CURRENT LITERATURE

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

General and Historical

Hay, R. J. The control of infective skin diseases—the lessons of leprosy research. Br. J. Dermatol. **119** (1988) 495–502.

Infectious disease research has covered much ground in 100 years. In 1888 the first attempts to isolate and categorize infectious organisms were being made, but in many cases it had not been possible to establish their involvement in the disease process by objective criteria. Methods for laboratory diagnosis and treatment were necessarily crude. In the succeeding years progress has been rapid, particularly in the fields of diagnostic microbiology, chemotherapy and immunology. The ability to sequence sections of the genome of many organisms is the latest, and perhaps most remarkable, of these achievements. The progress in our understanding of one of the oldest known infections, leprosy, amply illustrates the extent of these advances.

Although it is an important example, leprosy displays a number of unusual features. Firstly, it has not been possible to maintain the bacterium in laboratory culture, a problem seen with other skin pathogens from human papilloma viruses to the fungus *Loboa loboi*. The new technology of molecular genetics has proved an invaluable tool in circumventing this problem. Secondly, *Mycobacterium leprae* parasitizes Schwann cells, among other sites, and is almost certainly afforded some protection thereby from immune surveillance. The natural history of the disease is also incompletely understood. Little is known, for instance, about the exposed individual who does not develop the disease. There have been reports that bacilli can be found in uninvolved skin in subjects who never develop any of the features of leprosy. The status of these individuals and the conditions which determine progress to the polar variants of leprosy need to be defined. The advent of new serological tests which utilize specific antigens may provide some of the answers.

While much of this account has dealt with clinical and laboratory aspects of leprosy, subsequent progress toward the elimination of the disease is largely dependent on the ability of countries in the endemic areas to deliver therapeutic measures and to monitor their short- and long-term effects. That such measures are necessary is well illustrated by the example of another infection principally affecting the skin, yaws, which was the subject of a worldwide eradication program in the early 1960s. In the last few years, the disease has re-emerged in West Africa and the West Pacific. While the exact reasons are not clear, discontinuation of surveillance in the face of other health priorities is a likely explanation. The process of recruitment and maintenance of an infrastructure for disease eradication is both costly and time consuming. Unfortunately, without it control of the major endemic infections is not possible, even though the scientific goals are probably achievable within the foreseeable future.—Author's Conclusion

Lorentsen, M. and Solheim, T. [Viking-age skeleton exhibiting pathologic changes in the dentition and maxillary and mandibular bones—scurvy or leprosy?] Nor. Tannlaegeforen Tid. **98** (1988) 132–139. (in Norwegian)

The skeletal remains of a girl, aged approximately 14 years, were found in northern Norway, near Harstad, in 1975. They were estimated to be from the years 600 to 1000 A.D. Dental examination revealed enamel hypoplasias and shortened peaked roots. Furthermore, destruction of the periodontal ligament of the upper front teeth

and widening of the periodontal membrane together with pitting of the cortical bone along the upper and lower jaw, in the palate, nose and eye cavities, were found. Various diseases are discussed, and it is concluded that scurvy and leprosy can best explain the findings, with the former as the most likely because of the time the girl lived. The importance that such archeological findings should be examined by interested dentists is stressed.—Authors' English Summary

Olivier, H. R. On being diagnosed a "leper": a paradigm. So. Med. J. **81** (1988) 1426–1432.

The stigma of leprosy persists despite effective treatment for the disease, educational campaigns, positive publicity, and a change in the name of the disease. These negative attitudes cross cultural, geographical, and religious boundaries and are ingrained in the collective unconscious. It is not surprising that the diagnosis of Hansen's disease has an enormous, negative emotional impact on the patients as well as their families and friends. Four case histories are presented from the literature from the presulfone era, together with two recent patients. The sense of loss caused by the diagnosis triggers a series of reactions: denial, bargaining, anger, depression and, finally, acceptance.—RCH

Chemotherapy

Bourée, P., Carré, N. and Drahmane, S. [Guinea: detection of leprosy and multidrug therapy.] Bull. Soc. Pathol. Exot. Filiales **81** (1988) 683–691. (in French)

For the past year, the implementation of multidrug therapy in leprosy control in Guinea has required close cooperation between the Department of Leprosy Control and local nurses. The known prevalence of leprosy in the Pita area is 1.23 per thousand; 246 patients have been detected, 36 multibacillary and 210 paucibacillary. The sex ratio of the patients has changed during the year with an increase in the proportion of males. With the increased awareness of leprosy among the local population, the number of new cases detected is increasing and the proportion of patients regularly receiving treatment is now 87.6%.—Authors' English Summary

Carvalho Costa, I. M., Daniel, L. L. and Carneiro, R. M. [Ethionamide in combined chemotherapy.] An. Bras. Dermatol. **63** (1988) 351–352. (in Portuguese)

The applicability of ethionamide in various clinic forms of leprosy in combined chemotherapy is reported by the authors.—Authors' English Summary

Chen, J., *et al.* [The toxic reaction in treatment of leprosy anti-relapse with prothionamide, rifampicin and dapsone.] Chin. J. Clin. Dermatol. **17** (1988) 231–233. (in Chinese)

Thirty-four cases of multibacillary leprosy were treated with rifampin plus dapsone plus prothionamide as anti-relapse for 6 months. The treatment of 24 (70.6%) cases was discontinued because of toxic reactions and an elevation of SGPT. The results showed that the toxicity of this combined therapy was obvious and therefore it was suggested that the regimen should not be extended into the field.—Authors' English Abstract

Dey, S. K., Chanda, M., Chowdhury, A. and Panja, S. K. Treatment of paucibacillary leprosy by WHO regimen. Indian J. Dermatol. **32** (1987) 11–13.

Fifty cases of paucibacillary leprosy were selected for study with multidrug therapy (MDT) as recommended by the World Health Organization for 6 months. At the end of 6 months, 46 cases showed no clinical activity and four cases showed increased clinical activity with flaring up of the lesions during treatment.—Authors' Abstract

Floch, H. A. and Floch, H. H. Biorésistance en general—chimiorésistance comparée sulfonorésistance du bacille de Hansen ce qu'il faut faire en vérité pour gagner le combat contre la lèpre. Inter-Fac. Afrique **5** (1988) 29–35. (in French)

Soulignant que la "chimiorésistance" (et "l'antibiorésistance") microbienne n'est qu'un cas particulier de la "biorésistance" en général, liée directement à la vie elle-même et si souvent obstacle à nos actions thérapeutiques actuelles, il peut être enrichissant de rappeler les enseignements fournis par les insectes (Anophèles et Aedes notamment) face aux "pesticides" largement utilisés de par le monde. D'où le rappel des difficultés exemplaires de la Lutte Antipaludique et Antiamarile en Guyane Française, il y a quelques années.

La chimiothérapie ne doit pas être galvaudée.

La sulfono-résistance du Bacille de Hansen, prévue depuis longtemps, est présentée, actuellement, comme une catastrophe à l'égard de la monothérapie de la lèpre par la Sulfone-Mère.

Nous estimons que ces constatations sont le résultat de thérapeutiques sulfonées mauvaises, ayant abouti, chez les malades en question, à des sulfonémies insuffisantes, provoquées par l'utilisation de sulfones substituées complexes, par l'emploi de doses de D.D.S., insuffisantes, par des traitements inadéquats, irréguliers, mal suivis, trop tôt interrompus, etc.

Pour éviter les sulfono-résistances (secondaires ou primaires) des B.H., deux positions sont à prendre.

La première, la principale actuellement, position ancienne qui n'aurait jamais dû être abandonnée, est d'utiliser la D.D.S. à la dose "maxima-active-tolérée" de 200 mg/jour/adulte et non à celle de 100 mg devenue généralement habituelle.

La seconde, logique et parfaite théoriquement, est la mise en œuvre d'une polychimiothérapie triple, simultanée, centrée par la D.D.S. associée à la Rifampicine et à la Clofazimine ou à l'Ethionamine est malheureusement, d'une part très coûteuse, redhibitoire, de ce seul fait, dans la plupart des pays d'endémicité lépreuse, pauvres et sous-développés et, d'autre part, très difficile à mettre en œuvre de façon correcte sans risque d'apparition, elle catastrophique, d'une multichimiorésistance du B.H.—Authors' Summary

Franzblau, S. G. and Hastings, R. C. *In vitro* and *in vivo* activities of macrolides against *Mycobacterium leprae*. Antimicrob. Agents Chemother. **32** (1988) 1758–1762.

We previously demonstrated the potent *in vitro* activity of erythromycin against *Mycobacterium leprae* as determined by its effect on ATP pools and rates of palmitate oxidation and phenolic glycolipid-I synthesis. In the present study, the relative *in vitro* activities of a number of new macrolides with superior pharmacokinetic properties were assessed. In addition, for the most active compounds, concentrations in serum were determined by bioassay during continuous administration in the feed of mice, and *in vivo* activity against *M. leprae* was assessed by the kinetic mouse foot pad technique. Both clarithromycin and roxithromycin were more potent than erythromycin *in vitro*, with the former showing the highest activity in accelerating rates of ATP decay and reducing rates of palmitate oxidation. In mice, concentrations of clarithromycin in serum were higher than those of roxithromycin and erythromycin, with the latter undetectable even when administered at 0.1% (wt/wt) in the diet. When administered at 0.01% (wt/wt) in the diet, erythromycin and roxithromycin were unable to inhibit growth of *M. leprae* in mouse foot pads; whereas clarithromycin demonstrated bactericidal-type activity. On the basis of these data and other properties of macrolides, a clinical trial of clarithromycin in leprosy is warranted.—Authors' Abstract

Franzblau, S. G. and O'Sullivan, J. F. Structure-activity relationships of selected phenazines against *Mycobacterium leprae in vitro*. Antimicrob. Agents Chemother. **32** (1988) 1583–1585.

Structure-activity relationships of phenazines against *Mycobacterium leprae* were investigated by using an *in vitro* radiorespirometric assay. In general, activity in ascending order was observed in compounds containing no chlorine atoms, a monochlorinated phenazine nucleus, and chlorines in

the *para* positions of both the anilino and phenyl rings. The most active compounds contained a 2,2,6,6-tetramethylpiperidine substitution at the imino nitrogen. Most of these chlorinated phenazines were considerably more active *in vitro* than clofazimine (B663).—Authors' Abstract

Fumey, S. M. [Photodermatitis induced by DDS in a leprosy patient.] Z. Hautkr. **63** (1988) 53–54. (in German)

We report on a 60-year-old man suffering from borderline leprosy. He was treated many times with dapsone and clofazimine and underwent the so-called multiple drug treatment (MDT). Under this therapy, the patient developed allergic photodermatitis. Unfortunately his file was lost and, as nobody was informed about his allergic reaction, he was again treated with the preparations mentioned above. Consequently, he responded once more with photodermatitis.—Author's English Summary

Girdhar, A., Mishra, B., Bagga, A. and Birdhar, B. K. Drug compliance among self-motivated leprosy patients. Indian J. Lepr. **60** (1988) 506–509.

Regularity of dapsone (DDS) intake among 366 leprosy patients attending our outpatient department voluntarily was assessed by urine spot test. It was found that only 54.6% of them had taken their last dose of drug within the previous three days. Those who kept their appointments showed better compliance than those who did not. Urinary DDS positivity was found to be unrelated to sex, occupation or the type of the disease. In the younger age group the compliance was low, as also among the patients coming from nearby places as compared to those who were residing in far off districts.—Authors' Abstract

Grugni, A., Nadkarni, N. J. and Kini, M. S. Multidrug therapy in paucibacillary leprosy—a five year experience. Indian J. Lepr. **60** (1988) 589–592.

A total of 736 paucibacillary (PB) patients were given multidrug therapy (MDT) for at least 6 months. Overall, 44% became inactive after six doses, and 69% after 12 doses. However, 27% remained active at the time of analysis. It is recommended that at least 12 doses of MDT be given to PB patients irrespective of the type.—Authors' Abstract

Horai, Y. and Ishizaki, T. N-Acetylation polymorphism of dapsone in a Japanese population. Br. J. Clin. Pharmacol. **25** (1988) 487–494.

The frequency of slow acetylators determined using the plasma monoacetyldapsone to dapsone ratio after 3 hr was 6.6%. The incidence of slow acetylators was lower in males than in females. The mean plasma concentration of the metabolite was significantly lower in the slow compared to the rapid acetylators. Slow acetylators showed a significantly lower urinary metabolite/drug ratio and excreted less metabolite than rapid acetylators.—Victor Origoni (Int. Pharm. Abstracts)

Li, W., *et al.* [Effects of MDT on multibacillary leprosy for three years.] China Lepr. J. **4** (1988) 129–131. (in Chinese)

The results of 3 years' treatment with rifampin, clofazimine, and dapsone in 35 cases of untreated multibacillary leprosy are reported. At the beginning of therapy, the clinical lesions in all patients were active, with an average bacterial index (BI) of 4.06. After 2 years of treatment, the active lesions regressed in most of the patients, but their skin smears did not become negative. At the end of the third year of treatment, the skin smears became negative only in 8 cases (22.9%), and the average BI was reduced to 1.1. The BI in 35 cases decreased by 0.98 per year on the average, which shows that the new and relapsed multibacillary patients who are highly bacilliferous are likely to need 4 to 5 years of treatment until skin smears become negative. In view of the fact that the clinical evaluation often carries some subjectivity, we suggest that more attention be paid to the use of the skin smear in judging the treatment of leprosy on a large scale.—Authors' English Abstract

Ramakrishnan, K. R., Arora, P. N., Aggarwal, S. K. and Ramachandra, S. Paucibacillary leprosy: a comparative study of

different schedules of multidrug therapy. Indian J. Lepr. **60** (1988) 542–548.

The study was undertaken to evaluate the efficacy of various multidrug regimens (MDT). Three groups of 10 cases each of paucibacillary cases were given different schedules of MDT. The first group (T-0) was administered modified WHO regimen consisting of rifampin 600 mg once a month, clofazimine 100 mg alternate days, and dapsone 100 mg daily for 6 months. In the second group (T-1) rifampin 600 mg was given daily for 6 weeks and in the third group (T-2) rifampin 600 mg was given daily for 6 months. In both the latter groups clofazimine 100 mg on alternate days and dapsone 100 mg daily was also administered for 6 months. Objective clinical scoring was done at the time of admission, 3 months and 6 months after treatment in all three groups. The best results were obtained by T-2 followed by T-1; and least effective was T-0 regimen. A pinkish color of urine and skin was observed in 26 cases and icthyosis in all the cases. All the patients remain under treatment. The work is in progress and subsequent results will be published later.—Authors' Abstract

Reddy, P. K. and Mohinuddin, S. K. Patterns of relapses in paucibacillary leprosy patients treated with MDT (WHO 1982). Indian J. Lepr. **60** (1988) 581–588.

Out of 92 paucibacillary leprosy patients treated with MDT (WHO 1982), two patients developed indisputable clinical signs of relapse during the 10th and 26th months of the observation period. Two more patients developed reversal reaction during the 8th and 12th months of the observation period, which we presume to be an early manifestation of relapse. The addition of a more bactericidal drug, rifampin, appeared to have a bearing on the incidence of replase, although not on its incubation period. No change of classification was noticed at the time of relapse. The incidence of relapse in female patients was much higher than in male patients.—Authors' Abstract

Thomas, A., Nagarajan, M., Chandrasekaran, V., Hari, L., Somasundaram, P. R., Prabhakar, R., Kumar, A., Bhatia, V. N. and Roy, R. G. A double-blind controlled clinical trial to assess the role of antihistamines in the treatment of multibacillary leprosy. Indian J. Lepr. **60** (1988) 499–505.

A double-blind controlled clinical trial to assess the role of antihistamines as a supplement in the treatment of leprosy was conducted in multibacillary cases of leprosy. In all, 120 patients with lepromatous or borderline leprosy were randomly allocated to a regimen of clofazimine and dapsone for 12 months with or without a supplement of pheniramine maleate for the first 3 months. During the 12-month period, 92% of the patients who received the supplement and 86% of the patients who had not received it had moderate or marked clinical improvement. The BI values decreased from 4.1 to 3.4 and 4.2 to 3.3, respectively. The results over the 12-month period showed that the addition of the antihistamine had not enhanced the efficacy of the regimen as evidenced by clinical and bacteriological findings.—Authors' Abstract

Wang, H., Li, W., Yang, L., Huang, H., Lu, W. and Yu, L. Survey of primary dapsone-resistant leprosy. Proc. Chin. Acad. Sci./Peking Union Med. College **1** (1986) 173–175.

A survey of primary dapsone-resistant leprosy was performed in seven counties of Jiangsu province from 1979 to 1984. A total of 28 previously untreated multibacillary leprosy patients was randomly selected. Six strains of dapsone-resistant *Mycobacterium leprae* were isolated, five were of low-degree resistance and only one was of high-degree. The prevalence of primary dapsone-resistant leprosy was 24%. Among all of the isolated strains, three failed to infect mice.—Authors' Abstract

Yu, X., *et al.* [Effects of clofazimine on the patients with ENL dependent upon corticosteroids.] China Lepr. J. **4** (1988) 141–142. (in Chinese)

Fifteen cases of BL and LL leprosy with chronic ENL reaction dependent upon corticosteroid have been treated with clofazimine. Its effect was very good in 9 cases

using a daily dose of 300 mg, but 5 out of 6 cases given routine doses of a multidrug regimen failed to respond.—Authors' English Abstract

Clinical Sciences

Chatterjee, G., Kaur, S., Sharma, V. K., Vaishnavi, C. and Kaur, I. Bacillaemia in leprosy: correlation with slit-skin and nasal smears. Indian J. Lepr. **60** (1988) 535–541.

Twenty-five multibacillary patients (BL/LL) were studied for bacillemia. The majority (76%) showed acid-fast bacilli in peripheral blood. There was good correlation between bacillary load in peripheral blood and the bacterial index (BI) but poor correlation with the morphological index (MI) of slit-skin smears and BI/MI of nasal smears.—Authors' Abstract

Chaudhary, S. D., Sen, R., Jain, V. K. and Dixit, V. B. Leukemoid reaction in erythema nodosum leprosum in a leprosy patient. Indian J. Lepr. **60** (1988) 572–576.

A case of lepromatous leprosy with erythema nodosum leprosum (ENL) presenting as a myeloid leukemoid reaction is reported. Very high leukocyte count with immaturity of the cells in the myeloid series was present in the peripheral blood. High leukocyte alkaline phosphatase score, absence of hepatosplenomegaly and the transient nature of the leukemoid reaction differentiated it from chronic myeloid leukemia and acute myeloblastic leukemia. The possible mechanisms of leukemoid reaction in ENL are discussed.—Authors' Abstract

de Menezes, J. A., Novisky Gallo, M. A. and Rocha de Almeida, S. M. [Tuberculoid leprosy with necrotizing neuritis and numerous bacilli in the fistulae.] An. Bras. Dermatol. **63** (1988) 375–377. (in Portuguese)

We report the case of a female patient, aged 37 in whom a necrotizing neuritis of the lateral popliteal nerve was diagnosed in the setting of tuberculoid leprosy after almost 2 years of evolution, mimicking other conditions. Nodular lesions along the nerve opened in fistulae. Smears from the fistulae showed solid-staining bacilli, isolated and in clumps. The patient also had a typical tuberculoid skin lesion on the inner side of the foot.—Authors' English Summary

Extremera Castillo, F., Serrano Ortega, S., Rodriquez-Contreras Pelayo, R., Delgado Rodriguez, M. and Batanero Bernabeu, M. C. [Clinico-diagnostic aspects of leprosy in the province of Jaén (Spain).] Actas Dermosifiliogr. **79** (1988) 561–564. (in Spanish)

Today, leprosy still is an important health problem in the province of Jaén (Spain), which has the highest prevalence in Spain. The study population was formed by the patients under control of the provincial health office, a total of 305 patients. The clinical, diagnostic and therapeutic aspects of the patients were analyzed. The most frequent clinical pattern found in the study was lepromatous leprosy, although its importance changed according to the age of the patients. Most patients (43%) were diagnosed passively, at the physician's office, and not actively, in campaign, being detected 73% at the time by dermatologists. Diagnosis was above all made by clinical aspects, without taking in most cases biopsies. More than 40% of all patients point out a lack of continuity on the recommended treatment. The most frequent treatment prescribed was monotherapy with dapsone.—Authors' English Summary

Garg, R., Agrawal, J. K., Bajpai, H. S., Singh, G. and Srivastava, P. K. Adrenocortical function in leprosy. Indian J. Lepr. **60** (1988) 609–615.

Adrenocortical function was carried out in 43 cases of leprosy. These cases were further divided into tuberculoid, borderline, lepromatous and lepra reaction. Serum and urinary electrolyte, urinary 17-ketosteroid, and 17-ketogenic steroid and plasma cortisol levels were measured to assess the adrenocortical status in these different forms of leprosy. It was observed that these parameters were within normal limits in tuberculoid leprosy except for low values of urinary 17-ketogenic steroid. The borderline and lepromatous leprosy cases revealed low values of urinary sodium, potassium and 17-ketogenic steroid and high levels of serum potassium. However, the cases of lepra reaction revealed low values of serum and urinary sodium and potassium and urinary 17-ketogenic steroid. The basal plasma cortisol level was high in this group but it was statistically insignificant.—Authors' Abstract

Georgiev, G. D. and McDougall, A. C. The bacteriological examination of slit-skin smears in leprosy control programmes using multiple drug therapy; a plea for radical changes in current operational methodology. Indian J. Lepr. **59** (1987) 373–385.

The authors discuss in detail one of the most important, yet poorly performed, aspects of management in leprosy. Modern multidrug therapy for leprosy patients is administered according to the bacterial load as estimated by slit-skin smears (only a small proportion of patients are histologically assessed). Failure to enumerate bacilli in smears accurately results in patients having the wrong therapy—if underestimated, short-course therapy in multibacillary patients may lead to relapse; if overestimated, paucibacillary patients are overtreated, with ensuing logistic and financial problems.

In the authors' experience, very few programs have smears taken, fixed, dispatched, stained, reported and recorded properly and systematically. The common causes of this state of affairs are documented, among which the training, supervision, morale, and remuneration of smear technicians are highlighted.

Three major proposals are made: a) to reemphasize the importance of careful clinical examination of patients in the field, while rationalizing the performance of skin smears so that fewer, but more relevant, smears are taken; b) to improve and standardize the technique of smear taking; c) to concentrate the laboratory examinations of smears in a few centers rather than have them performed in numerous unsupervised peripheral units. This latter proposal would place the laboratories by the clinical referral centers, where problems and relapses could be evaluated, and would enable better quality control of smears. Cost-effectiveness of programs would also improve.—S. B. Lucas (Trop. Dis. Bull.)

Gupte, M. D., Raj, C. A. D., Kannan, S. and Desikan, K. V. Reliability of direct skin smear microscopy in leprosy. Indian J. Lepr. **60** (1988) 566–571.

Skin-smear direct microscopy is an important tool for the diagnosis of leprosy. The study was planned to understand the reproducibility of skin-smear reading by a trained technician. Skin smears were collected from known leprosy patients from the field area. They were stained for acid-fast bacilli following the standard cold staining procedure and were read following the Ridley scale. A sample of smears was re-examined on two occasions by the same technician, following blind procedure. There was a systematic underreading on the second occasion which was attributed to the defective storage of the slides. However, the agreement between the second and third examinations was very good (Concordance 81.34%, Kappa 0.74). The finding was confirmed on a repeat examination. It can be concluded that direct skin smear microscopy is a reliable and reproducible technique under experimental conditions.—Authors' Abstract

Hammond, C. J. and Klenerman, P. Protective sensation in the foot in leprosy. Lepr. Rev. **59** (1988) 347–354.

Plantar ulceration is a significant problem in leprosy patients and accounts for a large proportion of hospital admissions. Three methods of sensory testing were employed to see if a high-risk group of people with loss of protective sensation might be selected, so that the serious first ulcer might

be prevented. Three groups of patients were studied: 41 leprosy patients with ulcers, 41 without ulcers and 48 control subjects without leprosy. The results show that either or both Semmes-Weinstein nylon monofilaments and biosthesiometer may prove a more reliable method of sensory testing than the standard WHO pencil stimulus.—Authors' Summary

Janssen, F., Wallach, D., Khuong, M. A., Pennec, J., Pradinaud, R., Said, G. and Cottenot, F. [Association of leprosy and infection with the human immunodeficiency virus; two observations.] Presse Med. **17** (1988) 1652–1653. (in French)

Numerous infections with mycobacteria have been described for subjects seropositive for the human immunodeficiency virus. Nevertheless, in the case of numerous regions with endemic parishes, the association between leprosy and infection with the human immunodeficiency virus only one case has been described. We report here two new observations.

Observation no. 1: M.E., 28 years old from Martinique, bisexual, was diagnosed in 1976 as having lepromatous leprosy, treated with rifampin, dapsone, and clofazime until May 1985. The course of the disease was marked by numerous episodes of ENL with neurological sequellae. The bacterial counts responded to treatment and were negative from 1978 until 1986. In the recent past, he had developed syphilis and urethral gonorrhea. In February 1987, at the time of a polyarthritis due to *Chlamydia,* he simultaneously developed a bacteriologic relapse of his leprosy with a bacterial index of 1+, on the scale of Ridley, and additionally developed a positive serology for human immunodeficiency virus with a positive viremia, a T4 count of 121/mm^3 and a ratio of T4/T8 of 0.48, and a polyadenopathy which classified the disease as group III (CDC Atlanta).

Observation no. 2: M.A., 27 years old, from Guyana, heterosexual, without contact history, was treated from 1978 to 1982 for pure cutaneous leprosy with a multitherapy including depot dapsone. In September 1987, began a sensory motor multineuritis which was grossly symmetrical with palpable hypertrophy of the nerve trunks. Major sensory motor deficits with bilateral characteristic hand clawing rapidly established themselves in spite of resumption of triple-drug therapy. Neurological examinations confirmed the leprosy as the cause of the multineuritis. The negativity of the bacteriological samples, the development of a positive intradermal reaction to lepromin and the presence of a moderate tuberculoid infiltrate on cutaneous biopsy of an achromic zone were all in favor of a multineuritis relapse. In parallel, there was an alteration in the general state of the HIV1 serology, which is positive (HIV2 and HTLV1 negative). The total lymphocytes and the B and T subpopulations were normal in absolute value, the ratio of OKT4/OKT8 decreased to 0.29; the existence of buccal candidiasis and esophogeal candidiasis made the classification of the disease at this stage IV C2 (CDC Atlanta).

These two observations of leprosy with positive HIV, one case a bacteriologic relapse and the other a probable reversal reaction, emphasize the complexity, foreseeable, of the association between these two infectious diseases involving cellular immunity.—(*Translated from the* Article)

Kumar, N., Saraswat, P. K. and Shanker, A. Estimation of high density lipoprotein cholesterol in the diagnosis of lepromatous leprosy. Indian J. Lepr. **60** (1988) 600–603.

A high incidence of increased plasma level of high-density lipoprotein cholesterol (HDL-C) has been reported in cases of lepromatous leprosy. HDL-C levels were estimated in 96 (50 under treatment and 46 untreated) lepromatous leprosy patients and 84 randomly selected, matched control patients suffering from other skin diseases attending skin out-patients' department. HDL-C estimation was performed for the diagnosis of lepromatous leprosy in patients aged below 60 years, taking plasma HDL-C levels as 28–71 mg/dl in men and 34–91 mg/dl in women, as ranges of normal values. The study revealed that HDL-C levels in the lepromatous leprosy group were raised and significantly different when compared with the control group ($t = 35.1668$ and $p < 0.001$). The sensitivity of the test was very high, 97.9% (94/96), but specificity was

low 80.95% (68/84). False-positive and false-negative results were 19.04% (16/84) and 2.08% (2/96), respectively. It is opined that a negative test will be mainly useful in excluding the diagnosis of lepromatous leprosy.—Authors' Abstract

Ndiaye, N., Gueye, M. M. and Kane, A. W. [Epidemiologic study of the orodental health of the lepers in MBalling (MBour-Senegal).] Odontostomatol. Trop. **8** (1985) 130–132. (in French)

The authors made a survey about a population living in a village for leprous people in Senegal, but where there are also nonleprous inhabitants. The sample was made up by 30% of each group. They found that the mean oral hygiene index was 2.03 for leprous and 1.50 for nonleprous people. Concerning caries, the mean index was found 4.05 for leprous and 1.98 in the nonleprous people. The authors point out the difficulty for leprous people to clean their teeth which explains the results of the survey. They underline also the difficulties of the dental service in such remote villages and the fear of contagion of the dental personnel.—Authors' English Abstract

Pattyn, S. R. La lèpre importée en Belgique: diagnostic. Rev. Med. Liège **43** (1988) 125–128. (in French)

Il n'y a pas de réaction sérologique qui puisse être utilisée dans le diagnostic de la lèpre. La réaction après injection intradermique de la lépromine n'est utile que pour la classification: elle est positive dans les formes tuberculoïdes, négative dans les formes lépromateuses. Il est possible de poser le diagnostic de lèpre en présence d'au moins deux des signes suivants: l'existence de lésions cutanées hypo- ou hyperchromiques bien ou mal délimitées, la perte de la sensibilité, l'épaississement des troncs nerveux, la présence de bacilles acido-résistants dans le suc dermique. Il s'agit ici du cinquième article que le professeur E. Marck et ses collaborateurs ont consacré à une actualisation des maladies d'importation. Ces articles ont également été publiés dans le Tijdschrift voor Geneeskunde.—Author's Summary

Ponnighaus, J. M. and Fine, P. E. M. Leprosy in Malawi. 1. Sensitivity and specificity of the diagnosis and the search for risk factors for leprosy. Trans. R. Soc. Trop. Med. Hyg. **82** (1988) 803–809.

The sensitivity and specificity of the diagnosis of leprosy in the context of a total population survey are examined. It is apparent that diagnostic tools are unsatisfactory with regard to reaching a highly sensitive and specific case definition of paucibacillary leprosy, particularly in actively found suspects. Histopathological examination of 4-mm punch-biopsy specimens contributed appreciably to both the sensitivity and specificity of the diagnosis of leprosy, although there was evidence for false-positive and false-negative histopathology results. The needs for high sensitivity during the intake phase of a vaccine trial and for high specificity during follow-up surveys for risk factors are discussed.—Authors' Abstract

Razack, E. M. A., Dharmaraj, S., Krishnaram, A. S. and Selvaraj, A. M. Multicentric reticulohistiocytosis masquerading as lepromatous leprosy. Indian J. Lepr. **60** (1988) 604–608.

A 23-year-old male presented for evaluation of skin colored, non-scaly, asymptomatic papulonodules of sizes varying from 0.5 cm to 2 cm of 4 years' duration distributed all over the body including the ears. The plaques present on the face gave the appearance of a "leonine facies." Clinically mistaken for lepromatous leprosy in reaction the patient was treated with antileprosy and anti-inflammatory drugs in three other centers for months with no improvement. Systemic involvement included painful swelling of both knee joints, pericardial effusion episcleritis and enlarged liver. Negative slit smears for AFB from the nodules repeatedly and the histology of one on the skin modules clinched the diagnosis of multicentric reticulohistiocytosis. The case is reported not only for its rarity and varying clinical lesions simulating lepromatous leprosy but also to alert leprologists to avert unreasonable delay in diagnosis.—Authors' Abstract

Saxena, N., Sharma, R. P. and Singh, V. S. Study of serum zinc level in leprosy. Indian J. Lepr. **60** (1988) 556–561.

The serum zinc level was estimated in different types of leprosy by the dithiazone extraction method in 75 leprosy patients comprising 15 each of tuberculoid tuberculoid (TT), borderline tuberculoid (BT), borderline borderline (BB), borderline lepromatous (BL) and lepromatous lepromatous (LL). These findings were evaluated in comparison to 15 normal subjects serving as controls. The serum zinc level was observed to be significantly low in all types of leprosy except tuberculoid leprosy (TT). No significant difference was observed in serum zinc levels before and after 90 days of dapsone therapy. The findings of our study are of considerable importance since zinc deficiency can be one of the factors involved in nonspecific suppression of cell-mediated immunity in lepromatous leprosy.—Authors' Abstract

Singh, N. B. and Choudhary, A. Detection of leprosy antigenuria through DOT-ELISA. Indian J. Lepr. **60** (1988) 526–529.

Fifty-five samples of urine from different grades of leprosy patients and normal persons were processed for detection of PGL-I antigen through DOT-ELISA on nitrocellulose paper strips using anti-human IgG horseradish peroxidase conjugate. About 66.6% of the paucibacillary and 100% of the multibacillary leprosy cases were detectable through this technique on the basis of differential color development on the strips. Possibility of its use in field conditions has been discussed.—Authors' Abstract

Sinha, S., Ramu, G., Girdhar, B. K. and Sengupta, U. A monoclonal antibody based competition radioimmunoassay for monitoring anti-*M. leprae* antibodies in leprosy patients and contacts. Ann. Natl. Acad. Sci. (India) **21** (1985) 109–117.

An antibody competition radioimmunoassay based on a murine monoclonal antibody against *Mycobacterium leprae* for determination of circulating titers of *M. leprae*-specific antibodies in human subjects has been described. The test is specific and all of the lepromatous leprosy patients showed high titers of this antibody. The titers and positivity in the tuberculoid leprosy patients and in apparently healthy contacts of leprosy patients was low. The contacts are being followed up; 23.5% of antibody-positive contacts and 5.3% of antibody-negative contacts have developed disease within the follow-up period of 1 year. Chemotherapy is not remarkably effective in reducing the level of antibody in lepromatous leprosy patients.—Authors' Abstract

Soni, N. K. Epistaxis and leprosy. Indian J. Lepr. **60** (1988) 562–565.

Forty-four leprosy patients with epistaxis were analyzed. Etio-pathogenesis of epistaxis in leprosy is discussed in the light of available literature. It has been suggested that epistaxis is more frequent and severe in leprosy patients and more liable to have complications. Epistaxis in leprosy with nasal lesions may alarm the physician that the patient has some systemic disorder.—Author's Abstract

Watanabe, I., Satoh, S., Fujimori, C., Tsukahara, S. and Takizawa, H. [Ocular leprosy—clinical statistics.] Folia Ophthalmol. **38** (1987) 1810–1816. (in Japanese)

The incidence of ocular involvement in leprosy is common, especially lepromatous leprosy. The ocular symptoms of leprosy in Japan are worth investigating, in view of the decreased numbers and aging of these patients in recent years, although some Japanese ophthalmologists have reported on ocular leprosy.

We examined 425 patients with leprosy [mean age 66.4 years; 331 lepromatous leprosy (L type) and 94 others (non-L type)] as to ophthalmological findings. The overall incidence of blindness was 17.8%; incidence was higher in the lepromatous leprosy and older-aged groups. Characteristic findings of the active stage, such as scleral leproma, iris pearl and corneal nerve beading, were rare. On the other hand, iris atrophy and pannus-like corneal opacity, produced by old inflammation, were frequently ob-

served. Exposure keratitis due to lagophthalmos was commonly seen in both lepromatous and other types of leprosy, and is a very important problem in ophthalmological treatment in the leprosarium.—Authors' English Abstract

Yebra Sotillo, I., Errazquin S. Tejada, L., Sotillo Gago, I. and Camacho Martinez, F. [Thermography as a method for diagnosing leprosy.] Actas Dermosifiliogr. **79** (1988) 561–564. (in Spanish)

Thermographies have been made on hands and feet of 11 patients suffering from leprosy and who had been previously X-rayed. The thermographic alterations were more advanced than the radiological osseous lesions and four cases of highly evolved thermographic alterations were observed on cases which seemed normal on the X-ray. Therefore, the authors recommend the use of thermography as a technique for early diagnosis in the distal alterations caused by leprosy.—Authors' English Summary

Yebra Sotillo, I., Sabate Diaz, J. J., Sotillo Gago, I. and Camacho Martinez, F. [Bone changes in leprosy; a study of distal lesions by means of soft X rays.] Actas Dermosifiliogr. **79** (1988) 451–456. (in Spanish)

The distal osseous lesions occurring in 42 nonhospitalized patients who presented different clinical forms of leprosy have been studied. All these patients were histologically negative and, apparently, in good general condition. This research has been carried out by the means of a soft X-ray technique, which has enabled us to obtain plaques with great definition power. Two new features are described: vascular calcifications and periosteal reaction. Having revised the bibliography, the early diagnostic value of this data is discussed.—Authors' English Summary

Immuno-Pathology

Bach, M.-A. and Launois, P. Mechanisms of *Mycobacterium leprae*-specific T-cell deficiency in lepromatous leprosy. Biochimie **70** (1988) 1013–1018.

Patients suffering from lepromatous leprosy fail to develop an efficient cell-mediated immunity toward *Mycobacterium leprae,* the causative agent. The mechanism of such a specific T-cell tolerance to the bacillus remains a key question in the pathophysiology of leprosy. Macrophages do not show any intrinsic defect in phagocytizing and killing *M. leprae* or in presenting antigen to helper-T cells. On the other hand, *M. leprae*-reactive helper-T cells do persist in lepromatous patients, but their activation appears to be prevented by active suppressor mechanisms, involving both suppressor-T cells and macrophages. The target of this specific suppression could be the interleukin 2-producing T-cell subset. A better molecular definition of *M. leprae* antigens, both by monoclonal antibodies and T-cell clones, should open new perspectives for further analysis of the regulation of immune responses to *M. leprae.*—Authors' Summary

Bharadwaj, V. P. Immunodiagnostic approaches to the early detection of subclinical infection in leprosy. Ann. Natl. Acad. Med. Sci. (India) **21** (1985) 128–139.

For establishing the extent of infection, course of the disease and for instituting proper therapeutic or prophylactic measures, the detection of subclinical infection is of paramount importance. Besides the clinical and bacteriological parameters, several tests which measure the cell-mediated immune (CMI) response to *Mycobacterium leprae* antigens have been tried to measure the subclinical infection. These tests are lepromin response, lymphocyte transformation test (LTT), and lymphocyte migration inhibition test (LMIT). Various serological assays have also been tried to assess the subclinical infection. These tests include

nonspecific, crossreactive and specific assay systems. During recent years, the FLA-ABS tests, radioimmuno-assay systems, ELISA tests, and monoclonal antibody based SACT tests have been described for measuring the antibody responses. The advantages and limitations of these assay systems besides other described techniques for serology as well as tests for measuring CMI have been detailed in this paper.—Authors' Abstract

Blair, A. L., Cree, I. A. and Swanson Beck, J. Measurement of phagocyte chemiluminescence using a microtitre plate luminometer. Trans. R. Soc. Trop. Med. Hyg. **82** (1988) 943.

Lucigenin-dependent chemiluminescence (CL) is used to detect reactive oxygen species, particularly superoxide, produced by phagocytes following phagocytosis. Previous CL methods required large numbers of cells and relative few experiments could be performed at once. The Amerlite CL reader (Amersham International, Amersham, England) uses 96-well microtiter plates, allowing many experiments to be performed simultaneously and a reduction in the number of phagocytes required. Using this machine, opsonization of zymosan can be measured simply and reliably. Preliminary experiments with mycobacteria using serum from healthy subjects show that opsonization of *Mycobacterium tuberculosis* is not solely complement-dependent, while the response to *M. avium-intracellulare* is abolished by heat inactivation of the serum. There is no CL response to *M. leprae*.—Authors' Abstract

Booth, R. J., Grandison, P. M., Prestidge, R. L. and Watson, J. D. The use of a "universal" yeast expression vector to produce an antigenic protein of *Mycobacterium leprae*. Immunol. Lett. **19** (1988) 65–70.

This report describes the use of a recombinant yeast expression vector to synthesize and secrete the *Mycobacterium leprae* 18-kDa antigenic protein. The protein is secreted with a short hydrophilic "flag" octapeptide fused to its amino-terminus. The fusion protein can be purified directly from yeast culture supernatant through an anti-flag antibody affinity column and the flat octapeptide removed using enterokinase. The method provides a simple and rapid means of obtaining recombinant 18-kDa antigen in quantities suitable for immunological studies.—Authors' Summary

Cherayil, B. J. and Young, R. A. A 28-kDa protein from *Mycobacterium leprae* is a target of the human antibody response in lepromatous leprosy. J. Immunol. **141** (1988) 4370–4375.

The gene for a 28-kDa *Mycobacterium leprae* protein antigen, a major target of antibodies from patients with lepromatous leprosy, was cloned from a λ gt11-*M. leprae* DNA expression library and sequenced. Antibodies to this protein were detected in the serum of the majority of 15 individual lepromatous patients that were tested. The predicted amino-acid sequence of the 28-kDa protein suggests that it is localized to the bacterial plasma membrane or cell wall.—Authors' Abstract

Cree, I. A., Sharpe, S., Sturrock, N. D. C., Cochrane, I. H., Smith, W. C. and Swanson Beck, J. Mucosal immunity to mycobacteria in leprosy patients and their contacts. Lepr. Rev. **59** (1988) 309–316.

Since the development of leprosy may follow the formation of an initial lesion in the nose, mucosal immune responses might be important in the protective immune response to *Mycobacterium leprae*. Salivary antibody responses to *M. leprae* and other mycobacteria were therefore investigated in leprosy patients and healthy contacts using ELISAs against whole mycobacteria and an *M. leprae*-specific glycolipid constituent (PGL-I) of the external surface of *M. leprae*. Lower levels of salivary IgA directed against *M. leprae* were found in household contacts (at high risk of developing leprosy) than in hospital contacts (low risk of leprosy). Samples from the local indigenous population with no known leprosy contact showed an intermediate number of positive salivary IgA responses against *M. leprae* and untreated patients were less likely to be positive than treated patients. Correlation was found between salivary antibody responses to *M. leprae, M. scrofulaceum* and *M. tu-*

berculosis, suggesting the presence of some crossreacting antibody. Few patients and no healthy subjects had detectable antibody responses against an epitope of PGL-I, suggesting that this important serum antibody response is not a major component of the mucosal immune response to *M. leprae.* Since there appears to be a secretory IgA response to *M. leprae* which is least likely to be found among those with the disease and in those individuals with increased risk of developing leprosy, we suggest that the mucosal immune system might be of importance in a putative protective response to infection by the leprosy bacillus.—Authors' Summary

Cree, I. A., Smith, W. C. and Swanson Beck, J. Serum antibody responses to mycobacteria in leprosy patients and their contacts. Lepr. Rev. **59** (1988) 317–327.

The aim of this descriptive study was to investigate the relationships between serum antibody responses to different mycobacteria in leprosy patients and contacts. The results of ELISAs for serum antibody against whole mycobacteria (*Mycobacterium leprae, M. tuberculosis,* and *M. scrofulaceum*) were compared with the results of an *M. leprae*-specific ELISA for antibody against an epitope of PGL-I. The IgG response was found to be predominant in ELISAs for antibody directed against whole *M. leprae,* while the IgM response was greatest in the assay for antibody against PGL-I. Some healthy hospital workers were found to have appreciable levels of IgM anti-PGL-I. Since infection in this group is unlikely, chronic exposure may result in humoral responses to PGL-I in addition to subclinical leprosy. None of the ELISAs studied were able to give greater than a 55% sensitivity at 95% specificity and none were considered suitable for serodiagnostic use. Significant correlation was found between the results from the whole mycobacterial ELISAs, which could be explained on the basis of cross-reaction between antibodies directed against common antigens. However, similar correlations were found between the results of the *M. leprae*-specific ELISA and the assay for antibody against whole *M. tuberculosis* and *M. scrofulaceum* which were greater than those for antibody against whole *M. leprae.* Infection with *M. leprae* may produce general stimulation of immunological memory for common mycobacterial antigens resulting in responses to antigens belonging to other mycobacteria to which the host has been exposed previously.—Authors' Summary

Cree, I. A. and Swanson Beck, J. Assessment of histological features in leprosy lesions by histometry. Trans. R. Soc. Trop. Med. Hyg. **82** (1988) 943.

The proportion of the dermis occupied by granuloma in skin biopsies from leprosy patients falls with effective treatment and is known as the granuloma fraction (GF). Estimation of the GF by direct microscopy was found to be inaccurate in comparison with measurement using a simple computerized planimeter. In established leprosy lesions the GF was greatest at the edge of the lesion, but in early tuberculoid lesions the GF was greatest in the center of the lesion. The GF was similar in biopsies taken from opposing edges of the same lesion, but showed marked variation between lesions. Hence diagnostic biopsies should be taken from the edge of established leprosy lesions, but in early lesions a biopsy from the center of the lesion may be useful. The planimeter-derived measurements of granuloma area can also be used to determine the density of histological features which can be counted visually. By studying the densities of mitoses and apoptotic bodies within leprosy lesions, we have been able to study aspects of cell turnover within leprosy lesions. There were clear differences in cell turnover between leprosy patients which may correlate with the clinical activity of the disease.—Authors' Abstract

Duggan, D. B., Mackworth-Young, C., Kari-Lefvert, A., Andre-Schwartz, J., Mudd, D., McAdam, K. P. W. J. and Schwartz, R. S. Polyspecificity of human monoclonal antibodies reactive with *Mycobacterium leprae,* mitochondria, ssDNA, cytoskeletal proteins, and the acetylcholine receptor. Clin. Immunol. Immunopathol. **49** (1988) 327–340.

The origin of autoantibodies against ubiquitous autoantigens [e.g., single-stranded (ss)

DNA, cytoskeletal proteins, mitochondria] is obscure. Patients with lepromatous leprosy have many such autoantibodies in their serum. In order to study the polyspecificities of human autoantibodies expressed during infection with *Mycobacterium leprae,* we prepared human monoclonal antibodies derived from the fusion of peripheral blood lymphocytes of a patient with lepromatous leprosy to the human lymphoblastoid line GM 4672. Hybridomas were tested for binding to a DNAse-treated sonicate of *M. leprae* and a panel of autoantigens. Of the primary (uncloned) cultures, 14% bound ssDNA, 35% bound *M. leprae,* 11% bound both *M. leprae* and ssDNA, and 16% bound to mitochondria. Several also bound to the acetylcholine receptor of *Torpedo marmorata.* Monoclonal antibodies derived from separate primary cultures revealed similar crossreactions between several autoantigens and *M. leprae.* In addition, one antibody was identified which bound to mitochondria and the acetylcholine receptor, and which was recognized by an anti-idiotypic antibody which bears the "internal image" of the acetylcholine receptor. These results suggest that antigenic mimicry may play a role in eliciting autoantibody expression from the immune repertoire.—Authors' Abstract

Gupte, M. D. and Anantharaman, D. S. Use of soluble antigens in leprosy epidemiology. Lepr. Rev. **59** (1988) 329–335.

Rees and Convit antigens prepared from armadillo-derived *Mycobacterium leprae* are presently available. This study was undertaken to understand the skin-test reactions produced by these antigens in comparison to tuberculin. A standard tester skin-tested about 250 individuals. The indurations were read at the end of 48 hr for Rees and Convit and at the end of 72 hr for tuberculin by a standard reader who read these reactions following blind procedures again after 2 hr. The values of standard deviations for the mean differences were 1.0, 2.6, and 2.4 mm for tuberculin, Rees and Convit antigens, respectively. Standard deviations for the mean differences for two different tests using the same antigen on the same individual twice were 3.0, 6.0 and 5.3 mm, respectively. Two batches of Rees antigen gave reasonably consistent results, but the skin-test readings with two batches of Convit antigen differed substantially. The available antigens need further improvement.—Authors' Summary

Hastings, R. C., Gillis, T. P., Krahenbuhl, J. L. and Franzblau, S. G. Leprosy. Clin. Microbiol. Rev. **1** (1988) 330–348.

This review focuses mainly on cell wall structure and associated antigens of *Mycobacterium leprae* and immunology, but also includes sections on epidemiology, clinical aspects and microbiology.—(*From* Trop. Dis. Bull.)

Kaplan, G., Laal, S., Sheftel, G., Nusrat, A., Nath, I., Mathur, N. K., Mishra, R. S. and Cohn, Z. A. The nature and kinetics of a delayed immune response to purified protein derivative of tuberculin in the skin of lepromatous leprosy patients. J. Exp. Med. **168** (1988) 1811–1824.

We have analyzed the nature and kinetics of a delayed, cell-mediated immune response to a purified protein derivative of tuberculin (PPD) in the skin of 154 naturally sensitized patients with lepromatous leprosy. After the intradermal injection of 5 U of PPD, biopsies were taken at 1–21 days and studied for the composition, extent, persistence, and organization of the emigratory cell response by light and electron microscopy. Induration of positive sites occurred promptly, reached a maximum diameter at 4 days, displayed a major extravasatory element, and was evident for as long as 21 days. The cellularity of the site exhibited a biphasic course, reached a maximum at 7 days involved as much as 70% of the dermis and millions of new cells, and was elevated threefold above preinjection levels at 21 days. The emigratory cells were limited to T cells and circulating monocytes. T cells were more evident as they entered a preexisting lepromatous lesion containing parasitized macrophages and only occasional T cells many of the CD8+ phenotype. The predominant emigratory T cell was CD4+ although CD8+ cells were in evidence. The CD4/CD8 ratio of the lesions started at less than unity and in two distinct steps reached levels as high as 5:1. In most

sites CD4+ cells were in the majority at 21 days. A well-defined granulomatous response with epithelioid and giant cells was apparent at 4 days, reached a maximum at 7 days, and involved all PPD sites at this time point. The generation of these differentiated mononuclear phagocytes from newly emigrated monocytes was never observed in the underlying lepromatous lesion but is a constant feature of the tuberculoid leprosy response. Epidermal thickening and keratinocyte proliferation, sequellae of the dermal reaction, reached a maximum at 7 days and gradually resolved by 3 weeks. A constant feature of the PPD response was the extensive destruction of preexisting macrophages containing *Mycobacterium leprae* or their products. This was associated with the presence of and intimate contact with highly polarized lymphoid cells of unknown phenotype. Cell destruction did not involve other elements of the dermis and spared parasitized Schwann cells. Newly emigrated T cells and monocytes were never seen within the perineural sheath in contact with neural elements.

It appears that a single antigenic stimulus leads to a very long-term, defined series of events with distinct temporal patterns. It includes waves of emigratory T cells, the maturation and organization of monocytes, the generation of killer cells, and the extensive destruction of parasitized macrophages. We suspect that the chronicity and complexity of the reaction involves antigen-independent amplification signals, the recruitment of other cells in the dermis and epidermis, and the eventual disposal of the intracellular pathogen *M. leprae*.—Authors' Summary

Karanth, S. S., Springall, D. R., Lucas, S., Levy, D., Ashby, P., Levene, M. M. and Polak, J. M. Changes in nerves and neuropeptides in skin from 100 leprosy patients investigated by immunocytochemistry. J. Pathol. **157** (1989) 15–26.

The cutaneous innervation is now known to contain neuropeptides including substance P (SP) and calcitonin gene-related peptide (CGRP) in sensory nerves, and vasoactive intestinal polypeptide (VIP) and neuropeptide Y (NPY), principally in autonomic nerves. Skin biopsies from 100 leprosy patients and equivalent areas from 50 nonleprosy controls were fixed in *p*-benzoquinone solution for immunofluorescence staining, and in Bouin's fluid for classification of leprosy type. Antisera to the neural markers, neurofilaments, and protein gene product 9.5 (PGP 9.5), and to neuropeptides were used. Cutaneous nerves and nerve endings immunoreactive for neuropeptides, neurofilaments, and PGP 9.5 were seen in all nonleprous control cases. In leprosy, PGP 9.5- and neurofilament-immunoreactive nerve fibers were seen in all 14 cases of the indeterminate (early) type and in the majority (33/43) of lepromatous cases, but in a smaller proportion (15/43) of tuberculoid cases. Neuropeptide immunoreactivity was seen in only 2/14 of the indeterminate leprosy specimens and was completely absent in other types. This early disappearance may be of diagnostic significance. Thus, cutaneous sensory and autonomic dysfunctions in leprosy are well reflected by changes in nerve fibers and neuropeptides.—Authors' Summary

Liu, J., *et al.* [Pathologic changes and bacillation of blood vessels in LL and BL leprosy.] China Lepr. J. **4** (1988) 143–145. (in Chinese)

In this paper, blood vessel involvement and endothelial bacillation were observed histopathologically in 60 cases of LL, BL and BL-LL leprosy divided into three groups: a) 20 cases of new patients, b) 20 cases of relapsing cases, and c) 20 cases after treatment with combined chemotherapy for 6–18 months. The histopathological changes and bacillation in group a were basically similar to that of group b. Three cases of group a and three cases of group b were observed by electron microscopy also. The ultrastructural changes and bacillation of blood vessels were the same in both groups, but in group c the endothelial bacillation and the occurrence of vasculitis were much less than in groups a and b histopathologically. However, a few bacilli were still found in arrector pili muscles, small bundles of nerve, follicles, and the muscular layer of small vessels in group c. Therefore the remnant bacilli after the treatment of combined chemotherapy are still to be investigated.—Authors' English Abstract

Mehta, R., Mukherjee, R., Landon, D., Verghese, G. and Antia, N. H. *In vitro* interaction of *M. leprae*-infected Schwann cells and splenic cells. Acta Neuropathol. **76** (1988) 407–410.

The interaction between *Mycobacterium leprae*-infected cultured Schwann cells and sensitized splenic cells was noted both under light and electron microscopy. No evidence of cytomorphological changes in infected Schwann cells was obtained. However, sensitized splenic cells were noted to undergo degenerative changes suggestive of the phenomenon of apoptosis. Subsequently a large number of these degenerated cells were observed within the Schwann cell. Such a process has not been hitherto reported in the histopathology of leprous nerves. Nevertheless, these findings indicate an aberrant metabolic function in *M. leprae*-infected Schwann cells.—Authors' Summary

Moudgil, K. D., Gupta, S. K., Sharma, A. K., Narang, B. S. and Talwar, G. P. Development of Epstein-Barr virus transformed human B-cell lines secreting anti-*M. leprae* antibodies. Ann. Natl. Acad. Med. Sci. (India) **21** (1985) 118–122.

Peripheral blood lymphocytes (PBL) were isolated on Ficoll-hypaque density gradient from the blood obtained from untreated lepromatous leprosy patients: Purified PBL were immortalized by transfection with Epstein-Barr virus (EBV). Four EBV-transformed human B-cell lines were developed. The product of these cell lines reacted specifically with *Mycobacterium leprae* sonicate and had no crossreaction with the sonicates prepared from seven other mycobacteria as well as with *Escherichia coli*. The potential clinical applications of these antibodies in early diagnosis and prompt treatment of symptomatic leprosy and carriers with subclinical leprosy is discussed.—Authors' Abstract

Moudgil, K. D., Singh, G. and Talwar, G. P. Detection of lepromatous leprosy patients shedding *M. leprae* in nasal droppings by enzyme immunoassay. Indian J. Lepr. **60** (1988) 549–553.

Enzyme immunoassays (EIAs) for detection of lepromatous leprosy (LL) patients harboring *Mycobacterium leprae* in the nasal mucosa are described. One EIA measures IgM antibodies against the synthetic disaccharide (ND-BSA) residue of phenolic glycolipid-I of *M. leprae*; whereas the other titrates primarily IgG antibodies against sonicate supernatant antigens of *Mycobacterium w.* (*M.w.*). Fifty coded leprosy sera were analyzed by EIAs under a double-blind code. Among the 20 LL patients with positive nasal smear, 18 (90%) were positive in EIA based on ND-BSA, in comparison to 19 (95%) in EIA using *M.w.* antigens. The assays can be performed on fresh serum samples or on blood samples collected on filter paper discs. These assays can be useful for leprosy control programs.—Authors' Abstract

Muthukkaruppan, V., Chakkalath, H. R. and Malarkannan, S. The classical and alternate pathways of T cell activation are impaired in leprosy. Immunol. Lett. **19** (1988) 55–58.

The proliferative response of circulating T lymphocytes from bacterial index-positive lepromatous patients to mitogenic anti-CD3 and pairs of anti-CD2 monoclonal antibodies was significantly reduced. In these patients, the CD2 but not CD3 receptor expression was down-regulated. Further, the CD2 modulation and the associated suppression of proliferative response to monoclonals was brought about in T cells of healthy subjects by prior incubation of mononculear cells *in vitro* with *Mycobacterium leprae*. Thus, the T-cell activation pathways through the CD3 and CD2 receptors are impaired in lepromatous leprosy patients and the impairment appears to be due to the modulation of the CD2 receptor specifically by *M. leprae*.—Authors' Summary

Pemajayantha, V., Pinto, M. R. M. and Eriyagama, N. B. The relationship between reactivities to lepromin A and soluble protein antigen of *Mycobacterium leprae* and tuberculin. Ceylon J. Med. Sci. **29** (1986) 39–52.

The relationship between reactivity to tuberculin (PPD-RT23) and reactivities to

antigens of *Mycobacterium leprae* (Fernandez, Mitsuda and to a soluble protein antigen of *M. leprae*) was studied using three methods. A clear relationship could be demonstrated with two of the methods. A statistically significant correlation could be demonstrated by the method of regression analysis between tuberculin and all three types of reactivities; however the level of correlation (r^2) was unusually low. This study also revealed an increase of all three types of reactivity with BCG vaccination.—Authors' Summary

Rana, N. S., Gupta, H. P. and Singh, N. B. Use of nonconventional antigen, *M. habana*, in detecting *M. leprae* antibodies from leprosy patients and contacts in FLA-ABS test. Indian J. Lepr. **60** (1988) 593–599.

An indirect immunofluorescent (FLA-ABS) test has been developed to detect *Mycobacterium leprae*-specific antibodies in the active and subclinical cases of leprosy. An antigenically related mycobacterium, *M. habana*, was used as an antigen to detect *M. leprae*-specific antibodies in the sera samples of leprosy patients. A comparison was made with *M. leprae* antigen using the same set of sera samples. *M. habana* is capable of detecting anti-*M. leprae* antibodies in the serum samples of leprosy patients, previously absorbed with various mycobacterial antigens, cardiolipin and lecithin, almost to the same percentage as *M. leprae*. Possible use of *M. habana* antigen as an alternative to *M. leprae*, in the serodiagnosis of leprosy, is discussed.—Authors' Abstract

Roy, A., Agarwal, A. and Ralhan, R. Arabinogalactan; a complementary antigen to phenolic glycolipid in leprosy diagnosis. Ann. Natl. Acad. Med. Sci. (India) **21** (1985) 124–127.

Arabinogalactan and phenolic glycolipid have been compared by enzyme linked immunosorbent assay for their ability of detecting circulating antibody in leprosy. In untreated leprosy sera, anti-arabinogalactan (AG) IgG is more than the corresponding IgM. With long-term treatment of the disase IgM level goes up compared to IgG; whereas anti-phenolic glycolipid IgM is much higher in leprosy patients (LL) compared to normal individuals. In leprosy control programs, arabinogalactan and phenolic glycolipid can be used complementary to each other for detection and follow-up response of therapy in lepromatous cases.—Authors' Summary

Sagaro Delgado, B., Diaz de la Rocha Quevedo, A., Diaz Garcia, M. A., Martinez Granja, R., Rodriquez Garcia, M. A. and Collazo Caballero, S. [Current thoughts on the immunology of leprosy.] Rev. Cubana Med. Trop. **40** (1988) 80–90. (in Spanish)

Basic concepts on immune mechanisms in the activation of T cells and, further, the nature of immunologic defect causing incapacity of lepromatous leprosy to an efficient cell immune response are studied. In like manner, it has been considered that suppressive-T cells have a main function in the immunodeficiency of lepromatous leprosy. Several hypotheses trying to explain where this defect has roots are exposed. Emphasis is made on importance of learning about causes of immunodeficiency of lepromatous leprosy linked to possible attainment of a vaccine against this disease. Reference is made to determining the value of cell-mediated immunity in the Ridley and Jopling classification.—Authors' English Summary

Vaishnavi, C., Ganguly, N. K., Sharma, V. K., Kaur, H. and Kaur S. Effect of multidrug therapy on the levels of antibodies to *Mycobacterium leprae* glycolipid-I in the leprosy spectrum. Indian J. Lepr. **60** (1988) 530–534.

Sera from 145 untreated leprosy patients, 10 proven cases of active pulmonary tuberculosis, and 25 healthy volunteers not exposed to *Mycobacterium leprae* infection were assayed for PGL-I antibodies. All available follow-up samples after multidrug therapy were also assayed. A decline in the level of PGL-I antibodies was seen in many of the post-treatment samples, giving an indirect assessment of the bacterial load and the prognosis of the disease.—Authors' Abstract

Vega-Lopez, F., Stoker, N. G., Locniskar, M. F., Dockrell, H. M., Grant, K. A. and McAdam, K. P. W. J. Recognition of mycobacterial antigens by sera from patients with leprosy. J. Clin. Microbiol. **26** (1988) 2474–2479.

Mycobacterium leprae sonic extracts prepared from armadillo-derived bacteria were subjected to sodium dodecyl sulfate-polyacrylamide gel electrophoresis and Western blotting (immunoblotting) procedures and probed with serum or plasma samples from 20 patients with lepromatous leprosy and 14 healthy endemic controls. Five proteins of 33, 25, 18, 15, and 12 kilodaltons (kDa) were frequently recognized; the 33- and 15-kDa proteins were, respectively, recognized with high intensity by 16 and 13 of the 20 samples from patients with leprosy; whereas only one healthy donor had antibodies that recognized the 15-kDa protein. By the use of *M. leprae*-specific murine monoclonal antibodies it was demonstrated that the 33-, 25-, and 15-kDa antigens were different from those bound by the available murine monoclonal antibodies. The 18- and 12-kDa proteins detected had molecular masses similar to those detected by the corresponding murine monoclonal antibodies. The serum and plasma samples from patients with leprosy were also used to probe Western blots of a soluble extract of *M. tuberculosis*. They recognized, among others, antigens with molecular weights similar to those detected in the *M. leprae* antigenic preparations, although with less intensity and at a lower frequency.—Authors' Abstract

Wabitsch, K. R. and Meyers, W. M. Histopathologic observations on the persistence of *Mycobacterium leprae* in the skin of multibacillary leprosy patients under chemotherapy. Lepr. Rev. **59** (1988) 341–346.

In the study of 782 biopsy specimens from 195 patients during and after chemotherapy we compared the numbers of *Mycobacterium leprae* stained by the Fite-Faraco (FF) and the Gomori methenamine-silver (GMS) techniques. In many patients large amounts of nonacid-fast *M. leprae* or remnants thereof remained 66 months after starting effective multidrug therapy. The GMS stain is a useful method for assessing the efficacy of methods for enhancing bacillary clearance in multibacillary leprosy patients.—Authors' Summary

Williams, W., Zumla, A., Behrens, R., Locniskar, M., Voller, A., McAdam, K. P. W. J. and Isenberg, D. A. Studies of a common idiotype PR4 in autoimmune rheumatic disease. Arthritis Rheum. **31** (1988) 1097–1104.

A new common idiotype, designated PR4, is described. This idiotype was originally identified on a human hybridoma-derived monoclonal antibody from a patient with leprosy, which binds the major *Mycobacterium leprae*-derived antigen, phenolic glycolipid-I, poly(ADP)-ribose, DNA, and poly(dT). The PR4 idiotype was found in patients with systemic lupus erythematosus (SLE) (70%), rheumatoid arthritis (40%), and Sjögren's syndrome (15%). It was not, however, found in the spouses of the SLE patients or (unlike other lupus idiotypes) in their healthy first-degree relatives. Although no correlation between PR4 idiotype levels and disease activity in SLE was found, a subset of rheumatoid arthritis patients with high levels of the idiotype was identified.—Authors' Abstract

Wu, Q., Ye, G., Li, X., Liu, Q. and Zhou, L. A preliminary study on serological activity of phenolic glycolipid and its application in diagnosis of leprosy. Proc. Chin. Acad. Sci./Peking Union Med. College **1** (1986) 58–61.

In this article, we report: 1) Comparison studies on serological activity between phenolic glycolipid (PGI) and its terminal sugar, the latter being a synthetic antigen conjugated to bovine γ-globulin. Sera for comparison were collected from leprosy patients (182), tuberculosis patients (20), and normal subjects (108, in nonendemic area of leprosy). The results indicate that the correlation is highly significant ($r_{M\text{-}BGG} = 0.9953$, $p < 0.005$). M_{OD} values in sera from tuberculosis patients are similar to those from normal persons. These suggest that PGI-ELISA and M-BGG-ELISA are highly specific for *Mycobacterium leprae*. Comparison analysis of PGI-ELISA with ML-

ELISA in leprosy patients show similar sensitivity, indicating PGI-ELISA and M-BGG-ELISA are as sensitive as ML-ELISA diagnosis of leprosy. 2) Correlation studies on PGI-ELISA, ML-ELISA and FLA-ABST indicate high correlation ($r_{FLA\text{-}ABST} = 0.945$, $p < 0.01$; $r_{ML\text{-}ELISA} = 0.972$, $p < 0.005$). 3) Studies on blocking nonspecific binding indicate that EA be used instead of BSA and GS, the efficiency of EA being the same as BSA and GS with the advantages of cheapness and facileness. The authors suggest using EA for blocking nonspecific binding in ML, PGI or M-BGG-ELISA.—Authors' Abstract

Young, D. B., Mehlert, A., Bal, V., Mendez-Samperio, P., Ivanyi, J. and Lamb, J. R. Stress proteins and the immune response to mycobacteria—antigens as virulence factors? Antonie van Leeuwenhoek **54** (1988) 431–439.

The immune response to mycobacterial infection includes pathogenic as well as protective activities. It is possible that different types of immune responses are associated with recognition of different antigenic determinants. Among the antigens which are prominent in antibody and T-cell recognition of mycobacteria, we have identified members of highly conserved stress protein families. Mapping of antigenic determinants on stress proteins shows that both species-specific and conserved regions of these proteins can take part in immune recognition. Induction of an immune response to conserved, "self-like," determinants on stress proteins could play a role in the immunopathology associated with chronic mycobacterial infections.—Authors' Summary

Zumla, A., Williams, W., Shall, S., Locniskar, M., Leigh, I., McAdam, K. P. W. J. and Isenberg, D. Human monoclonal antibodies to phenolic glycolipid-I from leprosy patients crossreact with poly(ADP-ribose) polynucleotides and tissue bound antigens. Autoimmunity **1** (1988) 183–195.

Antibodies which bind to poly(ADP-ribose) have been described in systemic lupus erythematosus (SLE) and a variety of infectious diseases. Two IgM kappa human monoclonal antibodies (MAbs), TH3 and PR4, produced from the fusion of peripheral blood lymphocytes of leprosy patients with the GM4672 lymphoblastoid cell line, were found to bind to poly(ADP-ribose) in direct binding and inhibition ELISAs. Significant inhibition of binding of these MAbs to poly(ADP-ribose) occurred with phenolic glycolipid-I, the *Mycobacterium leprae*-specific glycolipid, ssDNA, dsDNA, poly(dT), as well as poly(ADP-ribose) itself. Up to 80% of binding of TH3, and 90% of binding of PR4, to poly(ADP-ribose) was inhibited by 10 mcg of ssDNA, suggesting that there may be sharing of some conformational determinants. Although the serological binding profiles of TH3 and PR4 are similar, only PR4 was found to bind to basal keratinocytes of normal human interfollicular epidermis and astrocyte cytoplasm in normal brain tissue. These results support the concept that an antibody binding site may accommodate more than one epitope. Furthermore, small differences in antigen binding potential may distinguish relatively innocuous antibodies from those which may be more pathogenic.—Authors' Abstract

Microbiology

Chakrabarty, A. N., Das, S., Pal, N. K. and Dastidar, S. G. Significance of culture granules of leprosy derived acid-fast chemoautotrophic nocardioform bacteria. Indian J. Exp. Biol. **26** (1988) 144–146.

Development has been described of the granules in *in vitro* culture of all the 22 human, 4 mouse foot pad and 1 armadillo-leprosy-derived nocardioform bacteria through successive stages; these are: free bacillary forms, bacillary rings, clumps, small and large mycelia-bound globi, and finally free granules and those enmeshed in mycelial lattices called "veils." Concepts on the taxonomic and pathogenic significance of

these specialized, organized units are presented.—Authors' Abstract

Clark-Curtiss, J. E. and Docherty, M. A. A species-specific repetitive sequence in *Mycobacterium leprae* DNA. J. Infect. Dis. **159** (1989) 7–15.

A 2.2-kilobase *Mycobacterium leprae* DNA insert fragment from a recombinant genomic library (pYA1065) was found to hybridize to at least 19 fragments of chromosomal *M. leprae* DNA by Southern hybridizations. The probe hybridized to identical fragments of chromosomal DNA from four *M. leprae* isolates (two from patients with leprosy, one from a naturally infected armadillo, and one from a naturally infected mangabey monkey) whether the chromosomal DNA was digested with *Bam*HI, *Bst*EII, *Pst*I, or *Sac*I. The pYA1065 probe is specific for *M. leprae*; it did not hybridize to chromosomal DNA from 14 cultivable slow- and fast-growing mycobacterial species. Dot-blot hybridizations between pYA1065 and purified *M. leprae* chromosomal DNA indicate that the probe can detect DNA equivalent to 4×10^3 *M. leprae* cells in a spot. The probe can also hybridize to DNA in *M. leprae* cells spotted on a filter from homogenized skin biopsy specimens from patients with lepromatous leprosy.—Authors' Abstract

Gan, S. C., Gan, S. N. and Tanaka, Y. Preliminary results on the detection of mycolic acids from *Mycobacterium leprae* by gel permeation chromatography and proton nuclear resonance spectroscopy. Malays. J. Pathol. **9** (1987) 79–84.

The presence of mycobacteria can be detected by identifying the mycolic acids from its cell wall. The acidic components of human biopsy material can be extracted and esterified with *p*-bromo-phenacyl bromide. The success of the esterification process may be verified by nuclear magnetic resonance (NMR). Since the molecular weights of mycolate esters are relatively higher than those of the other components, they could be identified by the gel permeation chromatography technique using a high resolution column. Samples from lepromatous leprosy patients were shown to contain high molecular weight fractions while those of the control samples did not have any component with molecular weight larger than 1000. The techniques described in this paper could be developed as a quick method for screening large numbers of patients suspected of having leprosy, although at this stage it is not possible to differentiate the several strains of mycobacteria.—Authors' Summary

Garsia, R. J., Hellqvist, L., Booth, R. J., Radford, A. J., Britton, W. J., Astbury, L., Trent, R. J. and Basten, A. Homology of the 70-kilodalton antigens from *Mycobacterium leprae* and *Mycobacterium bovis* with the *Mycobacterium tuberculosis* 71-kilodalton antigen and with the conserved heat shock protein 70 of eucaryotes. Infect. Immun. **57** (1989) 204–212.

Two λgt11 recombinant clones, JKL2 and JKL15, each containing an insert coding for part of the highly immunogenic 70-kilodalton (kDa) protein antigen, were isolated from a *Mycobacterium leprae* genomic library by immunoscreening with the monoclonal antibody L7. Clone JKL2 contained the largest insert, 2.3 kilobase pairs. Nonoverlapping fragments of this insert were used as probes and showed strong hybridization to a number of *M. tuberculosis*-λgt11 recombinants producing proteins recognized by an anti-*M. tuberculosis* 71-kDa monoclonal antibody, IT11. One clone from a recombinant *M. bovis* library was also characterized by using L7, and the insert from this clone, B5bt, hybridized strongly to the *M. leprae* probes as well. The nucleotide sequence of the 1037-base-pair coding region of the JKL2 *M. leprae* clone which encodes the carboxy-terminal half of the 70-kDa protein had extensive homology with genes from a number of species. In all cases, these genes, including the recently described Ag63 and Ag361 of *Plasmodium falciparum*, were found to be members of the heat shock protein 70 (hsp70) family of genes. At the amino acid level, homology was maximal between amino acids 83 through 107 and 159 through 184, which showed extreme conservation (92 and 85% identity) with *Escherichia coli* DnaK amino acids 386 through 409 and 460 through 485,

respectively, and was 51% homologous over the entire coding region (amino acids 1 through 344 of JKL2). In contrast, amino acids 129 through 158 had maximal homology with the phylogenetically more distant *Xenopus laevis* hsp70. Homology declined substantially in the carboxy-terminal 34 amino acids. The predicted ATP-binding functional activity of the 70-kDa antigen from *M. bovis* was confirmed with affinity purification of the antigen by binding to ATP-agarose and elution with ATP. In view of the conservation of sequences between these mycobacterial antigens and mammalian endogenous cellular enzymes, further evaluation of these molecules *in vivo* may aid in understanding tolerance to self-antigens as well as provide potentially useful immunodiagnostic reagents.—Authors' Abstract

Jagannathan, R., Patil, D. and Mahadevan, P. R. Correlation of *in vitro* Fc receptor assay with *in vivo* mouse foot pad method. Indian J. Lepr. **60** (1988) 517–525.

Resistant strains of *Mycobacterium leprae* have been reported to the various antileprosy drugs. There is currently no accepted test to identify the susceptibility pattern of *M. leprae* to the drugs in a short period. The only accepted test is the mouse foot method which takes a long period to yield results. The Fc receptor assay using the ability of viable *M. leprae* to alter the membrane of the macrophage is well established. It takes only 10 days and is inexpensive. In six cases of leprosy patients the susceptibility pattern was worked out both with the *in vitro* Fc receptor assay and the *in vivo* mouse foot method. The results correlated very well leading to the fact that the assay system is reliable. Hence, it can be used not only to study the status of a patient, but also to shortlist the number of compounds to be tested on the mouse foot pad as antileprosy drug candidates.—Authors' Abstract

Meng, M., *et al.* [Determination of the viability of *M. leprae* with fluorescent staining.] China Lepr. J. **4** (1988) 135–138. (in Chinese)

A fluorescent staining procedure (FDA/EB) for determining the viability of *Mycobacterium leprae* was used in 58 multibacillary leprosy patients. We modified the final concentration of FDA to 10 g/ml and EB to 8 g/ml. Viable mycobacterial organisms can hydrolyze FDA to free fluorescein to bring out green. Nonviable mycobacteria are unable to hydrolyze FDA, but absorb the EB counterstain to yield orange. The data indicate that the average percentages of green-stained *M. leprae* in 8–12, 13–24, 25–48, and > 48 months after chemotherapy were 8.7%, 9.4%, 6.0% and 4.0%, respectively. Five cases have been treated by triple-drug regimen for an average period of 16.6 months; among them, the average percentage of green-stained *M. leprae* was 14.6%. These facts suggest that the viable bacilli decreased after treatment. There were few patients without viable bacilli who still had nonviable ones. The green bacilli nearly disappear if the smears are stored at room temperature for 24 hr. Viable bacilli decreased to about 1% after smears were incubated at 60°C for 30–40 min. The percentage of viable bacilli show no significant change if the smears are stored at −20°C for 17 days. All these data are encouraging, and suggest that the FDA/EB staining method can provide an accurate measure of the viability of *M. leprae,* being sensitive, objective and simple to perform.—Authors' English Abstract

Nagesha, C. N., Mallya, S., Parvathi, C. N. and Shetty, J. N. A concentration method for detection and quantitation of bacillaemia in leprosy and its comparison with other techniques. Lepr. Rev. **59** (1988) 337–340.

Detection and quantitation of bacillemia in 50 untreated cases of leprosy were evaluated by the buffy coat method, the hemolysis method and the present Petroff's method. Bacillemia was detected in 29 (58%) out of 50 cases and in 32 LL-BL cases it was detected in 28 patients with a success rate of 87.5%. Both the hemolysis method and Petroff's method were found useful in estimating the bacillary load per milliliter of blood. Importantly, the smears of concentrated deposit obtained by Petroff's

method revealed only AFB free from any artefacts and also yielded high bacterial counts. In conclusion, Petroff's method of concentration was found superior over other methods for detection and quantitation of bacillemia in the lepromatous spectrum (LL-BL) of the disease.—Authors' Summary

Nerland, A. H., Mustafa, A. S., Sweetser, D., Godal, T. and Young, R. A. A protein antigen of *Mycobacterium leprae* is related to a family of small heat shock proteins. J. Bacteriol. **170** (1988) 5919–5921.

The gene encoding an immunologically important 18-kDa protein antigen of *Mycobacterium leprae* has been sequenced, and the amino acid sequence of the antigen has been deduced. The 18-kDa antigen is strikingly similar in size and sequence to a family of eucaryotic heat shock proteins.—Authors' Abstract

Portaels, F. [The leprosy bacillus; expectations for culturing and vaccination.] Bull. Mem. Acad. R. Med. Belg. **142** (1987) 416–425. (in French)

With the availability of large numbers of *Mycobacterium leprae* bacilli, new efforts have been made to cultivate this organism "in vitro" and to prepare a vaccine with bacilli extracted from infected tissues. Up to now, *M. leprae* has not been cultured "in vitro." Based on our successful results with the "in vitro" cultivation of *M. lepraemurium,* we tried to cultivate *M. leprae* from *M. leprae*-infected armadillo tissues. Cultivation of *M. leprae* could not be achieved but several cultivable mycobacterial strains were isolated from these tissues. The wide variety of mycobacteria demonstrated in armadillo tissues indicates that appropriate measures must be taken to detect cultivable mycobacteria in tissues of armadillos experimentally infected with *M. leprae.* In view of this, chemical markers specific for different mycobacterial species were studied in order to be able to detect all the various cultivable mycobacteria which may be present as contaminants in *M. leprae* preparations. Different factors responsible for the inability of cultivating *M. leprae* are being analyzed. Among them, studies on the viability revealed a peculiar fragility at the *M. leprae* membrane level.

Three vaccine preparations (BCG, killed armadillo-derived *M. leprae,* and a mixture of BCG and killed *M. leprae*) were compared in volunteers from endemic areas; the mixed vaccine seemed to induce the best sensitization. Studies are now in progress to develop second-generation leprosy vaccines based on well defined *M. leprae*-specific antigens produced in *Escherichia coli* and in other cultivable organisms (*M. bovis* BCG) by genetic engineering techniques. These recombinant vaccines, if available, will reduce the dependence on armadillos, will represent "pure" sources of antigens and will permit large scale vaccine trials.—Author's English Summary

Sela, S., Clark-Curtiss, J. E. and Bercovier, H. Characterization and taxonomic implications of the rRNA genes of *Mycobacterium leprae.* J. Bacteriol. **171** (1989) 70–73.

The number of rRNA genes of *Mycobacterium leprae* was determined by restriction analysis of *M. leprae* total chromosomal DNA. A single set of rRNA genes was found. This set was subcloned from a cosmid library of *M. leprae* DNA into pUC13 and was characterized by restriction analysis and hybridization with *Escherichia coli* rRNA genes. The 16S, 23S, and 5S genes of *M. leprae* were clustered on a 5.3-kilobase DNA fragment. On one hand, restriction analysis of the set of rRNA genes showed the uniqueness of *M. leprae* among mycobacteria, but on the other hand, it suggested that *M. leprae* strains of several origins are very much alike. Quantitative hybridization studies between *M. leprae* rDNA and total DNA of various bacteria demonstrated a close relatedness between *M. leprae* and corynebacteria, nocardia, and mycobacteria, especially *M. tuberculosis.*—Authors' Abstract

Experimental Infections

Vaishnavi, C., Ganguly, N. K., Kaur, S., Singh, M. and Kumar, B. Influence of *in vitro* administered immune complexes on serum levels of complement and circulating immune complexes in *Mycobacterium leprae* infected mice. Indian J. Exp. Biol. **26** (1988) 9–12.

Normal and immunosuppressed Swiss albino mice were inoculated into the foot pads with *Mycobacterium leprae* obtained from untreated lepromatous patients. Uninfected controls were also included. *In vitro* prepared immune complexes (IC) were administered either at zero day period (0dIC), 3-month period (3mIC), or 6-month period (6mIC) to both uninfected and infected groups. Parallel groups without IC were also maintained as controls. Sera collected during different period of sacrifice were assayed for C3 and circulating immune complexes (CIC). Apart from an increase in the bacterial load in the foot pads, the levels of C3 and CIC were also found to be highly elevated. The possible influence of *in vitro* administered IC on these factors in relation to human leprosy is discussed.—Authors' Abstract

Epidemiology and Prevention

Alvarez Mesa, M., Perez Dube, M., Gutierrez de la Solana Dumas, J., Valdes-Miranda, V. V. and Sanchez Sanchez, S. [A comparative study of epidemiologic surveys of the incidence of leprosy in the years 1980 to 1984 in the cities of 10 Octubre and Arroyo Naranjo.] Rev. Cubana Med. Trop. **39** (1987) 105–116. (in Spanish)

A study of epidemiologic surveys on leprosy incidence is carried out. In a high percentage of the cases, the infection sources were not found. It is necessary to stress that the cases under study did not present physical incapacity.—Authors' English Summary

Fine, P. E. M. Implications of genetics for the epidemiology and control of leprosy. Philos. Trans. R. Soc. Lond. [Biol.] **321** (1988) 365–376.

This paper reviews the rationale and history of genetic studies related to leprosy, and considers their implications for the epidemiology and control of the disease. A long tradition of genetic studies in leprosy was initiated by early impressions that the disease clusters within families. Investigations were first motivated by an attempt to understand population patterns, and the focus shifted from investigations of racial differences to investigations of families, of twins and ultimately of genetic markers. The strongest evidence for genetic influence has come from studies of HLA segregation patterns within families, and this has led to elegant *in vitro* work demonstrating the role of HLA-DR alleles in mediating T-cell reactions in conjunction with antigens of *Mycobacterium leprae.* The epidemiological implications of this work are not yet clear. The emphasis on family-segregation studies may have given a biased impression because of their requirement for multicase families. There is evidence that the genetic mechanisms underlying leprosy differ within and between populations. One possible application of the current work would be the use of HLA-DR-specific reactions to identify epitopes of *M. leprae* which should be excluded from future vaccine preparations.—Author's Abstract

Fine, P. E. M. and Ponnighaus, J. M. Leprosy in Malawi. 2. Background, design and prospects of the Karonga Prevention Trial, a leprosy vaccine trial in northern Malawi. Trans. R. Soc. Trop. Med. Hyg. **82** (1988) 810–817.

The Karonga Prevention Trial is the largest vaccine trial ever mounted in Africa. It

is designed to test two hypotheses: a) whether the addition of killed *Mycobacterium leprae* can increase the protection against leprosy (and tuberculosis) imparted by BCG alone; and b) whether repeating a BCG vaccination can increase upon the protection provided by an initial dose. The rationale and design of the trial are discussed in relation to the history of vaccination against leprosy and to several contending arguments which determined the ultimate protocol. The potential of the trial to reveal statistically significant differences between the vaccines being compared is discussed, as are the implications of possible results for future research and control of leprosy.—Authors' Abstract

Frankel, R. I. Hansen's disease in Hawaii; current status. Hawaii Med. J. **47** (1988) 48–52.

Known to the Hawaiians as "the Chinese sickness" leprosy may have been introduced into Hawaii by Chinese immigrants working in sugar plantations, or alternatively by Europeans. The incidence of the disease in Hawaii has increased progressively since its first recognition there in the 1830s to a peak of > 1% in the third quarter of the 19th century. The Board of Health passed a law in 1865 enforcing isolation of leprosy patients, and two facilities were set up for evaluation and treatment and patient settlement, respectively. The site of the settlement on Molokai was later moved to Kalaupapa.

Since 1983 the US Government has supported outpatient therapy for leprosy patients within the community, the care being provided by private physicians. This program, currently known as the Hansen's Disease Community Program, provides funds for both inpatient and outpatient care; the staff of 14 also undertake contact screening and health education. At present there are 639 patients on the State Hansen's Disease Registry, 97 of whom remain on the Kalaupapa registry (although isolation is no longer required). Over the past decade Hawaii has had some 30–50 new cases of leprosy each year, about 60% of whom are immigrants from the Philippines and 8% are patients born in Hawaii.—C. A. Brown (Trop. Dis. Bull.)

Kaur, P., Sharma, U. C., Pandey, S. S. and Singh, G. Epidemiology of leprosy in tribals of Adhaura Plateau. Indian J. Lepr. **60** (1988) 577–580.

A door-to-door survey was carried out in the Adhaura plateau of Bihar to find out the magnitude of leprosy problems in that area. Out of a total of 7521 persons, mostly tribals, 5476 were examined given a coverage of 72.8%. Prevalence rate of leprosy was 20.6/1000 population. Maximum prevalence was seen in the age group of 55 and above. The disease was more common in males and in the literate and educated group. The ratio of tuberculoid was 57.5%, borderline 29.0% and lepromatous 10.0%; indeterminate type constituted 3.5%. The population had a poor nutritional status with caloric intake of 1471 calories per day.—Authors' Abstract

Pan, B., *et al.* [Fit and analysis of the trend curve of leprosy epidemic.] China Lepr. J. **4** (1988) 138–141. (in Chinese)

The curve of the incidence of leprosy in Fujian Province shows an exponential decline. The authors used two methods to fit it and results as follows: for the method A, $\hat{y} = 10^{0.8876-0.0879x}$ and for the method B, $\hat{y} = 8.11(1 - 0.1951)^x$. The rate of decrease by degrees of the incidence is close to 20%, suggesting that in recent years the effect of leprosy control is very good there, and therefore the aim of basic eradication of the disease might be reached by 1995.—Authors' English Abstract

Qian, A., *et al.* [Endemicity of leprosy in Shaanxi Province.] China Lepr. J. **4** (1988) 131–135. (in Chinese)

In Shaanxi Province (PRC), there was only one leprosarium which admitted 85 leprosy patients before 1949. Since then, the leprosarium has been enlarged, another two leprosy hospitals set up, and the leprosy control implemented, containing the training of professional workers, surveys for case finding and hospitalization of all patients found. By the end of 1985, there were accumulatively 10, 629 cases of leprosy of which the proportion of male to female equals 3.26 to 1. The lepromatous (L) form of the disease accounts for 70.23%; tuber-

culoid (T), 27.07%; borderline (B), 1.27%, and indeterminate (I), 1.31%. The patients with leprosy are distributed over 93 out of 106 counties (cities) of the province, the vast majority of them in the southern part of the province. A total of 1513 cases (14.23%) have died; 303 (3.9%) have relapsed out of 7788 cured patients (73.27%). At present in the province there are 1403 active patients. The prevalence is 0.047 per thousand. The number of counties with active leprosy has obviously decreased; children with the disease lessened; and the duration of newly found cases remarkably shortened.—Authors' English Abstract

Radhakrishna, S., Nair, N. G. K., Kumar, B. K. and Jayabal, P. Implications of prior BCG vaccination programmes in the community on the protective efficacy of new antileprosy vaccines. Indian J. Med. Res. **88** (1988) 197–208.

This mathematical study demonstrates that the interpretation of the findings of field trials of new antileprosy vaccines could be complicated by partial protection against leprosy conferred by BCG vaccination programs for tuberculosis. First, the trial's ability to detect protective effect (power) is reduced; this can be compensated by scaling up the trial size, but the increases often tend to become large. Secondly, if the new vaccine has a lower protective effect in those who had prior BCG vaccination, than in those who had not, the trial will underestimate vaccine efficacy, the extent of underestimation being substantial when BCG coverage is high or the relative efficacy of the vaccine in the BCG vaccinated is low. Despite these problems, it is argued that it would be more realistic to undertake the vaccine trial in the total population, irrespective of prior BCG status, especially in countries with moderate BCG coverages.—Authors' Abstract

Yang, Z. [Evaluation of effects of leprosy control using the life table.] China Lepr. J. **4** (1988) 148–151. (in Chinese)

The life-table method can be used not only in calculating the average length of life, but also in measuring some indices of leprosy control work, such as the cure rate, relapse rate after being cured, negativity rate of the bacterial index, and probability of deformity and disability from leprosy. The author gives a demonstration of collecting, processing and calculating the data according to the life table for the cure rate. The use of the life table in evaluating the efficiency of leprosy control is of distinct advantage, particularly when making a comparison between data from different periods or places.—Author's English Abstract

Rehabilitation

Chattopadhyay, S. P., Arora, P. N. and Aggarwal, S. K. Neurolysis: an approach to leprous claw hand. Med. J. Armed Forces (India) **44** (1988) 27–30.

Ten cases of ulnar claw hand, 8 males and 2 females from 19 to 56 years, were subjected to neurolysis. The patients were from the spectrum of leprosy TT-4, BT-5 and BB-1. The patients were observed for the period of 18 months and there was sensory and motor recovery.—Authors' Abstract

Nores, J. M., Redondo, A., Vernerey, C. and Gentilini, M. [Surgical treatment of leprous neuritis; results of 114 operations.] Presse Med. **17** (1988) 1756–1759. (in French)

One hundred-fourteen surgical operations for neuritis were performed in 50 patients coming from areas where leprosy is endemic. The neurological signs included pain and/or sensorimotor deficit. The surgical procedure consisted of transposition and/or neurolysis. Pain subsided in 86% of the cases, and the sensorimotor deficit was reduced in 78.9%. The effects of surgery on pain always appeared on recovery from anesthesia or on the day following the operation. The results were particularly good in young subjects and in patients with neuro-

logical signs of recent onset. Poor results were observed only in cases of old and painless neuritis with motor deficit, the latter being usually unchanged. Few studies have been published on large series of leprous neuritis patients treated surgically. Surgery in such cases must be associated with a medical treatment, failing which the patient is exposed to relapses.—Authors' English Abstract

Zhou, D., *et al.* [Personality analysis of leprosy patients.] China Lepr. J. **4** (1988) 145–148. (in Chinese)

The personality measure of 100 hospitalized cases of leprosy in Baoying County, Jiangsu Province, was investigated with the Eysenck Questionnaire. The results show that the type N personality amounts to 77% and is seen more in female patients, being 93.8%, and it is also seen more in people under 60 years of age with a lower cultural level. The higher rate of suicide among leprosy patients might in part just result from their unstable emotions.—Authors' English Abstract

Other Mycobacterial Diseases and Related Entities

Bhattacharya, C. P., Chakrabarty, A. N. and Dastidar, S. G. Comparison of sensitivity of *Mycobacterium* spp. to combinations of clavulanic acid & penicillins with certain antitubercular agents. Indian J. Med. Res. **88** (1988) 118–123.

The sensitivity to amoxycillin and clavulanic acid of several reference strains of mycobacteria was assessed by colony reduction and disc-diffusion techniques on Lowenstein-Jensen medium as well as by the tube-dilution technique using Kirchner's liquid medium. With the exceptions of *Mycobacterium smegmatis* and *M. skinsnes,* the other mycobacteria, including *M. tuberculosis* (H37Rv, H37Ra) showed remarkable sensitivity to amoxycillin and clavulanic acid; further, this drug combination in combination with other antitubercular drugs (INH, ethambutol, rifampin and streptomycin) exhibited synergistic and powerful inhibitory effects.—Authors' Abstract

Brett, S. J. and Butler, R. Macrophage activity in resistant and susceptible mouse strains infected with *Mycobacterium lepraemurium.* Immunology **63** (1988) 701–706.

The level of activation of peritoneal macrophages following subcutaneous inoculation of resistant (C57BL) and susceptible (BALB/c) mice was assessed by monitoring superoxide anion and hydrogen peroxide production and also tumor cell cytostasis. The level of systemic macrophage activation appeared to correlate with bacterial load, rather than resistance to infection. It was observed that the more susceptible (BALB/c) strain developed higher and more sustained levels of systemic macrophage activation; whereas the more resistant (C57BL) strain showed only low transient levels of macrophage activation. In contrast, *in vivo* challenge of subcutaneously infected C57BL mice, via the intraperitoneal route, with heat-killed *Mycobacterium lepraemurium* and thioglycollate resulted in a high level of macrophage activation compared with similarly treated uninfected mice. Similar treatment of susceptible BALB/c mice, however, did not result in enhanced macrophage activation. It was also observed that high levels of macrophage activation occurred in T-cell-deprived C57BL mice following infection with *M. lepraemurium.*—Authors' Summary

Cutler, S. J. Investigation of the effect of heat enhancement on the growth of mycobacteria in radiometric medium. Tubercle **69** (1988) 197–203.

The enhancement of the growth rate of 11 clinical isolates of mycobacteria, covering six species, were investigated in vials of Middlebrook 7H12 medium which had

previously been heated to 60°C, 70°C or 80°C. The optimal temperature which enhanced growth was 70°C. The enhancing effect remained stable for over 3 months. Trypsin treatment of the medium abolished the enhancing effect of heat, but this could be restored by the addition of heated or unheated bovine serum albumin (BSA). Protein electrophoresis demonstrated altered electrophoretic mobility of heated BSA. It is suggested that this altered BSA is the component which promotes enhanced mycobacterial growth.—Author's Summary

de Bruyn, J., Bosmans, R., Nyabenda, J. and van Vooren, J. P. Effect of zinc deficiency on the appearance of two immunodominant protein antigens (32 kDa and 65 kDa) in culture filtrates of mycobacteria. J. Gen. Microbiol. **135** (1989) 79–84.

After growth of six strains of mycobacteria on Sauton medium in the absence of added Zn^{2+}, cell yields were lowered, to between 22% and 67% of the yields obtained when Zn^{2+} (5μM) was added. Two immunodominant proteins, named P_{64} and P_{32} (antigens of 62–65 kDa and 29–33 kDa, respectively) were abundant in culture filtrates after growth of mycobacteria. P_{64} was present at elevated concentrations (showing a 9- to 16-fold increase as a percentage of the total protein released) after Zn^{2+}-deficient growth of five of the six strains studied; in *Mycobacterium tuberculosis* it represented 25% of all released proteins. However, little P_{64} was detected in culture filtrates of *M. fortuitum* and of *M. phlei* grown under Zn^{2+} deficiency, and in the latter there was no increase of P_{64} during Zn^{2+} deficiency.—Authors' Abstract

du Moulin, G. C., Stottmeier, K. D., Pelletier, P. A., Tsang, A. Y. and Hedley-Whyte, J. Concentration of *Mycobacterium avium* by hospital hot water systems. JAMA **260** (1988) 1599–1601.

Water from 34 sites on two temporarily vacant hospital floors was analyzed for the presence of mycobacteria. These sites included 18 cold water taps and 16 hot water taps, including shower heads. A total of 14 sites (41%) demonstrated the presence of *Mycobacterium avium* as confirmed by biochemical characterization, DNA/rRNA probe analysis, and seroagglutination. Of positive sites, 11 were hot water sources with an average temperature of 55°C and yielding up to 500 colony-forming units per 100 ml. Seven of 11 strains analyzed for glycolipid antigens were identified with the type 4 serovar, the preponderant serovar of *M. avium* in patients with acquired immunodeficiency syndrome from the Boston area. Potable hot water systems, particularly those that generate aerosols, may contain concentrations of *M. avium* greater than those found in cold water systems and could serve as an environmental source for colonization and infection of immunocompromised persons.—Authors' Abstract

Ha, D. K. K., Lawton, J. W. M. and Collins, R. J. A histopathological study of pulmonary infection of mice with *Mycobacterium lepraemurium*. J. Comp. Pathol. **99** (1988) 421–429.

Intranasal instillation of *Mycobacterium lepraemurium* (MLM) into mice produced pulmonary infection. MLM multiplied rapidly in the lung tissue during the first few weeks without involvement of other organs. The increase in number, size and confluence of lung granulomas paralleled the multiplication of MLM which could be found both intracellularly and extracellularly. It is postulated that extracellular bacteria may find their way to the bloodstream and thus spread to other visceral organs. Extensive destruction of alveoli and occupation of airspaces by lepra-like cells invariably occurred as the disease progressed.—Authors' Summary

Hoffner, S. E. Improved detection of *Mycobacterium avium* complex with the BACTEC radiometric system. Diagn. Microbiol. Infect. Dis. **10** (1988) 1–6.

A reconsideration of the laboratory methods used for primary isolation of mycobacteria other than *Mycobacterium tuberculosis* is needed due to the increasingly recognized importance of such mycobacterial infections in immunocompromised patients. One example of this is the severe opportunistic infections caused by *M. avium* complex among AIDS patients. In this study, the

BACTEC radiometric system was compared to conventional culture on solid medium for the detection of *M. avium* complex in 3612 selected clinical specimens, mainly of extrapulmonary origin. Of a total number of 63 *M. avium*-complex isolates, the BACTEC system detected 58 (92%), compared to 37 (59%) for conventional culture. A much more rapid detection was attained with radiometric technique than with conventional culture. The mean detection time for the cultures positive with both methods was 7.1 and 28.3 days, respectively. The BACTEC radiometric system achieves a rapid and significantly more sensitive detection and seems to be an excellent complement to conventional culture in the laboratory diagnosis of infections with the *M. avium* complex.—(*From* Excerpta Medica)

Hong Kong Chest Service/British Medical Research Council. Five-year follow-up of a controlled trial of five 6-month regimens of chemotherapy for pulmonary tuberculosis. Am. Rev. Respir. Dis. **136** (1987) 1339–1342.

The authors report on the follow up after 5 years of pulmonary tuberculosis patients in Hong Kong treated with five 6-month multidrug regimens. The four drug regimens that included pyrazinamide continued to show excellent results against drug-sensitive bacilli—total relapse rates being 3.4% over 5 years. In contrast the total relapse rate for the non-pyrazinamide regimen was 10.3%. Drug-resistant (isoniazid and/or streptomycin) strains were also effectively treated with the pyrazinamide regimens, with 3 of 104 patients relapsing over the 5-year period.—M. Hooper (Trop. Dis. Bull.)

Inderlied, C. B., Kolonoski, P. T., Wu, M. and Young, L. S. Amikacin, ciprofloxacin, and imipenem treatment for disseminated *Mycobacterium avium* complex infection of beige mice. Antimicrob. Agents Chemother. **33** (1989) 176–180.

The *Mycobacterium avium* complex (MAC) is a common cause of disseminated infection in patients with acquired immunodeficiency syndrome and is increasingly seen as a cause of infection in other immunocompromised patients. Traditional antimycobacterial therapy often is ineffective, and there is a clear need for antibiotics with proven activity against the MAC. Three agents, amikacin, ciprofloxacin, and imipenem, were tested *in vitro* for activity against MAC strain 101. Amikacin was bacteriostatic, with an MIC of 4.8 μg/ml, which is significantly lower than the concentration in serum obtained with standard dosing. Imipenem and ciprofloxacin had little or no activity alone (MICs, >16 and 4.7 μg/ml, respectively), but when they were combined with amikacin there was bactericidal activity. Each agent was tested individually and in combination by using the beige mouse model of disseminated MAC infection. There was no mortality in a group of animals infected with MAC 101 and treated with amikacin alone; also, there was a significant decrease in the infection of the blood, liver, and spleen. There was no apparent improvement in therapeutic effectiveness when amikacin was combined with the other agents. Neither ciprofloxacin nor imipenem was active as a single agent, which was consistent with the *in vitro* activities of these agents. Amikacin in combination with traditional antimycobacterial agents warrants further study as potential therapy for disseminated MAC infections.—Authors' Abstract

Kostromin, A. P., Chernushenko, E. F., Borovok, M. I. and Demidov, S. V. [Changes in the system of T-lymphocyte cyclic nucleotides in animals with experimental tuberculosis.] Probl. Tuberk. **11** (1988) 50–54. (in Russian)

The levels of cAMP and cGMP, the activity of the enzymes of the synthesis and hydrolysis of the cyclic nucleotides of T lymphocytes in the thymus and spleen, and the functional state of T lymphocytes in peripheral blood in experimental tuberculosis were studied in guinea pigs. Pronounced shifts in the functional state of the immunocompetent T cells in the experimental tuberculous animals were revealed. The shifts were accompanied by impairment of DNA biosynthesis due to inadequate response of different structures of the membrane ade-

nylate cyclase complex. The shifts led to changes in synthesis and hydrolysis of the cyclic nucleotides, which had an impact on the immune response of T lymphocytes. PPD, a specific allergen activated the sensitized lymphocytes in the cell culture, lowered the cAMP/cGMP ratio at the expense of activizing guanylate cyclase and acted as a β-adrenostimulator. The decrease in the cAMP/cGMP ratio in response to PPD was indicative of the host sensitization to the allergen.—Authors' English Abstract

Lamoureux, G., Davignon, L., Turcotte, R., Laverdière, M., Mankiewicz, E. and Walker, M. C. Is prior mycobacterial infection a common predisposing factor to AIDS in Haitians and Africans? Ann. Inst. Pasteur Immunol. **138** (1987) 5–21.

The authors argue that: a) the different transmission modes of African/Haitian AIDS (predominantly heterosexual intercourse) and European and USA AIDS (predominantly male homosexual intercourse and intravenous drug abuse), and b) possibly different (increased) susceptibilities of Africans/Haitians for HIV infection, are related to previous infection with *Mycobacterium tuberculosis*. The known high incidence of tuberculosis in African and Haitian AIDS patients is documented. The mechanisms involve activation of CD4+ T cells by *M. tuberculosis* and the general immunosuppression induced by tuberculosis.—S. B. Lucas (Trop. Dis. Bull.)

Libonati, J. P., Stager, C. E., Davis, J. R. and Siddiqi, S. H. Direct antimicrobial drug susceptibility testing of *Mycobacterium tuberculosis* by the radiometric method. Diagn. Microbiol. Infect. Dis. **10** (1988) 41–48.

Direct-drug-susceptibility tests were performed on clinical specimens positive for acid-fast bacilli by either Ziehl-Neelsen or fluorochrome staining. The results of conventional agar dilution and a modified radiometric (BACTEC) method were compared. A total of 580 smear-positive specimens were tested by the BACTEC method at three separate sites; 377 of these were culture positive for *Mycobacterium tuberculosis*, and 343 (91%) yielded acceptable direct-susceptibility-test results. We used the conventional method to determine that 343 of 519 smear-positive specimens were culture positive for *M. tuberculosis*, and 212 (62%) produced acceptable results within 3 wk. Conventional results were reported in 3–4 wk, while the time required to obtain results with the BACTEC method ranged from 5 to 21 days (average 11.5 days). Results indicate that the radiometric method provides reportable results more frequently with time savings as compared to the conventional method.—(*From* Excerpta Medica)

McManus, I. C., Lockwood, D. N. J., Stanford, J. L., Shaaban, M. A., Ati, M. A. and Bahr, G. M. Recognition of a category of responders to group ii, slow-grower associated, antigens amongst Kuwaiti senior school children, using a statistical model. Tubercle **69** (1988) 275–281.

A mathematical model previously developed to test the validity of categorization of skin test responders has been applied to data obtained from three age groups of Kuwaiti school children. Two specially designed sets of four new tuberculins were tested on senior school children to determine whether extra categories of responders might exist among them. Strong statistical evidence has been obtained that a proportion of the children respond to group ii, slow-grower associated antigen, creating a fourth responder category, but no evidence was found for responses to group iii, fast-grower associated antigen. The significance of group ii antigens in immune protection from tuberculosis has never been considered specifically. It is of special interest to note that responders to these antigens have been readily found in Kuwait, a country where BCG is thought to be effective; whereas no such category could be found in India or Sri Lanka, where the efficacy of the vaccine is less certain.—Authors' Summary

Mehta, P. K. and Khuller, G. K. Protective immunity to experimental tuberculosis by mannophosphoinositides of mycobacteria. Med. Microbiol. Immunol. **177** (1988) 265–284.

Mannophosphoinositides isolated from mycobacterial cells were found to induce both humoral and cell-mediated immune responses in mice when injected as mannoside-methylated bovine serum albumin (MBSA) complexes. Immunization of mice with mannoside-MBSA complexes elicited significant protection against challenge with LD_{50} dose of *M. tuberculosis* H37Rv as revealed by high survival rate, low values of root-specific lung weight, lung densities and colony-forming units recovered from lung, liver and spleen, compared to the nonimmunized group. These observations were further substantiated by histopathological studies. The protective immunity elicited by mannoside-MBSA complexes against challenge with *M. tuberculosis* H37Rv was mediated by the cooperation of T-B cells, as shown by the passive transfer of immune cells/sera into syngeneic sublethally irradiated recipient mice.—(*From* Excerpta Medica)

Mehta, P. K. and Khuller, G. K. Serodiagnostic potentialities of enzyme-linked immunosorbent assay (ELISA) using mannophosphoinositides of *Mycobacterium tuberculosis* H37Rv. Med. Microbiol. Immunol. **177** (1988) 285–292.

The serological response to mannophosphoinositides of *Mycobacterium tuberculosis* H37Rv and to tuberculin-purified protein derivative (PPD) was examined by enzyme-linked immunosorbent assay (ELISA) in patients suffering from tuberculosis and related diseases. In sputum-positive cases 94% samples were found to be positive to mannoside antigens and 77% to PPD, while in sputum-negative cases, 71% of samples gave a positive reaction to mannosides and 54% to PPD. The high specificity of mannoside ELISA was demonstrated to be 97% in healthy individuals and 100% in patients suffering from other respiratory diseases; whereas PPD ELISA was 84% and 82% in healthy and infected patients, respectively. Thus, ELISA is more specific and sensitive for mannosides than for PPD for the diagnosis of tuberculosis. However, antibodies to mannosides and PPD were detected in lepromatous as well as tuberculoid leprosy patients.—(*From* Excerpta Medica)

National Tuberculosis Programme. (Editorial) Indian J. Tuberc. **35** (1988) 43–45.

The progress of the Indian National Tuberculosis Programme is reviewed but it is noted that extension of the program to cover the entire country has proceeded at "a snail's pace" during the last phase. There are some 2.5 million sputum-positive patients in India with an additional 800,000 each year. Altogether the total case load is estimated to be 10 million. In 1986, 2.8 million patients were treated but only 26% are estimated to have completed treatment. Sociological and epidemiological problems remain.—D. W. FitzSimons (Trop. Dis. Bull.)

Resnick, M., Fibach, E., Lebastard, M., Levy, L. and Bercovier, H. Response of the murine hematopoietic system to chronic infection with *Mycobacterium lepraemurium*. Infect. Immun. **56** (1988) 3145–3151.

Mycobacterium lepraemurium infection of mice produces a chronic lethal disease that is characterized by massive accumulation of macrophages throughout the mononuclear-phagocyte system. We studied the influence of *M. lepraemurium* infection on the composition and function of the hematopoietic system. Medullary erythropoiesis was virtually abolished, as reflected by a small number of erythroid elements and a decrease in the number and frequency of erythroid progenitors in the bone marrow, together with reduced uptake of ^{59}Fe into bone marrow hemin. On the other hand, erythropoiesis was observed in the spleen, as demonstrated by a large number of erythroid cells, a sixfold increase of ^{59}Fe uptake, and a pronounced increase in the number of erythroid progenitors. A considerable increase of monocyte progenitors was observed in the spleen, and a more modest increase was observed in the bone marrow. This increase may be accounted for, at least in part, by greatly increased levels of macrophage-colony-stimulating factor in the serum of infected mice. Thus, *M. lepraemurium* infection produces important changes in the hematopoietic system, during the course of which the spleen becomes the major hematopoietic organ.—Authors' Abstract

Schnittman, S., Lane, H. C., Witebsky, F. G., *et al.* Host defense against *Mycobacterium avium* complex. J. Clin. Immunol. **8** (1988) 234–243.

Mycobacterium avium complex (MAC) is an intracellular pathogen and the most common cause of widely disseminated bacterial infection in patients with the acquired immunodeficiency syndrome (AIDS). MAC is infrequently seen in other immunocompromised adults, suggesting that the host defense defect allowing for MAC infection is relatively unique for AIDS. A system was developed for studying the immune response to MAC infection, utilizing MAC isolated from patients with AIDS and monocytes from normal controls and patients with AIDS. Phagocytosis, superoxide anion (SOA) production, and killing were measured. Monocytes from normal controls and AIDS patients were identical with respect to phagocytosis of MAC. In contrast, baseline SOA production was elevated in monocytes from patients compared to normal monocytes and was minimally augmented in response to either phorbol myristate acetate or MAC. Fourteen-day kinetic studies revealed in patients and controls a biphasic pattern with 50–99% killing of AIDS-derived MAC initially, followed always by a rapid outgrowth of surviving bacilli. Despite a modest enhancement of MAC killing by normal but not patients' monocytes pretreated with either recombinant interferon-γ or recombinant tumor necrosis factor-α, outgrowth of MAC was always observed in both, typically faster in patients than in controls. Even monocytes in the presence of lymphocytes stimulated with interleukin-2 did not demonstrate enhanced MAC killing. In contrast, high-titered anti-MAC immune serum derived from a patient with polymyositis and disseminated MAC significantly enhanced the killing of MAC by monocytes from both AIDS patients and healthy controls and prevented their outgrowth. These findings suggest that the host defense defect allowing for MAC infection appears not to reside in the monocyte and that the *in vitro* lymphocyte functions examined in this study do not appear to play a major role. What role specific antibody plays *in vivo* in preventing disseminated MAC is uncertain, but the lack of such antibody may help explain the propensity for AIDS patients to develop systemic infection.—(*From* Excerpta Medica)

Senesi, S., Zolfino, I., Batoni, G., *et al.* Lymphocytic purine metabolic disorders in tuberculin anergic mice. Med. Sci. Res. **16** (1988) 949–950.

The *in vitro* responsiveness to the purified protein derivative of the tuberculin and to concanavalin A of splenic lymphocytes from mice infected intravenously with large doses of *Mycobacterium bovis* strain BCG was investigated and was found to be significantly impaired 2 weeks after infection. This hyporeactivity was associated with a marked increase of adenosine deaminase (ADA) and purine nucleoside phosphorylase (PNP) activity within lymphocytes, while 5′-nucleotidase (5′-N) remained substantially unaffected over the period of the study. Since an intact purine metabolism, in which ADA, PNP and 5′-N are involved, is essential for the biochemical control of lymphocyte immunoreactivity, altered levels of such enzymes might represent another mechanism by which immunosuppression is achieved in tuberculin anergy.—(*From* Excerpta Medica)

Sherman, I., Harrington, N., Rothrick, A and George, H. Use of a cutoff range in identifying mycobacteria by the Gen-Probe rapid diagnostic system. J. Clin. Microbiol. **27** (1989) 241–244.

Commercial DNA probes (Gen-Probe Corp., San Diego, Calif.) for *Mycobacterium tuberculosis* complex, *M. avium,* and *M. intracellulare* were compared with conventional methods for accuracy, applicability, and speed for the identification of putative isolates of the *M. tuberculosis* and *M. avium* complexes. Results are expressed as percent hybridization. Values of $>15\%$ were considered positive, and values of $<5\%$ were negative. Cultures having hybridization values within an indeterminate range of 5% to 15% were repeated. Mycobacterial isolates resembling *M. tuberculosis* and *M. avium* complex from cultures of 589 specimens, representing 432 patients, were entered into this study; 294 cultures were tested with the *M. tuberculosis* complex

probe, and 326 cultures were tested with the *M. avium* probe. In all cases, probe results agreed with our biochemical identification of the isolates. The *M. intracellulare* probe was used with 117 isolates morphologically resembling *M. avium* complex, and one false-negative result was observed. Seventy-two cultures gave initial hybridization results that fell within the indeterminate range and were repeated. If the manufacturer's recommended 10% cutoff value had been used, the original hybridization values would have resulted in 27 misidentified cultures, 16 false-negatives and 11 false-positives.—Authors' Abstract

Simpson, L. O. Altered blood rheology in the pathogenesis of diabetic and other neuropathies. Muscle Nerve **11** (1988) 725–744.

Although a substantial literature confirms the abnormal flow properties of diabetic blood, in only a few papers has the vasculitis of diabetic neuropathy been considered to have a hemorheological cause. It is proposed that the pathogenesis of nerve lesions involves an interaction between the specialized nerve vascular system and focal ischemic lesions resulting from rheologically induced stasis. The proposition is extended into other conditions with abnormal blood rheology such as hypothyroidism, uremia, dysglobulinemia, polyarteritis nodosa, and lepromatous leprosy. It is concluded that the treatment of such polyneuropathies should include an agent which would improve the flow properties of the blood.—Author's Abstract

Stanford, J. L., Ganapati, R., Revankar, C. R., Lockwood, D., Price, J., Ashton, P., Ashton, L. and Rees, R. J. W. Sensitisation by mycobacteria and the effects of BCG on children attending schools in the slums of Bombay. Tubercle **69** (1988) 293–298.

Quadruple skin testing with new tuberculins was used to evaluate the effects of previously administered BCG Madras in children attending schools in the slums, or living in Kopri Leprosy Colony in Bombay. There were differences between schools both in the level of sensitization of children without BCG scars and in the effects of BCG vaccination. Results obtained at one school resembled those obtained in a previous study in Agra, where BCG was thought to be ineffective. Results from the other schools and Kopri were more like those previously reported from Ahmednagar, where BCG was considered to be much more effective. Thus, within the same city groups of children of the same social status may vary widely both in their contact with mycobacteria and in their capacity to benefit from BCG vaccination.—Authors' Summary

Swartz, R. P., Naai, D., Vogel, C.-W. and Yeager, H., Jr. Differences in uptake of mycobacteria by human monocytes; a role for complement. Infect. Immun. **56** (1988) 2223–2227.

We investigated the influence of serum factors on the uptake of various species of mycobacteria by human peripheral blood monocytes (PBM). On the basis of the percentage of PBM involved during *in vitro* uptake, the mycobacteria were of two distinct groups. The mycobacteria of one group, which consisted of *Mycobacterium avium* complex and *M. chelonae,* were taken up by many PBM; the other group, consisting of *M. tuberculosis, M. kansasii, M. fortuitum,* and *M. gordonae,* were taken up by fewer PBM. *M. scrofulaceum* was intermediate to these two groups on the basis of its uptake by PBM. Serum depleted of complement by heating or treatment with cobra venom factor significantly reduced the extent of PBM involvement with *M. avium* complex, indicating that complement is an important serum component mediating the uptake of *M. avium* complex organisms. Preincubation of mycobacteria with serum containing 10 mM EGTA [ethylene glycol-bis(β-minoethyl ether)-N,N,N′,N′-tetraacetic acid] and 10 mM $MgCl_2$ resulted in uptake by a high percentage of PBM, while preincubation in heated serum or serum containing 10 nM EDTA resulted in a significantly reduced percentage of PBM involved in uptake of *M. avium* complex organisms, indicating that these organisms are activators of the alternative pathway of complement. Incubation of *M. avium* complex organisms in human serum consumed 51% of the hemolytic complement activity. Parallel ex-

periments indicated that serum had a lesser effect on the uptake of *M. tuberculosis*. Thus, serum is important in *in vitro M. avium* complex uptake by PBM; complement has a major role in the effect of serum, but this role is less important with *M. tuberculosis*.—(*From* Excerpta Medica)

Venkataraman, P., Paramasivan, C. N., Ilampurnam, K. J. and Prabhakar, R. Intraspecies differentiation of strains of *Mycobacterium tuberculosis* obtained from Czechoslovakian, Mongolian and South Indian patients. Indian J. Med. Res. **88** (1988) 211–216.

Twenty-nine strains of *Mycobacterium tuberculosis* from Czechoslovakia, 46 from Mongolia, and 50 from South India were tested for virulence in the guinea pig, sensitivity to thiophen-2-carboxylic acid hydrazide (TCH) and phage type. Most of the Czechoslovakian and Mongolian strains (93% and 80%, respectively) were highly virulent in the guinea pig while only 36% of the South Indian strains showed high virulence. Similarly very high proportions of Czechoslovakian (97%) and Mongolian strains (85%) were resistant to TCH as against only 22% of South Indian strains. The phage type I was observed in none of the Czechoslovakian strains, 4% of Mongolian strains and in 68% of South Indian strains. Thus, the Czechoslovakian and Mongolian strains, in general, resembled the classical *M. tuberculosis*, while the South Indian strains were generally of low virulence, susceptible to TCH and of phage type I.—Authors' Abstract

Wallace, R. J., Jr., Nash, D. R., Tsukamura, M., Blacklock, Z. M. and Silcox, V. A. Human disease due to *Mycobacterium smegmatis*. J. Infect. Dis. **158** (1988) 52–59.

Mycobacterium smegmatis is a rapidly growing environmental species not considered a human pathogen. We identified 22 human isolates of *M. smegmatis* from Australia and the southern United States: 19 were from skin or soft-tissue infections, and none were from urine or the male genital tract. These isolates closely resembled *M. fortuitum*, except for a negative 3-day arylsulfate test; growth at 43–45°C; a low semiquantitative catalase test; and, in 50% of isolates, a late-developing, yellow-to-orange pigment. The isolates were biochemically identical to four reference strains and the type strain of *M. smegmatis*. Isolates were resistant to isoniazid and rifampin but susceptible to ethambutol, doxycycline, sulfamethoxazole, ciprofloxacin, imipenem, and amikacin. Eleven patients treated on the basis of *in vitro* susceptibility tests responded well to therapy. The similarity of *M. smegmatis* to *M. fortuitum* and the failure to recognize that the former is an environmental species may have contributed to previous failures to recognize it as a human pathogen.—Authors' Abstract

Yajko, D. M., Kirihara, J., Sanders, C., Nassos, P. and Hadley, W. K. Antimicrobial synergism against *Mycobacterium avium* complex strains isolated from patients with acquired immune deficiency syndrome. Antimicrob. Agents Chemother. **32** (1988) 1392–1395.

Pairs of 11 antimicrobial agents were tested *in vitro* for their ability to act synergistically against three strains of *Mycobacterium avium* complex isolated from patients with acquired immune deficiency syndrome. From the combinations tested, four drugs (ethambutol, rifampin, ciprofloxacin, and erythromycin) were selected for more extensive study against 20 strains of *M. avium* complex. The inhibitory and killing synergism obtained with combinations of two, three, or four drugs was assessed by determining the fractional inhibitory concentration index and fractional bactericidal concentration index. Inhibitory synergism occurred against 90% to 100% of the strains for all drug combinations in which ethambutol was included. Killing synergism occurred against 85% to 95% of the strains when ethambutol was used in combinations which included either rifampin or ciprofloxacin. However, killing synergism occurred against only 45% of the strains when drugs were tested at concentrations that can be obtained in patient serum. In other experiments, rifabutin (ansamycin) gave results that were comparable to those obtained with rifampin. Clofazimine did not show synergistic killing activity at a con-

centration that is achievable in serum for any of the drugs tested. Our results indicate that there is considerable variability in the antimicrobial susceptibility of *M. avium* isolates obtained from patients with acquired immune deficiency syndrome. This variability could have significant impact on the clinical response to various therapies.—Authors' Abstract