, preparation and evaluation of a program; and the role of research as a priority activity.—Author's Summary

Sansarricq, H. Recent changes in leprosy control. Lepr. Rev. **54** (1983) 7S–16S.

The implementation of the secondary prevention strategy for leprosy control based on dapsone monotherapy had to face many difficulties. The main global results obtained during the period of the dapsone monotherapy approach may be summarized as follows:

a) Worldwide. More than 5 million leprosy cases out of an estimated total of about 10 million existing cases are now under treatment. It can be estimated that from 1–

1.5 million leprosy patients have been released from control during the last decade.

b) Under favorable circumstances reductions of prevalence of 80% were achieved in a few countries or areas.

The shortcomings of dapsone monotherapy have been increasingly realized over the last 15 years. A new approach to secondary prevention of leprosy through multidrug therapy of all cases has been recently recommended by WHO. The contribution of the THELEP Scientific Working Group to the development of the newly recommended regimens has been essential, clearly demonstrating transfer of the results of research to control efforts. For the first time the results of worldwide research efforts, stimulated and coordinated at the global level, have been translated into important changes in the strategy for leprosy control.

However, in the long term, primary prevention methods, the most important being an effective vaccine, are an essential need in an effective strategy for leprosy control. In addition, immunological tools which would allow the identification of individuals at high risk of developing lepromatous leprosy will be of great help.

In any case, it is unlikely that conclusions on the efficacy of a vaccine will be available within the next decade, or that new potent drugs can be developed.

Therefore, for the years to come, and despite the shortcomings and limitations of the secondary prevention approach, the implementation of effective chemotherapeutic regimens based on combinations of bactericidal drugs is a must if we do not want the leprosy problem to become unmanageable and the gains made so far to be lost. Consequently, in the WHO leprosy program for the next quinquennium top priority has been given to the implementation of multidrug therapy.—(*From* the article)

Smith, J. H., Folse, D. S., Long, E. G., Christie, J. D., Crouse, D. T., Tewes, M. E., Gatson, A. M., Ehrhardt, R. L., File, S. K. and Kelly, M. T. Leprosy in wild armadillos (*Dasypus novemcinctus*) of the Texas Gulf Coast: Epidemiology and mycobacteriology. J. Reticuloendothel. Soc. **34** (1983) 75–88.

A significant prevalence of leprosy has been demonstrated in wild Louisiana armadillos. The Texas Gulf Coast still has endemic human leprosy, and recent mores in Texas have markedly increased armadillo-human contact. Armadillos were screened by physical examination, and by ear-snip and slit-scrape technique. Animals that screened "positive" were sacrificed and necropsied under aseptic conditions. Liver, spleen, gross lesions, and four groups of lymph nodes were cultured for mycobacteria and were studied histologically. Base ratios and DNA homology with *Mycobacterium leprae* were determined on mycobacteria from two armadillos (and two tissues from one of these); these studies indicate that the organism found in Texas armadillos is *M. leprae*. Twenty-one of the armadillos were leprous—4.66%. The local prevalence varied from 1.0% to 15.4%. Epidemiologic implications of these findings and the occurrence of other concomitant mycobacterial infections are discussed.—Authors' Abstract

Xu Keyu, *et al.* HLA and leprosy. II. The associate of HLA-DR_2 with lepromatous leprosy. Chin. J. Dermatol. **16** (1983) 24–27. (in Chinese)

HLA-DR typing was performed in 69 patients of Jiangsu Han nationality with leprosy including 37 cases of lepromatous type (LL and BL) and 32 cases of tuberculoid type (TT and BT), together with 65 healthy controls of the same nationality matched for locality, age and sex.

Three groups of the leprosy patients (all patients, lepromatous patients and tuberculoid patients) were compared with the healthy controls, respectively. Statistically shown, increased frequency of DR2 was observed in all patient groups as well as in the lepromatous patient group, even after corrected for the number of DR antigens tested ($\chi^2 = 9.16$, $p = 0.003$, $Pc = 0.024$, $RR = 3.15$ and $\chi^2 = 11.69$, $p = 0.0006$, $Pc = 0.005$, $RR = 4.68$, respectively). Slightly increased frequency of DR2 was observed in tuberculoid cases, but it was not statistically significant.

In a total of 216 haplotypes the relative delta parameters of the tri-locus linkage disequilibrium between HLA-A, DR and -B, DR, and the supposed leprosy susceptibility

gene were calculated with the Porta-McHugh's formulas by computer according to AR model. Three haplotypes relatively susceptible to leprosy were found, namely A11-DR2 to lepromatous, A9-DR2, A11-DR5 and Bw60-DR3 to tuberculoid.

The results obtained further indicated that the susceptibility gene of leprosy is very likely linked with the HLA region and indirectly demonstrated that the gene might be on the DR side.

The fact that lepromatous and tuberculoid patients were associated with different HLA haplotypes suggested that leprosy appeared to be a disease of heterogeneous nature.—Authors' Abstract

Rehabilitation

Angulo, M. H., Fraguela Rangel, J. V., Baquero, G. F., Sanabria Negrin, J. and Guzman, C. S. Hallazgos radiológicos osteoarticulares en manos y pies clínicamenta normales en enfermos de lepra. Informe preliminar. [Radiological bone and joint findings in clinically normal hands and feet of leprosy patients. Preliminary report.] Rev. Cub. Med. Trop. **34** (1982) 54–64. (in Spanish)

Radiographic examinations were made of the hands and feet of 20 lepromatous leprosy patients. The patients presented no clinical manifestation of disease of their hands and feet. A review was made of the evolution and pathogenesis of bone and joint lesions due to leprosy. A classification of these lesions is presented.—(*From* Authors' Summary)

Boucher, P. Correction de la griffe cubitale lépreuse par le procédé du "lasso" de Zancolli. [Correction of cubital contractures in leprous patients employing Zancolli's lasso technique.] Chirurgie **108** (1982) 753–757. (in French)

A new technique known as the lasso procedure has been proposed by Zancolli for correction of cubital contractures. It involves attaching the superficial flexor tendon to itself after section, and following its looping around the proximal flexor pulley, with subsequent possible flexion of the first phalanx.

This technique, or a variation, was employed in 22 patients with supple or stiffened claw hands from leprosy. Good results were obtained in supple contractures, only moderate results being observed in fingers with stiffness of the proximal interphalangeal joints.

The technique is simple and reliable and merits wide use in therapy for cubital contractures in general and those in leprous patients in particular.—Author's Summary

Bourrel, P. Place de la chirurgie dans le traitement et la réhabilitation des lépreux. [Contribution of surgery to the treatment and rehabilitation of patients with leprosy.] Chirurgie **108** (1982) 744–752. (in French)

The hypertrophic neuritis complicating leprosy associates "internal compression" due to increase in nerve volume within a thickened inextensible neurilemma, and "external compression" of the canals of the ulnar nerve at the elbow, the median nerve at the wrist, the external popliteal nerve at the neck of the fibula, and the posterior tibial nerve at the bend of the foot.

These compressions provoke a hyperalgic syndrome, or more frequently a deficiency syndrome which becomes more or less rapidly irreversible. When well conducted and usually effective medical treatment is insufficient, a useful procedure is well timed, surgical decompression before definite axon destruction has occurred. This frequently provides functional recovery and prevents paralysis and particulary the trophic disorders and mutilations that follow loss of sensitivity in the extremities.—Author's Summary

Brandsma, J. W. and Lijftogt, T. Timing of tendon-transfer surgery. Lepr. Rev. **54** (1983) 109–114.

Thirty-five leprosy patients who had tendon-transfer surgery recovered nerve function postoperatively. The tendon transfers were performed to correct paralytic deformities resulting from ulnar, median and common peroneal nerve damage. Nerve function recovery was found in 2.8% of the hands that had claw-finger correction for ulnar palsy; in 5.1% of the hands that had opponens replacement for median palsy, and in 6%–9% of the operated drop-feet.

Analysis of the records showed that none of the patients had been operated on within six months after the onset of nerve damage.

Postoperative deformity following nerve function recovery was rare in the hand, but occurred in 5 out of 18 of the feet that showed postoperative recovery.—Authors' Summary

Chopra, J. S., Kaur, S., Murthy, J. M. K., Radhakrishnan, K. and Kumar, B. Clinical, electrophysiological and teased fibre study of peripheral nerves in leprosy. Indian J. Med. Res. **77** (1983) 713–721.

Motor nerve conduction velocity was studied in the median, ulnar, lateral popliteal and posterior tibial nerves in 43 patients with leprosy. Significant slowing of motor nerve conduction, as compared to controls, was detected in the elbow and arm segments of the ulnar nerve and in the knee-to-ankle segments of the posterior tibial and lateral popliteal nerves. Structural changes were studied in sural nerve biopsies in 41 patients. Axonal loss, myelin fiber loss and peri- and endo-neurial fibrosis were seen in all biopsies. Segmental demyelination, remyelination and axonal degeneration were demonstrated by single nerve fiber teasing.—Author's Abstract

Price, J. E. A study of leprosy patients with deformities, and the implications for the treatment of all leprosy patients. Lepr. Rev. **54** (1983) 127–137.

The attendance of leprosy patients with grade 2 and 3 deformities for treatment and physiotherapy care at clinics run by the Bombay Leprosy Project (BLP) in the slums of Bombay, India, was very poor. A survey was conducted to try to discover what factors might affect attendance. This showed that many patients had misconceptions about the disease and their deformity. The clearer their understanding, the more motivated they were to attend for treatment.

Appropriate education to improve knowledge about the disease may play a large part in motivating all patients, including those with deformities, to take treatment. To carry out this education effectively necessitates an understanding by leprosy workers of local attitudes and ideas about the disease.—Author's Summary

Sabato, S., Yosipovitch, Z., Simkin, A. and Sheskin, J. Plantar trophic ulcers in patients with leprosy. A correlative study of sensation, pressure and mobility. Int. Orthop. **6** (1982) 203–208.

Thirty patients with leprosy were studied to correlate the presence and the site of ulcers with the neurological status of the plantar surface of the foot, the range of motion of the ankle, and the pattern of ground pressure beneath the foot as obtained by a footprint apparatus. A highly significant association was found between the presence of an ulcer and the ground pressure beneath the foot, between the presence of an ulcer and the degree of sensation to pinprick, and between the latter and the ground pressure beneath the foot. No significant association was found between the range of ankle movement and the presence of an ulcer. Possible pathophysiological mechanisms are discussed.—Authors' Summary

Other Mycobacterial Diseases and Related Entities

Allen, B. W., Mitchison, D. A., Chan, Y. C., Yew, W. W., Allen, W. G. L. and Girling, D. J. Amikacin in the treatment of pulmonary tuberculosis. Tubercle **64** (1983) 111–118.

Sensitivity tests on strains from 11 patients with pulmonary tuberculosis, previously treated with kanamycin and/or capreomycin, showed incomplete cross-resistance between amikacin and capreo-

mycin but complete crossresistance between amikacin and kanamycin. Treatment with amikacin of four patients with multiple resistant strains resulted in no response as assessed by sputum smears and cultures, but resistance emerged to amikacin, kanamycin and capreomycin. Amikacin has no role in the treatment of tuberculosis as it cannot be given as an alternative to kanamycin, has no advantages over it and is more expensive.—Authors' Summary

Barriere, H. Sarcoïdes cutanées. Traitement par la thalidomide. [Cutaneous sarcoidosis. Treatment with thalidomide.] Presse Med. **12** (1983) 963. (in French)

Considering the helpful effects of thalidomide on lepromatous reactions and on lupus erythematosus, the author conducted a clinical trial on cutaneous sarcoidosis.

Two pulmonary and cutaneous sarcoidosis patients (whose cutaneous lesions had persisted in spite of a long-lasting corticotherapy) and two cutaneous sarcoidosis patients with lesions resistant to antimalarial treatment were studied. The author reports that the effects of thalidomide are slowly progressive and began to be observed after two months. Consequently, the treatment was prolonged for 6–12 months. The tolerance to thalidomide was good, except for an impression of weakness. Furthermore, thalidomide treatment normalized the level of angiotension convertase when it was abnormally elevated prior to therapy (in two cases).

The author concludes that thalidomide, whose teratogenic effect must be considered, seems to be a possible treatment for persistent forms of cutaneous sarcoides.—(*Translated from* the article)

Buechner, S. A., Winkelmann, R. K. and Banks, P. M. T-cell subsets in cutaneous sarcoidosis. Arch. Dermatol. **119** (1983) 728–732.

Skin lesions from four patients with systemic and cutaneous sarcoidosis were studied, by the use of monoclonal antibodies, for the presence of T cells and T cell subsets. Large numbers of lymphoid cells reacting with anti-pan T cell (Leu-1) and anti-helper and inducer subset (Leu-3) monoclonal antibodies were observed around and within the sarcoid granulomas in three of the four patients. Only rare Leu-2-reactive suppressor cells were observed in all four patients. Activated T lymphocytes with focal acid phosphatase activity, together with epithelioid cells and multinucleated giant cells with strong diffuse activity of acid phosphatase and nonspecific esterase, were identified within the granulomas. The two patients with active disease demonstrated substantially more T cells in the sarcoid granulomas than did the two patients with chronic disease. Our study results suggest the importance of helper T cells in the formation of the sarcoid granuloma by mononuclear phagocytes and imply that the activity and duration of disease may be related to the T cell populations.—Authors' Abstract

Gatti, C. F. and Sampaio, A. P. Leishmaniasis anergica difusa (leishmaniasis lepromatosa). [Diffuse anergic leishmaniasis (lepromatous leishmaniasis).] Rev. Fontilles **14** (1983) 21–25. (in Spanish)

A case of anergic diffuse leishmaniasis in a 14-year-old boy is presented. Montenegro's reaction was negative. We observed a big quantity of parasites in the lesions. The treatment gave unsatisfactory results. Differential diagnoses are discussed.—Authors' Summary

Gorzynski, T. J. and David, C. S. Immune-response gene-associated antigens (Ia/DR). Structure and function in immunologically related diseases. Mayo Clin. Proc. **58** (1983) 457–466.

Major histocompatibility complex-determined antigens were originally identified as a consequence of their ability to induce rejection of tissue grafts between organisms that are not genetically identical. Currently, much is known about their biochemical nature and intended biologic functions. Major histocompatibility complex antigens are found on three types of glycoprotein molecules. One type (class I) is associated with β_2-microglobulin in the cell-surface membranes of all body tissues and includes H-2K and D molecules in mice and HLA-A, B, and C molecules in humans. These antigens

are the major cause of rejection of transplanted organs. The other two types of glycoproteins (class II) are noncovalently linked to each other, are found in the cell-surface membranes of a limited number of cell types, and include H-2-Ia molecules in mice and HLA-DR molecules in humans. They are noted for their ability to elicit graft-versus-host disease. Both class I and class II molecules are, however, important for the immune recognition of pathogens, although the types of responses they modulate are different. Class I molecules are important in the recognition of cell-surface antigens, whereas class II molecules control responsiveness to soluble antigens. Major histocompatibility complex-encoded molecules are also involved in certain autoimmune diseases. As our understanding of major histocompatibility complex-controlled immune responsiveness broadens and hybridoma and gene-cloning technology advances, specific enhancement of desired immune responses and suppression of deleterious ones will most likely become possible.—Authors' Abstract

Khomenko, A. G., Golyshevskaya, V. I., Korolev, M. B., Litvinov, V. I., Ilyina, I. N. and Romanova, R. Y. Isolation and study of the morphological properties and immunogenicity of *Mycobacterium tuberculosis*. English abstract in Zh. Mikrobiol. Epidemio. Immunobiol. **5** (1983) 36.

The experimental study made on 185 guinea pigs revealed that during the chemotherapy of destructive tuberculosis the typical bacterial forms of *Mycobacterium tuberculosis* rapidly disappeared, but the cavities of destruction were retained and the presence of the filter-passing forms of *M. tuberculosis*, along with antigenemia and specific cell-mediated and humoral immunity could be detected. The use of repeated biological subculturing resulted in the reversion of the filter-passing forms of *M. tuberculosis* to their typical bacterial forms; simultaneously the increase of antigenemia (from subculture to subculture) and the enhancement of immune responsiveness occurred.—Authors' Abstract

Lavalle, P., de Ovando, F., Novales, J. and Ayala, J. L. Micobacteriosis cutanea ulcerosa. [Ulcerative cutaneous mycobacteriosis.] Rev. Mex. Dermatol. **25** (1981) 325–347. (in Spanish)

The authors review the wide distribution of *Mycobacterium ulcerans* infection in areas of four continents. They disagree with the use of local names for such infections. Taking into account the peculiar clinical, histopathological, and bacteriological characteristics of the disease, they propose to name it ulcerative cutaneous mycobacteriosis by *M. ulcerans* (micobacteriosis cutanea ulcerosa por *M. ulcerans*).

They review the main features of the first Mexican case of this mycobacteriosis, published in 1953 and 1956, and report a second case. The second case from Mexico was an 11-year-old boy from Tepepa, Hidalgo State, who had an ulcer on the right hand with a necrotic central zone and irregular and undetermined borders, of two-months duration, following a trauma. Smears of the necrotic material, as well as biopsy specimens, showed clumps of acid-fast bacilli in the center of the ulcer, but not in the border, in which granulomas with epithelioid and giant cells were seen. Only one colony of acid-fast bacilli was obtained on culture (Löwenstein medium) at 33°C.

Treatment was started with dapsone (DDS), 100 mg daily alone. Sulfamethoxazole-trimethoprim, two tablets daily, was added but after two months no improvement had occurred. Rifampin was then substituted for sulfamethoxazole-trimethoprim, and rapid clinical and bacteriological improvement occurred with complete cicatrization within five weeks. A skin graft was performed in order to complete the treatment.

These two cases came from neighboring areas of the state of Hidalgo, in which there are some small lakes and dams, as has been described in other endemic zones of the world.—Authors' Summary

Ledermann, J. A. and Hoffbrand, B. I. Dapsone in allergic vasculitis: Its use in Henoch-Schönlein disease following vaccination. J. R. Soc. Med. **76** (1983) 613.

Dapsone, a sulfone, is well known for its use in the treatment of dermatitis herpetiformis. It has also been used successfully in

other inflammatory skin diseases, including allergic vasculitis. Erythema elevatum diutinum, which in common with allergic vasculitis is a leukocytoclastic vasculitis, seems particularly responsive to dapsone. Henoch-Schönlein disease, a syndrome of allergic vasculitis, is often encountered in general medicine but there have been no reports of the use of dapsone in the treatment of this condition.

We describe a case of Henoch-Schönlein disease that followed typhoid and paratyphoid A & B (TAB), cholera and yellow fever vaccination, resulting in a chronic vasculitis that was successfully treated with dapsone.—(*From* the case report)

Portaels, F. and Kimanuka, T. Growth of actinomycetales in relation to the pH of the medium. Abstract in Ann. Soc. Belg. Med. Trop. **64** (1983) 178.

Ninety strains belonging to the genus *Nocardia* and 60 strains belonging to the genus *Mycobacterium* were studied.

The growth at different pH values was tested for the mycobacteria on Löwenstein-Jensen and Dubos oleic agar media; pH gradients were obtained by use of the McIlvaine's citrate and Sörensen's citrate buffers. The growth of *Nocardiae* and some *Mycobacteriae* was tested on glucose yeast extract agar and modified Sauton's media; pH gradients were obtained with McIlvaine's citrate buffer and on media adjusted with HCl or NaOH.

The sensitivity of *Mycobacteriae* and *Nocardiae* for different pH values was independent of the culture medium and the buffer used.

Most of the strains tested grew within a defined pH range. Minimal, maximal and optimal pH values were characteristic of each species, strains of the same species producing identical results. However, strains belonging to the *N. asteroides* taxon and the *M. avium-intracellulare-scrofulaceum* (MAIS) group, multiplied within various pH ranges. These results are in agreement with other systematic analyses which also demonstrated the heterogeneity of the "asteroides" and the "MAIS" complexes.

In general, rapidly growing *Mycobacteriae* and *Nocardiae* exhibited a wide pH range. All strains, except *M. chelonei* and *N. vaccinii* optimally grew between pH 7 and 9. The slowly growing *Mycobacteriae* generally had a narrower pH range. The optimal pH growth range was between 5.8 and 6.5 for all the slow growers with the exception of *M. lepraemurium* which had the narrowest optimal pH range (between pH 5.8 and 6.1).

The specificity of the pH growth range of *Mycobacteriae* and *Nocardiae* constitutes an additional taxonomic character differentiating difficult to identify organisms. The pH growth range studies allowed us to confirm the identification of some of these strains at the species level and provided an additional taxonomic character to classify some isolates in new taxa.—Authors' Abstract

Prabhu, R. and Reddy, M. V. Active and total E-rosette forming T-lymphocytes in pulmonary tuberculosis. Indian J. Med. Res. **77** (1983) 308–313.

Active and total E-rosette forming cells (A-RFC and T-RFC) were estimated in the peripheral blood of pulmonary tuberculosis patients with active disease and relapse as well as treated cases. It was observed that in active cases A-RFC and T-RFC levels were decreased, whereas in patients with relapse A-RFC were significantly reduced—the T-RFC were similar to the percentage in controls. Treated patients as well as control subjects had higher levels of both cell types. In patients who showed improvement after two months of treatment there was a concomitant increase of both the cell types. However, A-RFC appeared to be the more significant sub-population of T lymphocytes in all the types of patients. There was no relationship between the intensity of delayed hypersensitivity and the level of A-RFC and/or T-RFC.—Authors' Abstract

Sisk, J. E. and Sanders, C. R. Analyzing the cost-effectiveness and cost-benefit of vaccines. World Health Forum **4** (1983) 83–88.

There are currently more than 50 types of vaccines in the USA that offer protection against diseases as well known as mumps and others as unfamiliar as anthrax. How worthwhile are these vaccines? Whereas pa-

tients and their physicians may be in the best position to evaluate the benefits of the vaccines for individual use, economists and policy analysts have attempted to evaluate the benefits of some of these vaccines for the population as a whole or for certain groups in the population. In doing so, analysts have relied on two related techniques, cost-effectiveness analysis and cost-benefit analysis.

This medical perspective considers seven vaccines that have been studied by cost-effectiveness or cost-benefit analysis. Four of the vaccines—pertussis, poliomyelitis, measles virus, and rubella virus—are intended for the general population and primarily for routine immunization of children. The other three vaccines—influenza virus, pneumococcal, and bacille Calmette-Guérin (BCG)—are recommended for persons (primarily adults) who are at high risk.

The four vaccines for routine immunization during childhood are not only cost-effective, but also save money; they confer net health benefits and reduce net medical costs. Two of the vaccines intended primarily for adults and special populations—influenza virus and pneumococcal—are cost-effective because they improve health at a low cost. These vaccines, however, do not result in net medical care savings. The third vaccine for special populations, BCG, may improve health, although the cost savings from vaccination are uncertain and may be small.—(*From* the article)

Sivaraman, S. Tuberculosis in India—the prospect. Indian J. Tuberc. **29** (1982) 71–86.

The extensive lecture on which this paper is based surveyed tuberculosis from China to Peru. There are highly informative maps of the various regions of the world illustrating the extent of the tuberculosis problem in each country. The main interest of the lecturer is, however, India—where the tuberculosis death rate is estimated to be 80–100/100,000, the highest anywhere in the world but declining. Extensive tuberculin testing in various BCG vaccination campaigns provided data from which it may be estimated that the annual infection rate may be 10–20/1000, which is at least double the average rate in developing countries and ten times that in developed countries. As regards prevalence, there is evidence of a rate of bacillary cases of about 400/100,000. There is no evidence of improvement throughout the country. Without diagnostic facilities and systematic notification of cases it is difficult to present satisfactory information about the incidence of the disease. There are very few reports on attack rates.

In the absence of statistical data it is impossible to judge the effect of 30 years' BCG vaccination campaigns and of the National Tuberculosis Control Programme which has now been in operation for 15 years. Its objectives are widespread BCG vaccination and case-finding with adequate treatment of patients discovered to have tuberculosis, priority being given to those with positive sputum. These activities are to be carried on as an integral part of general health services and should involve both government and private institutions and medical practitioners. Using data from the national survey it may be estimated that there would be 5000 infectious tuberculous patients and 15,000–20,000 with abnormal skiagrams suggestive of tuberculosis but with negative sputa to be dealt with at any one time.

At present about 47% of India is not covered by the control program because of operational and managerial problems. "We [in India] will have to shout at our fellow men in the medical profession and tell them that we can no longer be indifferent to our tuberculosis situation. Jointly we may then shout to the decision makers and tell them what is to be done."—H. G. Calwell (Trop. Dis. Bull.)