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The 1990 JOURNAL—A Continuing Perspective

In 1990, rapid progress continues in learning more about leprosy. As reflected in the pages of the JOURNAL, this progress will again be summarized, emphasized and, to the extent possible, put into a personal perspective. In many areas our progress has been phenomenal since 1981 when the first of this series of editorials was written.

In the March issue, Cellona, *et al.* (1–11)* reported a multicenter, 5-year chemotherapy trial in 358 new and relapsed lepromatous patients. Eight regimens including five drugs—ranging from a single 1200-mg dose of rifampin followed by 5 years of dapsone 100 mg daily (new patients with dapsone-sensitive bacilli) to rifampin 600 mg daily for 4 weeks followed by 600 mg for 2 days each month for 5 years, plus prothionamide 375 mg daily for 8 weeks followed by thiacetazone 150 mg daily for 5 years (for dapsone-resistant patients). All gave comparable rates of clinical, bacteriologic and histopathologic improvement. N'Deli, *et al.* (12–18) showed that pefloxacin was active and bactericidal in 10 previously untreated lepromatous leprosy patients. Grugni, *et al.* (19–24) reported a clinical study of 1509 paucibacillary (PB) patients treated with conservative multidrug regimens until clinical inactivity and followed for 6 months to 5 years after stopping treatment. Relapses occurred in 85 patients for a relapse rate of 5.6% or 17.5/1000 person-years-at-risk. Bagshawe, *et al.* (25–30) studied serum IgM antibodies to phenolic glycolipid-I (PGL-I) in a leprosy-endemic village population in Papua New Guinea, and found that elevated antibody levels were common, particularly in young people, but that the antibody did not identify clinical leprosy, individuals at risk of clinical leprosy, or household contacts. Tyagi, *et al.* (31–38) isolated circulating immune complexes from leprosy patients' sera as polyethylene glycol precipitates, and showed that they were efficient activators of complement. Lewallen, *et al.* (39–43) found that low intraocular pressure and abnormally large postural changes in intraocular pressure were associated with avascular keratitis and iritis in leprosy patients. In a series of three papers, Schroff and colleagues (44–49, 50–57, 58–64) studied the immunogenicity of mycobacteria. The lack of immunogenicity of *Mycobacterium vaccae* by the intraperitoneal (i.p.) route in mice is likely due to inadequate antigen presentation by peritoneal macrophages. Both rapid-growing and slow-growing mycobacteria elicit T-cell-mediated suppression after i.p. but not after intradermal (i.d.) administration. Gormus, *et al.* (65–72) found IgG and IgM antibodies to mycobacterial lipoarabinomannan (LAM) in sooty mangabey monkeys inoculated with *M. leprae.* High levels of IgG, and to a lesser extent IgM, antibodies were associated with the development of lepromatous disease. Ibrahim, *et al.* (73–77) demonstrated quantitative and qualitative differences in different batches of *M. leprae* cell-free extracts prepared in the absence of protease inhibitors.

In the Editorial section of the March issue, Baker (78–97) pointed out the need for new drugs in leprosy control, and outlined currently promising leads. Hastings (98–110) reviewed the 1989 JOURNAL. In the Clinical Notes section, Fassin (111–114) discussed the influences of social perceptions of leprosy on public health programs.

In the Correspondence section, Balachandran, *et al.* (115–116) presented an interesting case of cutaneous non-Hodgkin's lymphoma masquerading as lepromatous leprosy. Sehgal and Battacharya (116–117) made a number of clarifying comments regarding a report by Job, *et al.* [IJL 57 (1989) 12–19] on single-lesion subpolar lepromatous leprosy. Job, *et al.* (117–118) offered some clarifications of the cases. Sehgal, *et al.* (118–120) explained in some detail their concepts of upgrading and downgrading reactions, downgrading reactions and downgrading per se, and relapse and type 1 (lepra) reaction. Pannikar (120–121) expressed appreciation for the new dimensions added by Sehgal, *et al.*, but continued to feel that it is difficult to differentiate relapse and late reversal reaction in PB patients. McDougall (121–123) advocated the use of blister-cal-

* Numbers in parentheses refer to page numbers in the INTERNATIONAL JOURNAL OF LEPROSY, Volume 58, 1990.

endar packs for monthly supplies of dapsone for those patients still taking dapsone monotherapy. Patil, *et al.* (123–126) demonstrated the equivalence of anti-*M. leprae* antibody determinations using sera and blood samples eluted from filter-paper blood blots. Fafutis-Morris, *et al.* (126–128) showed the development of receptors for interleukin-2 (IL-2) on peripheral blood mononuclear cells from lepromatous leprosy patients to the same extent as cells from normal controls on stimulation with phytohemagglutinin. Parkash, *et al.* (129–130), using rabbit nerve antigen, found that 22% of leprosy patients had detectable circulating antinerve antibodies. Pitule, *et al.* (130–133) developed a 22-mer synthetic DNA oligonucleotide probe based on the primary structure of the 16s ribosomal RNA of *M. leprae* and, under stringent conditions, found it specific for *M. leprae.*

The Obituary section (134–135) noted with sadness the death of Professor Francisco Eduardo Rabello of Brazil.

The News and Notes section contained the Indian Council of Medical Research (ICMR) Annual Report of the Director-General, 1987–1988, dealing with leprosy (137–140). There is interest in pyrazinamide as a possible drug to eliminate persisters. Glyoxylate bypass enzymes have been demonstrated in cell-free extracts of *M. leprae.* This pathway could be important in understanding persisters. A comparative field trial of two and possibly three Indian vaccines and the WHO vaccine is to be conducted in South India. The trial is to be designed and conducted by a committee of experts chosen by ICMR, and ICMR will fund the trial. WHO will provide only the vaccine and one scientist to sit on the monitoring committee.

In the Current Literature section of the March issue, Anderson, *et al.* (146) studied the effects of clofazimine on human neutrophils *in vitro* and found potentiation of superoxide generation which involved phospholipase A_2. Moulia-Pelat (147) reported that dapsone pretreatment antagonizes the bactericidal action of rifampin in *M. leprae*-infected mice. Pattyn, *et al.* (147–148, 148) reported no relapses at an average of 3.9 to 4.3 years after approximately 1 year's intensive combination chemotherapy of over 500 multibacillary (MB) patients. Revankar, *et al.* (148) observed a much higher inactivity rate in PB patients with fewer skin lesions than in those with four or more lesions when following the patients for 3 years after 6 months' treatment with WHO MDT.

In the Clinical Sciences section, Cristofolini, *et al.* (150–151) outlined the training of nurses to enable them to identify and treat the major eye problems in leprosy patients. Font, *et al.* (151) described clofazimine-induced keratopathy in a lepromatous patient treated with 100 mg twice daily for 3 years. Levis, *et al.* (152) found male lepromatous patients to have testicular dysfunction. Ponce, *et al.* (153–154) reported that leprosy caused frequent urinary sediment changes and concentration defects. Proteinuria and/or glomerular involvement was mainly due to amyloidosis. Saha and Rao (154) studied, in detail, the nutritional status of lepromatous leprosy patients with and without pulmonary tuberculosis and patients with pulmonary tuberculosis alone. Tuberculosis, but not lepromatous leprosy. caused weight loss, decreased serum transferrin levels, and increased inorganic phosphorus. Vieth, *et al.* (155) pointed out that 62% of the patients they examined had dry corneas. Wiener and Northcutt (155–156) found an association between membranoproliferative glomerulonephritis and lepromatous leprosy.

In the field of Immuno-Pathology, Agrewala, *et al.* (156) saw an increased frequency of HLA-A11 in erythema nodosum leprosum (ENL) patients compared to lepromatous patients without ENL. Bottasso, *et al.* (157) suggested that cell-mediated immune mechanisms may be responsible for ENL. Cooper, *et al.* (157–158) showed increased cells expressing mRNA for interferon-gamma (IFN-γ), T-cytotoxic cells, and T-helper cells in the lesions of reversal reactions. ENL lesions showed increases in T-helper cells but markedly less expression of mRNA for IFN-γ and T-cytotoxic cells. Chanteau, *et al.* (157) and Dhandayuthapani, *et al.* (158–159) found finger-stick blood spots on filter paper to yield comparable results to serum obtained by venipuncture in ELISA serologies to detect IgM antibodies to PGL-I. Filley, *et al.* (159) showed transient increases in circulating IL-2 receptors and a parallel increase in the proportion of oligosaccharide chains on the

Fc fragment of IgG terminating with *N*-acetylglucosamine and not galactose in ENL. This is additional evidence for changes in T-cell function in ENL. Filley, *et al.* (159–160) fractionated *M. leprae* and used 27 of the fractions to challenge peripheral blood mononuclear cells from leprosy patients, leprosy contacts, and noncontacts. Contacts most frequently responded to an 18-kDa fraction. A 36-kDa fraction stimulated tuberculoid, but not lepromatous, patients. Responses to the 65-kDa heat-shock protein (HSP) of *M. leprae* were similar in all groups. In a similar study Lee, *et al.* (163) found a wide range of responses to 20 different fractions of *M. leprae.* Almost every fraction stimulated some donors, but none seemed immunodominant. Gimenez, *et al.* (160) showed normal densities of Langerhans' cells in the epidermis of indeterminate patients, and in normal skin from TT and BT cases. There were increased densities in BT and TT lesions and decreased density of Langerhans' cells in lepromatous cases. Hancock, *et al.* (160) discussed the *in vitro* generation of antigen-specific, MHC class II restricted, CD4+ phenotype, cytotoxic-T lymphocytes. Harboe (161) suggested a possible protective role of rheumatoid factors in parasitic infections. Kaplan, *et al.* (161) found no effect of *M. leprae* on skin-test responses to tuberculin or IL-2 in leprosy patients. Kaufmann and Flesch (161–162) reviewed evidence that both helper- and cytolytic-T cells participate in the immune response to tuberculosis and that similar T-cell mechanisms are involved in both resistance and pathogenesis. Kingston, *et al.* (162) showed that Schwann cells can be induced to express MHC class II antigens, interact, and serve as antigen-presenting cells for histocompatible T cells in response to antigen and T cells alone. Makonkawkeyoon and Kasinrerk (163–164) found that *M. leprae* inhibited the production of IL-2 by peripheral blood mononuclear cells stimulated with mitogens or antigen *in vitro.* The inhibition was apparently mediated by prostaglandins produced by both mononuclear cells and adherent cells. Mittal, *et al.* (164–165) used dendritic-cell-enriched populations from lepromatous patients as *M. leprae* antigen-presenting cells *in vitro* and showed T lymphocyte proliferation and IFN-γ production, in a majority of cases. Modlin, *et al.* (165) reported high frequencies of $\gamma\delta$ T cells in leprosy granulomas. Lines of these cells proliferate in response to mycobacterial antigens and produce factor(s) which cause adhesion and aggregation of monocytes in the presence of granulocyte monocyte colony stimulating factor. Ottenhoff, *et al.* (166) fractionated *M. leprae* and BCG, and tested the *in vitro* responses of peripheral blood mononuclear cells from tuberculoid and lepromatous patients. Six of 18 lepromatous patients who did not respond to intact *M. leprae* responded strongly to isolated *M. leprae* antigens < 70 kDa in size which were also recognized by tuberculoid cases. Rasheed, *et al.* (167) demonstrated raised complement-dependent, IgM lymphocytotoxic autoantibodies in the sera of leprosy patients with histories of ENL or reversal reactions.

In Microbiology, Chan, *et al.* (168–169) found that PGL-I was highly effective in scavenging hydroxyl radicals and superoxide anions. Choudhury, *et al.* (169) reported that rifampin and deoxyfructoserotonin, but not dapsone, inhibited the association of *M. leprae* with Schwann cells *in vitro.* Ishaque (152) showed that intact *M. leprae* oxidize palmitic acid, and that this oxidation is mediated by the electron transport system using oxygen as the terminal electron acceptor. Katoch, *et al.* (169–170) monitored ATP concentrations in human *M. leprae in vitro* and found accelerated ATP decay with ethionamide, rifampin, clofazimine, dapsone, erythromycin and, to some extent, cycloserine but not with ethambutol or tetracycline. Mistry, *et al.* (170) utilized *M. leprae* in Schwannoma cell cultures *in vitro* and measured acetate incorporation into PGL-I. Acetate was not incorporated when the bacilli were cell-free, nor when cycloheximide or antileprosy drugs were added to the system.

In Epidemiology, Revankar, *et al.* (173) screened 22,287 industrial workers in Bombay and found 270 new leprosy cases. Walter (174) pointed out the value of a postlepromin scar as an indicator of good cell-mediated immunity (CMI) in leprosy patients.

In Rehabilitation, Kaada and Emru (175) reported that transcutaneous electrical nerve stimulation was beneficial in treating chronic soft-tissue ulcers of the foot or lower leg

in leprosy patients. Lamba, *et al.* (175) pointed out the benefits of surgery in patients with ocular leprosy.

In Other Mycobacterial Diseases, Buschman, *et al.* (176–177) reviewed the genetic aspects of innate and acquired resistance to mycobacteria in mice. Cooper, *et al.* (177) found 11 strains of *M. bovis,* isolated from cattle in Ireland, to be homogeneous by restriction fragment length polymorphism (RFLP) analysis.

The March issue contained the abstracts of the papers presented at the 24th U.S.-Japan Leprosy Research Conference in San Diego, California, 23–25 August 1989. Krahenbuhl and Chae (186) reported that there was a relatively rapid turnover of macrophages in the foot pads of *M. leprae*-infected nude mice, and that these newly arrived macrophages were responsive to IFN-γ. Salgame, *et al.* (186–187) cloned T-suppressor cells from lepromatous leprosy patients which were antigen-specific as to the induction of suppressions. Franzblau and White (187) reported structure activity relationships in a series of 19 fluoroquinolines against *M. leprae in vitro* using the BACTEC 460 system. Gelber (187–188) showed that a 4:1 mixture of amoxicillin and clavulanic acid was active and bactericidal against *M. leprae* in mouse foot pad infections. Saito and Tomioka (188–189) determined activities of a number of fluoroquinolines in *M. leprae*-infected mice. Sathish, *et al.* (189–190) infected avirulent strains of *Salmonella typhimurium* with plasmids containing DNA sequences coding for serologically defined antigens of *M. leprae.* Sela and Clark-Curtiss (190) described their technical approaches to isolating and sequencing the promoter of ribosomal RNA from *M. leprae.* Hunter and Brennan (190–191) fractionated *M. leprae* and analyzed the major protein components of the cytoplasmic membrane, cytosol, and cell wall. Modlin, *et al.* (191) studied $\gamma\delta$ T cells in leprosy lesions and found increases in positive lepromin skin tests and in reversal reactions. Izumi, *et al.* (191–192) discussed operational parameters in the field application of PGL-I-based serology. Williams, *et al.* (192) described the application of polymerase chain reaction (PCR) technology to detect *M. leprae.* Kohsaka, *et al.* (192) found that lyophilization reduced the viability of *M. leprae* by 99% to 99.9%. Walsh, *et al.* (193) described their experience in transmitting leprosy to Philippine cynomolgus monkeys. Nakamura and Yogi (193–194) reported that MRL/*lpr* mice were highly susceptible to *M. leprae.* Matsuo, *et al.* (194–195) studied the fraction of *M. scrofulaceum* HI-75 which combined with beta-glucuronidase. Hancock, *et al.* (195–196) generated cytotoxic-T lymphocytes from peripheral blood mononuclear cells from tuberculin-sensitive individuals with antigen which selectively destroyed mycobacterial antigen-pulsed monocytes. These cytotoxic-T lymphocytes were CD4+ and MHC class II restricted. Fukutomi, *et al.* (196) showed that phagocytosis of heat-killed mycobacteria by murine peritoneal macrophages was followed by production of IL-1 and tumor necrosis factor, enhanced consumption of glucose, and decreased Ia antigen expression. Rea, *et al.* (196–197) found marked increases in T-helper cells and, to a lesser extent, increases in T-cytotoxic cells using complementary DNA for mRNA coding for IFN-γ and human serine esterase, respectively, in *in situ* hybridization using skin biopsies. The distribution of the T-cytotoxic cells was identical to that of CD4+ T cells. Plikayetes and Shinnick (197) described PCR reactions with nested primers to identify *M. tuberculosis* and *M. leprae.* Mizuguchi, *et al.* (198) constructed recombinant plasmids from pMSC262 of *M. scrofulaceum* and pACYC177 of *Escherichia coli* and introduced them into BCG, by electroporation, where they were quite stable. Kaplan and Cohn (198) injected recombinant IL-2 into lepromatous leprosy patients and found local induration with mononuclear cell infiltrates and destruction of mononuclear phagocytes containing *M. leprae* with local reductions in the numbers of bacilli. Systemic anergy to *M. leprae* remained. Mehra, *et al.* (200) studied T-helper cell lines and clones from tuberculoid patients and individuals immunized to *M. leprae/M. tuberculosis,* and found that the most frequently recognized antigens of *M. leprae* were cell-wall proteins in the 7 kDa, 16 kDa and 28 kDa molecular size range. Schlesinger and Horwitz (200–201) showed that the phagocytosis of *M. leprae* was mediated by complement receptors CR1 and CR3 on monocytes and by C3 in serum which is fixed to

M. leprae by the alternative pathway. Snapper, *et al.* (201–202) reported the cloning of the gene coding for the 65-kDa HSP of *M. leprae* into the shuttle plasmid pYUB12, its introduction into both *M. smegmatis* and BCG, and its expression in both hosts.

In the Original Articles of the June issue, Thomas, *et al.* (273–280) treated MB (LL or near LL) patients with daily dapsone plus clofazimine for 3 months followed by daily clofazimine plus dapsone for 57 months. There were no detectable differences between the two regimens. Grosset, *et al.* (281–295) treated 21 MB patients with either pefloxacin or ofloxacin. The patients improved, and detailed mouse foot pad studies showed killing of about four logs of *M. leprae* with either drug by day 56 of treatment. Lechat, *et al.* (296–301) presented computer simulations of the effect of multidrug therapy (MDT) on the incidence of leprosy in which dramatic reductions could occur. Makonkawkeyoon, *et al.* (302–310) extensively studied *in vitro* peripheral blood mononuclear cell reactivities of leprosy patients across the spectrum. In general, the leprosy patients' cells responded normally to mitogens, but BL/LL patients' cells showed significantly less suppressive activities than cells from normal controls. Makonkawkeyoon, *et al.* (311–318) studied the *in vitro* production of cytokines by peripheral blood mononuclear cells from leprosy patients. IL-1 production in response to purified protein derivative (PPD) was reduced in BT/TT and BL/LL patients, particularly untreated patients. IFN production was normal in response to ConA or PHA but reduced in BL/LL patients and in treated BT/TT patients in response to PPD. Roche, *et al.* (319–327) analyzed the serological responses of untreated PB patients and found a heterogeneous response to 20% having an IgM response to PGL-I, 20% having IgG anti-LAM antibodies, and 33% showing antibodies to the *M. leprae*-specific epitope on the 35-kDa protein. Wu, *et al.* (328–333) developed latex agglutination tests (LATs) for antibodies to PGL-I and natural disaccharide-octyl-bovine serum albumin. There were no significant differences between these two LATs and their corresponding ELISAs. Chiplunkar, *et al.* (334–341) studied peripheral blood lymphocytes from lepromatous patients and found significantly reduced natural killer (NK) cell-mediated cytotoxicity and antibody-dependent cellular cytotoxicity. IL-2 and IFN-γ enhanced NK cytotoxicity in most of the patients' cells. Vachula, *et al.* (342–346) cultured normal peripheral blood monocytes with PGL-I, dimycocerosyl phthiocerol or mycoside A with or without IFN-γ and measured their oxidative responses to *M. leprae,* phorbol myristate acetate, and opsonized zymosan. PGL-I-treated monocytes released less superoxide anion in response to *M. leprae* and only *M. leprae,* both with or without IFN-γ. Cree, *et al.* (347–353) presented findings suggesting that the expected inverse relationship between delayed-type hypersensitivity (DTH) and humoral immunity in groups of leprosy patients is less strong in individual patients than is often thought. Kazda, *et al.* (353–357) isolated acid-fast bacilli (AFB) from sphagnum vegetation in Norway which reacted with a monoclonal antibody to PGL-I. Baskin, *et al.* (358–364) described three rhesus monkeys that were experimentally infected with *M. leprae* and, inadvertently, also with the simian immunodeficiency virus (SIV). The animals died of an immunodeficiency syndrome and had lesions caused by *M. leprae.*

In the Editorial section of the June issue, Bloom (365–375) reviewed the state-of-the-art in the molecular biology of mycobacteria.

In the Correspondence section, Chatterjee (377–378) and Grosset and Ji (378–379) discussed approaches to conducting controlled clinical trials for the evaluation of antimicrobial drug activity against *M. leprae.* Reddy (379–380) and Kurz (380) discussed relapse rates in MB patients receiving dapsone monotherapy for life after skin smears become negative. Kurz feels the data show that continuation of dapsone reduces relapses. Srinivas, *et al.* (382–383) reported a patient who developed allergic contact dermatitis over a tuberculoid leprosy lesion. Saad, *et al.* (384–385) presented a lepromatous leprosy patient who developed pure red cell aplasia. Pavithran (385–387) described a lepromatous patient with recurrent ENL reactions who had developed "saber tibiae." Esterre, *et al.* (387–388) analyzed cellular infiltrates in dermal lesions caused by atypical mycobacteria and found similarities with leprosy lesions. Fan-

dinho, *et al.* (389–391) found a modified cold method of Kinyoun to be equivalent to the standard Ziehl-Neelsen staining method in evaluating smears from leprosy patients. Job, *et al.* (392–393) found the immunoperoxidase technique for demonstrating S-100 protein on Schwann cells of dermal nerves to be useful in diagnosing tuberculoid leprosy and in distinguishing it from cutaneous sarcoidosis and tuberculosis.

In the Obituary section of the June issue, we were saddened to note the deaths of Dr. René Rollier of Morocco (394–395) and Professor Fernando Latapí of Mexico (396).

In the News and Notes section, Dr. Ruth Pfau (397) received the order Hilal-e-Pakistan from the Pakistan government for her 30 years' work for leprosy. Dr. Michel Lechat of Belgium and Dr. R. V. Wardekar of India received the prestigious International Gandhi Award for 1990 (398–399). Dr. H. Srinivasan became the new Editor of the Indian Journal of Leprosy.

In the Current Literature section in Chemotherapy, Chou, *et al.* (406) found that 31 of 70 (44%) strains of *M. leprae* from previously untreated MB cases showed primary dapsone resistance, one sixth (5) showing full resistance. Figueiredo, *et al.* (405) reported a case of severe hemolytic anemia and agranulocytosis induced by dapsone in a patient with normal glucose-6-phosphate dehydrogenase activity. Franzblau, *et al.* (406–407) studied structure activity relationships in a series of clofazimine analogs against *M. leprae in vitro* using radiorespirometry. Lin (408) reported 8th cranial nerve toxicity due to clofazimine. Richardus and Smith (409) have noted a tenfold increase in hypersensitivity reactions to dapsone when incidence during dapsone monotherapy (0.3%) is compared to that since the introduction of MDT (3.6%), and raised the possibility of an unexplained drug interaction with rifampin. Vaz, *et al.* (409) reported "flu" syndrome in a patient receiving rifampin once monthly. White (410) noted a 4.7-fold increased risk of lower-limb, deep vein thrombosis in patients receiving rifampin for tuberculosis.

In Clinical Sciences, Chaudhury, *et al.* (410) demonstrated AFB in the serum of 100% of lepromatous cases, 60% of tuberculoid cases, and 20% of contacts of active lepromatous cases. Deguerry, *et al.* (410) analyzed almost 27,000 PB patients and concluded that patients with single macules were being detected early in the course of the disease. Eventual relapses were more likely in patients with multiple macules. Huang, *et al.* (411) detected antinerve antibodies in the sera of 83% of leprosy patients. Saxena, *et al.* (412–413) found decreased serum calcium and magnesium levels in lepromatous leprosy patients. Srinivasan (413) concluded that clinical trials of agents claiming to heal plantar ulcers are not worth the trouble. Srinivasan and Stumpe (413) found a hand-held, thermal-sensibility testing device capable of increasing the rate of diagnosing leprosy by 15%–20%.

In Immuno-Pathology, Bagshawe, *et al.* (414–415) made a final report of the Karimui BCG vaccination trial which began in 1963. BCG gave 48% protection overall, being most effective in preventing borderline tuberculoid disease and in children < 15 years old. Boddingius and Dijkman (415, 415–416) studied *M. leprae* antigen localization by immunogold labeling and electron microscopy. Brett, *et al.* (416) determined murine T-cell epitopes on the 65-kDa protein of *M. leprae.* Peptide-specific T-cell responses were distinctly influenced by the H-2 haplotypes of the different mouse strains. Dudani and Gupta (418) pointed out the extensive sequence homology between the human mitochondrial protein, P1, and the 65-kDa mycobacterial protein. Fine, *et al.* (419) found no evidence that *M. leprae*-soluble antigens suppressed tuberculin reactions when both were given together i.d. Harris, *et al.* (419–420) mapped the epitopes of the 18-kDa protein of *M. leprae* and showed one *M. leprae*-specific B-cell epitope between residues 110 and 115, and a crossreactive T-cell epitope between residues 116 and 121. Klatser, *et al.* (420–421) reported ELISAs based on IgM antibodies against PGL-I epitopes to be superior in following responses to chemotherapy in lepromatous patients than anti-whole *M. leprae* and an ELISA-inhibition test based on a specific epitope on the 35-kDa protein of *M. leprae*. Koga, *et al.* (421) showed that murine macrophages subjected to various stress stimuli, including IFN-γ activation and viral infection, were recognized by class

I-restricted CD8+ T cells raised against a mycobacterial 65-kDa HSP. Lecour, *et al.* (421) observed C3H mice to have a higher relapse rate with tuberculosis after 6 months' treatment with isoniazid and rifampin than C57BL/6 mice. C3H mice, which have the *Bcg-r* gene, may have less ability to develop a specific acquired resistance to virulent *M. tuberculosis.* Meeker, *et al.* (422) found seroreactivity to the recombinant 65-kDa protein of *M. leprae,* or to overlapping peptides making up the protein, in about one third of active MB cases. Different epitopes on the 65-kDa protein were recognized by the patients' sera from the seven mouse monoclonal antibodies against the protein. Moudgil, *et al.* (423) showed that antibodies against PGL-I and *Mycobacterium w.* developed in mice infected with *M. leprae* in the foot pads when the bacterial load was more than 7×10^5 bacilli. Pessolani, *et al.* (423) found that 92% of sera from lepromatous leprosy patients recognized a 28- and 30-kDa doublet in short-term culture filtrates of BCG and seven other mycobacteria by Western blots. Poulton, *et al.* (424) characterized a serum factor, thought to be an IgG autoantibody, in certain lepromatous patients which acts on a surface antigen of lymphocytes to interfere with their activation by mitogens. Rawlinson and Basten (424–425) did not see T-cell responses of leprosy patients to antigenic epitopes which are crossreactive between *M. leprae* and *M. tuberculosis,* suggesting that a vaccine based on antigens shared between *M. leprae* and other mycobacteria is unlikely to be useful in preventing leprosy. Rook, *et al.* (425) described agalactosyl IgG as a T-cell-dependent, acute-phase reactant being raised in tuberculosis, rheumatoid arthritis, and Crohn's disease but not in sarcoidosis or uncomplicated leprosy. Schwerer, *et al.* (426) studied the IgA-type antibodies to PGL-I in leprosy patients and found them to be of the IgA_1 subclass and to resemble IgM-class antibodies to the antigen in their distribution. Wu, *et al.* (427–428) compared the FLA-ABS test and PGL-I ELISA in over 3000 sera and found the two tests comparable but the PGL-I ELISA more practical. Yong, *et al.* (428) described elevated IgE-class antibodies to soluble mycobacterial antigens in leprosy patients.

In Microbiology, Clark-Curtiss and Walsh (429) conducted RFLP analysis on *M. leprae* from a variety of sources and demonstrated that < 0.3% of the nucleotides differ among the genomes. Hartskeerl, *et al.* (429) presented a PCR based on the nucleotide sequences of a gene coding for the 36-kDa antigen of *M. leprae.* The PCR was *M. leprae* specific and its sensitivity approached one bacterium. Lugosi, *et al.* (430) successfully transformed two BCG strains using a shuttle plasmid vector. The stable expression of foreign DNAs in BCG now makes it possible to construct polyvalent recombinant BCG vaccine vehicles expressing a variety of antigens. Thangaraj, *et al.* (431) cloned the gene for the Mn/Fe superoxide dismutase of *M. leprae.*

In Experimental Infections, Gormus, *et al.* (431) described five rhesus monkeys which were coinoculated with viable *M. leprae* and SIV from an infected mangabey monkey. Three of the five developed leprosy and simian acquired immunodeficiency, suggesting that SIV increases the susceptibility of rhesus monkeys to leprosy. Suarez Moreno and Rodriguez Silveira (431) found that surgical removal of the draining popliteal lymph node significantly enhanced the multiplication of *M. leprae* subsequently inoculated into the foot pad.

In Epidemiology and Prevention, Al-Sogair, *et al.* (432) described the characteristics of new leprosy cases in the Eastern Province of Saudi Arabia. Yang, *et al.* (435) used the ratio of relapsed cases to new active cases to estimate the impact of relapses on overall control in Guangdong Province in China.

In Rehabilitation, Carayon (436), and Malaviya, *et al.* (436, 436) described surgical techniques for hand disabilities. Rao and Saddalinga Swamy (436–437) found surgical decompression of the posterior tibial nerve to be helpful in restoring sensation to the plantar aspect of the foot. Thompson, *et al.* (437) outlined the development of a hand biomechanics computer workstation over the last 12 years.

In Other Mycobacterial Diseases, Barbolini, *et al.* (438) used various monoclonal antibodies to detected mycobacterial antigens in tissues and cells immunohistologically. Gilardini Montani, *et al.* (440–441) described *in vitro* T-cell anergy to tuberculin

in patients with advanced disseminated tuberculosis. Peters, *et al.* (444) observed that 32% of 72 AIDS patients had mycobacterial infections. Mycobacterial infections were rare in immunocompetent individuals (1 in 135), and mycobacterial infections were not seen at all in 134 patients with nonHIV-related immunosuppression. Thus, HIV-related immunosuppression seems specifically predisposing to mycobacterial infections. Prantera, *et al.* (445) treated 5 patients with Crohn's disease with dapsone 100 mg daily and 2 responded, possibly suggesting a mycobacterial etiology. Wallace, *et al.* (449) reported mutational frequencies of 10^{-5} to 10^{-7} for single step mutants of *M. fortuitum* resistant to ciprofloxacin.

In the Original Articles of the September issue, Paula Motta and Zuniga (453–461) documented the evidence for increased transmission of leprosy in Brazil since 1969. The average detection rate has increased 6% per year, with the greatest rates of increase in the Northeast and Center-west macroregions of the country. Desai (462–465) presented a lepromatous patient with a circulating lupus-like anticoagulant. Abraham, *et al.* (466–468) studied 30 male MB patients and found 30% had oligospermia and 10% had demonstrable AFB in their semen. Scollard, *et al.* (469–479) studied blister fluid induced by suction over skin lesions of type 1 (reversal) reactions and demonstrated increases in CD4+ (T-helper) cells and increases in Tac-peptide (soluble IL-2 receptor) in half of the lesions. Roche, *et al.* (480–490) did serologies on 100 untreated MB patients, and found that the bacillary load as measured by the bacterial index (BI) was moderately correlated with IgM antibodies to PGL-I by ELISA ($r = 0.34$), antibodies to the *M. leprae*-specific 35-kDa protein by monoclonal antibody inhibition ELISA ($r = 0.55$), and IgG anti-LAM by ELISA ($r = 0.20$). Hussain, *et al.* (491–502) did quantitative ELISAs for IgM antibodies to soluble sonicates of whole *M. leprae* and synthetic disaccharide reflecting specificity for PGL-I. Antibodies correlated with the BI among patients; 30% of household/family contacts were serologically positive as were 17% of staff contacts. Meeker, *et al.* (503–511) measured antibodies to PGL-I and LAM in sequential serum samples from leprosy patients under treatment, and felt they were useful in following responses to treatment. Cartel, *et al.* (512–517) determined IgM antibodies against PGL-I using synthetic disaccharide in ELISA in two populations of French Polynesia, one with an annual detection rate of leprosy over the last 30 years of 57.1 and the other, 4.4 per 100,000. The two populations had essentially identical seropositivity rates and distributions. Under these conditions, these antibody determinations were not useful in detecting *M. leprae* infections. Rapoport, *et al.* (518–525) determined the prevalence of autoantibodies in leprosy and tuberculosis patients, and reviewed the literature. Harshan, *et al.* (526–533) showed adenosine, hypoxanthine and thymidine incorporation in viable *M. leprae* in murine macrophage cultures, in that order of magnitude, over 6 to 9 days of culture. Adenosine incorporation was 10- to 14-fold higher in bacilli inside macrophages than in the same numbers of bacilli in axenic cultures. Vachula, *et al.* (534–539) presented findings that monocytes from bacteriologically positive leprosy patients released less superoxide anion to a variety of stimuli than normal, and that this could be induced in monocytes from normal individuals with PGL-I. Nair and Mahadevan (540–547) cultured murine peritoneal macrophages and exposed them *in vitro* to *M. leprae* obtained from frozen infected armadillo liver and spleen. After 24 hours, the washed macrophages were lysed by freezing and thawing, and the lysates used as antigen in an ELISA. Bacteriologically positive lepromatous patients' sera bound to the wells containing the lysates. Nair, *et al.* (548–553) studied the effects of different mouse strains on the ability of *in vitro* cultures of murine macrophages infected with *M. leprae* to produce a lysate which could bind to bacteriologically positive lepromatous patients' sera. This was seen with Swiss white mice but not with C57BL/6 mice. Bacilli released from macrophages by 10 cycles of freeze-thawing remained viable with Swiss but not with C57BL/6 macrophages. Malaty, *et al.* (554–559) inoculated armadillos in the cornea with viable *M. leprae,* followed the progression of the infection, and suggested that in leprosy-endemic areas the bacilli may gain access to ocular tissues

via the cornea. Cowley, *et al.* (560–565) used immunoelectronmicroscopy to demonstrate MHC class II expression in human leprosy peripheral nerves and found none in Schwann cells in either PB or MB biopsies.

In the Editorial section of the September issue, Kaufmann and Deo (566–570) summarized the Indo-European Community Joint Symposium on Leprosy and Other Mycobacterial Diseases held in Lonavla, India, 6–9 November 1989.

In the Correspondence section, Ramachandran and Laxman (571–572) described an interesting borderline tuberculoid patient who presented with innumerable plaques, papules, and nodules resembling lepromatous leprosy. Pfaltzgraff (573) applauded Kato for his earlier remarks on practical aspects of leprosy vaccination. Prabhavalkar, *et al.* (573–574) pointed out the potential drawbacks of lay publicity about leprosy vaccines on leprosy field work.

The obituary of Dr. Chapman H. Binford appeared in the September issue (575–578).

In the News and Notes section, the prestigious Damien-Dutton Award for 1989 was presented to the Catholic Medical Mission Board (579–580). LEPRA-U.K. launched LEPRA-India on 3 August 1989 with Dr. K. V. Desikan as chairman of the managing committee of the new society (581–582). Vaccinations have been completed in a population of 120,000 in the Karonga District of northern Malawi (584–585). Dr. Grace Warren retired from The Leprosy Mission (586). The first notice appeared for the next International Leprosy Congress in Orlando, Florida, U.S.A., 26 August–7 September 1993 (587).

In the Current Literature section of the September issue, in General and Historical aspects, Mull, *et al.* (595) emphasized the need for health education for not only the patient, but the extended family and the public at large if the treatment of leprosy is to be truly effective.

In Chemotherapy, Carmichael and Paul (595–596) and Gawkrodger (596) each reported a patient who developed manic depression induced by dapsone. Franzblau and White (596) studied structure activity relationships among 20 fluoroquinolones against *M. leprae in vitro* and found that a number of newer derivatives were more active than ofloxacin in this system. Mariette, *et al.* (597–598) reported a case of pure red cell aplasia due to rifampin. Sansarricq (598) reviewed results to date with WHO MDT and felt the regimens were well tolerated and effective with negligible relapse rates 1–3 years after treatment is stopped. Wang, *et al.* (599) found rifapentine to be bactericidal against *M. leprae* in MB cases.

In Clinical Sciences, Claque, *et al.* (600) did not find antibodies to native type II collagen in leprosy sera as they are in rheumatoid arthritis patients. Clark and Richardson (600) reported a pregnant woman with ENL and inappropriate ADH secretion. ffytche (600–601) pointed out that up to 20% of leprosy patients develop sight-threatening lesions and between 5% and 7% are blind. Kulkarni, *et al.* (601) reported a BL leprosy patient with ENL who regularly took WHO MDT. A year after beginning MDT, including 600 mg of rifampin monthly, he developed multiple cold abscesses due to tuberculosis and later tuberculosis of his hip joint. The tuberculosis cleared when treatment with four drugs for tuberculosis was begun. Sen, *et al.* (602–603) found bone marrow and buffy coat examinations for AFB to be more sensitive than skin-smear examinations in leprosy patients, particularly those with PB disease and those receiving treatment. Wei, *et al.* (603) reported eight histoid cases from Guizhou Province in China.

In Immuno-Pathology, Bharadwaj and Katoch (604) found that 46 of 1069 originally healthy contacts of leprosy patients developed the disease during almost 8 years of follow up. Of these 46 cases, 41 were FLA-ABS positive and Dharmendra-lepromin negative. Fournie, *et al.* (605–606) showed that phenolic glycolipids from *M. leprae,* BCG, and *M. kansasii* all inhibited human peripheral blood mononuclear cell proliferation in a concentration-dependent but stimulus-independent fashion. The inhibition did not involve antigen-presenting cells or antigen-specific CD8+ suppressor-T cells. Gelber, *et al.* (606) showed that cell-wall fractions of *M. leprae* could prevent the multiplication of the organism in the foot pads of normal mice. Gill, *et al.* (606–607) found that some, but not all, long-

term-treated lepromatous patients have CD4+CD8− T cells which can respond to *M. leprae* antigens. Izumi, *et al.* (607) reported the development of a new gelatin particle agglutination test based on the sugar moieties of PGL-I for serologic testing in leprosy. Kaufmann, *et al.* (608) discussed the autoimmune implications of immunologic crossreactivity between microbial and mammalian heat-shock proteins. Launois, *et al.* (609) found that the failure of *M. leprae* to induce a strong oxidative respiratory burst in human phagocytes *in vitro* was not improved by INF-γ. Marolia, *et al.* (610) outlined the immunomodulating activities of delipidified cell walls of *M. leprae* and suggested their use as a leprosy vaccine. Mohagheghpour, *et al.* (610) showed that the 35-kDa protein of *M. leprae* contained T-cell antigen(s). Molloy, *et al.* (610–611) found that mycobacterial LAMs and bacterial lipopolysaccharides contaminating mycobacterial preparations exerted nonspecific suppression of *in vitro* lymphoproliferation. Moudgil, *et al.* (611) developed a human IgM monoclonal antibody against PGL-I. van Schooten, *et al.* (612–613) mapped nine T-cell epitopes on the 65-kDa protein of *M. leprae,* and the response to each was exclusively restricted via one HLA-DR allele. The human T-cell response to the mycobacterial 65-kDa protein, and epitopes on it, is controlled by HLA-DR genes. Antileprosy vaccine development must consider this immune response (Ir) gene control of T-cell responses.

In Microbiology, Jackson, *et al.* (615) described fluorescein-conjugated lectins which might be useful in demonstrating low numbers of AFB microscopically. Sritharan, *et al.* (616) reported aspartokinase and homoserine dehydrogenase activities in *M. leprae.* Wheeler (616–617) showed that *M. leprae* would not take up uridine nucleotides directly but could utilize the pyrimidines by hydrolyzing them to uridine and then taking up the uridine. Wheeler, *et al.* (617) suggested that fatty-acid synthetase activity in *M. leprae* may be insufficient to support growth and that the organism preferentially scavenges lipids from host cells, the major scavenging activity involving acetyl-CoA-dependent fatty acyl-CoA "elongase." Woods and Cole (617) described the application of PCR technology for detecting small numbers of *M. leprae.*

In Experimental Infections, Sanchez and Foster (618) studied the growth of *M. leprae* in mouse foot pads and found high dietary fat, particularly fat of animal origin, to be associated with higher levels of bacillary multiplication. Truman, *et al.* (618) used serologic screening for IgM antibodies against PGL-I and found antibodies in Louisiana but not Florida armadillos in the southern U.S.A. Overall antibody prevalence was 12.5% compared to histopathological prevalence rates of 7.7% based on ear biopsies. Wang, *et al.* (618, 618–619) found multiplication of AFB to a level of 2.4×10^9 per gram of tissue in tree shrews inoculated with *M. leprae.* Winters and Humphres (619) tolerized Lewis rats with high doses of *M. leprae* intraveneously (i.v.), and showed that the animals nevertheless controlled the growth of viable *M. leprae* challenges as well as untreated rats.

In Epidemiology, Albuquerque, *et al.* (619–620) reported alarming increases in leprosy in northeastern Brazil. George, *et al.* (621) found in South India that intrahousehold contact with leprosy created a 2.5-fold relative risk of acquiring the disease. Irgens, *et al.* (621) analyzed the epidemiology of leprosy in Portugal from 1946–1980 and concluded that, as in other areas where leprosy has disappeared, no new disease transmission is occurring during this termination of an endemic situation. Pan, *et al.* (622–623) expressed optimism that leprosy will be basically eliminated from Shandong Province, China, by the year 2000, and Shao, *et al.* (623), in Fujian Province by 1995.

In Rehabilitation, Antia (624) described a rigid-sole plastic shoe which is effective in distributing weight-bearing forces in anesthetic feet. The shoe can be mass produced at low cost, is long lasting and nonstigmatizing. Becx-Bleumink, *et al.* (624–625) emphasized the prevention of disability and deformity as an integral part of leprosy control services.

In Other Mycobacterial Diseases, Abbot, *et al.* (627) reported an interesting transcutaneous method for measuring pO_2 and pCO_2 in skin which could be applied to DTH reactions. Barnes, *et al.* (628) provided ev-

idence that antigenic determinates associated with the protein-peptidoglycan complex of the cell wall of *M. tuberculosis* may be involved in protective immunity. Evans (632) showed antileishmanial activity with clofazimine. Jeevan and Kripke (634) showed in mice that ultraviolet radiation caused systemic immunosuppression and enhanced growth of BCG. Munk, *et al.* (635) showed that human T cells could be activated *in vitro* with *M. tuberculosis* and would then show cytolytic activity against autologous targets primed with synthetic peptides corresponding to self-epitopes shared by human and mycobacterial 65-kDa HSP. These epitopes were recognized in the context of HLA-DR (class II) molecules.

In the Original Articles of the December issue, Groenen, *et al.* (641–650) described a leprosy-hyperendemic area in Zaire. Annual incidence did not decrease over 4 years despite rapidly bactericidal treatment of all known cases. Antibodies to the PGL-I antigen of *M. leprae* were not helpful in the diagnosis, classification or prognosis of the disease. Amezcua, *et al.* (651–659) followed 79 household contacts for 6 years. Most were Mitsuda positive (72%) and FLA-ABS positive (94%). A new borderline lepromatous case arose from the Mitsuda-negative group. Saha, *et al.* (660–665) found a high frequency of sexually transmitted diseases and positive serologies for *T. pallidum,* HIV-1, cytomegalovirus, *Chlamydia trachomatis* and Australia antigen among leprosy patients compared to healthy controls. Despite this evidence for sexual promiscuity among this group of leprosy patients, none of their sera tested were positive for HIV antibody. D'Souza, *et al.* (666–673) showed that sera from lepromatous leprosy patients contained factors which induce chromosomal damage, depress the mitotic rate, and depress the proliferation rate of lymphocytes from normal individuals *in vitro.* Vijayalakshmi, *et al.* (674–680) found that presensitization of guinea pigs with BCG produced a granulomatous response to *M. leprae* resembling reversal reactions in human leprosy. Silbaq, *et al.* (681–689) studied the growth of *M. lepraemurium* in mice after foot-pad inoculation with small numbers of organisms. No protection against superinfection could be demonstrated. After initial multiplication, at least 97% of the organisms died. Banerjee and McDermott-Lancaster (690–696) saw evidence that INF-γ enhanced the killing effect of rifampin on *M. leprae* in nude mice. Furuta, *et al.* (697–703) reported the frequencies of malignancies among 252 autopsied leprosy patients in Japan. Over one third of the cases had malignant tumors, most commonly of the GI tract.

In the Editorial section, Ellard (704–716, part 1 of 2) reviewed the chemotherapy of leprosy. In the Clinical Notes section, Bansal, *et al.* (717–719) described an interesting case, presenting with an ulnar mononeuropathy due to leprosy, whose disease was first thought to be due to C8 T1 entrapment radiculopathy caused by cervical perineurial cysts. Cherian (719–721) reported two patients with granuloma mutliforme from South India.

In the Correspondence section, Negesse and Miko (722) examined 150 sural or radiocutaneous nerve biopsies from leprosy patients with new neurologic complaints 6 months to 3 years after completing MDT. In 72% of the cases, intra- and perineural fibrosis were found with no sign of active leprosy. Alteration in nerve function after MDT is most likely due to scarring rather than to renewed bacillary multiplication. Escobar-Gutierrez, *et al.* (723) found anticardiolipin antibodies in almost half of the lepromatous patients tested, usually of the IgM class. Ramani, *et al.* (724–725) isolated *Trichosporon beigelii* from a long-standing ulcer on a lepromatous patient in India. Garcia Lima and Laura (726) isolated the active fraction of sera responsible for the Rubino reaction. Job, *et al.* (726–729) observed the local development and subsequent spread of lepromatous lesions on the dorsum of the foot in nude mice when large numbers of viable *M. leprae* were placed on the surface of abraded skin.

The Obituary section noted with sadness the death of Dr. John H. Hanks.

In News and Notes, a pocket-size, thermal-sensibility tester is now available (731). Dr. H. Srinivasan was elected President of the Indian Association of Leprologists (734).

In the Current Literature section of the December issue in Chemotherapy, Chopra, *et al.* (736–737) observed a mean relapse

rate of 0.19% after MDT in PB cases with 76% of relapses occurring during the first 2 years after treatment. Dhople, *et al.* (737) and Seydel, *et al.* (740) reported marked synergism, both *in vitro* and in mouse foot pad infections, against *M. leprae* with dapsone and brodimoprim, a dihydrofolate reductase inhibitor. Franzblau (738) tested the drug susceptibilities of *M. leprae* from nude mice *in vitro* using the BACTEC 460 system. Pattyn, *et al.* (739–740) studied five treatment regimens in PB leprosy varying from 3 years of daily dapsone to rifampin once weekly for eight doses to WHO MDT for 6 months to rifampin plus dapsone daily for 6 days, and found all treatment outcomes were comparable with 80%–90% cure rates at 4 years after the start of therapy and relapse rates of about 0.5% per year. In contrast, Puavilai and Timpatanapong (740) used MDT and saw 48% of their patients defaulting, 17% with disease that was still active in PB cases after 6 months of treatment, a 2.3% recurrence rate, and side effects in 5.4% of the patients.

In Clinical Sciences, Balkrishna and Bhatia (741) reported a case of dapsone-induced psychosis. Barbancon, *et al.* (741) studied the peripheral nerves in leprosy patients with computed tomography. Brandt, *et al.* (741–742) studied specimens of iris tissue removed during cataract surgery in smear-negative leprosy patients treated with dapsone. Almost 90% of the specimens showed histopathological changes with cellular inflammatory infiltrates, and in 10% of the specimens AFB were present. Dixit, *et al.* (742) reported a tuberculoid leprosy patient with primary involvement of the scrotum. ffytche (743) pointed out that the eyes in lepromatous leprosy may harbor living organisms long after the skin is bacteriologically negative, and ocular supervision may be needed indefinitely for these patients. Kennedy, *et al.* (744–745) reported a case of HIV infection, progressing to AIDS and death with what clinically appeared to be BT/BB leprosy lesions but on biopsy were BL. The patient's leprosy responded rapidly to conventional MB MDT. Saxena, *et al.* (745–746) presented a healed tuberculoid (TT) patient with multiple superficial nerve abscesses involving the entire cutaneous network on the tuberculoid patch. Shah, *et al.* (746) found autonomic nervous system functional abnormalities in 22 of 65 lepromatous patients studied.

In Immuno-Pathology, Gonzalez-Abreu, *et al.* (748) tested sera from over 3000 contacts of leprosy patients for antibodies to PGL-I. Overall, 9.3% were positive, among whom 6 new leprosy cases were diagnosed, 3 with positive skin smears. Job, *et al.* (748) showed the rapid uptake of *M. leprae in vitro* by fetal cardiac muscle cells. *M. leprae* were free in the cytoplasm of the rhythmically contracting cells. The immunologic response to *M. leprae* in the cytoplasm of somatic cells needs further study. Li, *et al.* (748–749) characterized human T-cell clones that suppress antimycobacterial T-cell responses. The suppressor-T-cell clones proliferate and produce IFN-γ when stimulated with mycobacterial antigen. This proliferation depended on HLA-DR, α β T-cell receptors, and IL-2 receptors, was DR-restricted and seemed to have an additional restriction element present in family members but not in DR/Dw-matched healthy controls of different ethnic background. Naafs, *et al.* (749–750) found that 8 of 17 murine monoclonal antibodies against *M. leprae* reacted with normal human epidermis and 5 reacted with components of dermis as well. There seem to be antigenic similarities between *M. leprae* and its human host. Oftung, *et al.* (750) defined a T-cell epitope on the 18-kDa protein of *M. leprae* using synthetic peptides and CD4+ T-cell clones from healthy individuals vaccinated with *M. leprae.* The peptides were presented to T cells in an HLA-DR4,Dw4-restricted manner in all cases, but fine mapping of the minimal sequence required for T-cell recognition revealed heterogeneity among the T-cell clones as to the boundaries of epitopes they recognize. Pisa, *et al.* (750–751) found increased serum levels of tumor necrosis factor-α in patients with disseminated leishmaniasis and disseminated leprosy compared with patients with localized forms of the diseases. Sathish, *et al.* (751) screened the λgt11 *M. leprae* genomic library with pools of lepromatous and tuberculoid patients' sera, and identified 50 reactive recombinant clones, among which there were at least 22 new antigenic determinants. Smith, *et al.* (752) found non-

specific elevations in IgE among leprosy patients, but no increase in clinical atopy. Talwar, *et al.* (752) found autoclaved *Mycobacterium w.* to be active as immunotherapy in 54 MB, lepromin-negative leprosy patients. Thole, *et al.* (753) sequenced the gene for the 36-kDa antigen of *M. leprae* and found that it contained a proline-rich amino-terminal region with a number of repeated sequences. Vadiee, *et al.* (753) reported false-positive results with a competition antibody-binding assay using crude, native 65-kDa protein preparations of *M. leprae* and the IIIE9 epitope. Wu, *et al.* (754) described a new serologic test to detect PGL-I antigenemia using murine monoclonal antibody against PGL-I.

In Microbiology, Dhople and Ortega (755) described the testing of drugs in *in vitro* cultures of *M. leprae.* Lamb, *et al.* (755) found that heat-shocked *M. habana* expressed an 18-kDa protein with a monoclonal antibody-defined epitope identical to an epitope of the 18-kDa protein of *M. leprae* previously thought to be specific.

In Experimental Infections, Brandt, *et al.* (756) described the eye pathology in armadillos experimentally infected with *M. leprae.* Karanth, *et al.* (756) found reductions in nerve fibers containing cutaneous calcitonin gene-related peptides and substance P in the skin and spinal cord of *M. leprae*-infected nude mice.

In Epidemiology, Gupte, *et al.* (758) did not find soluble *M. leprae* antigens helpful as a skin test to identify *M. leprae* infection or to confirm a diagnosis of leprosy in a leprosy-endemic population. Howerth, *et al.* (758–759) found no histopathologic evidence of leprosy in the ears of 853 armadillos from Alabama, Arkansas, Florida, Georgia, and Mississippi in the southeastern U.S.A.

In Other Mycobacterial Diseases, Brandwein, *et al.* (761) described skin and lymph-node lesions in five AIDS patients due to nontuberculous mycobacteria which, in leprosy, would be termed histoid. Cambiaso, *et al.* (762) used a latex agglutination test to detect mycobacteria based on latex particles coated with $F(ab')_2$ against *M. bovis* carbohydrates and found a lower limit of detection of 15–20 mycobacteria. Hiu (765–766) found an immunosuppressive glycolipid in BCG. Katz, *et al.* (766) showed that NK cells lyse *M. avium*-complex-infected monocytes, and that this decreased the viability of the mycobacteria. Merali, *et al.* (768) reported a new assay procedure for dihydropteroate synthetase. Rastogi, *et al.* (769–770) tested agents active against cell-envelope synthesis with *M. avium,* and ethambutol (an inhibitor of arabinogalactan synthesis) and *m*-fluoro-phenylalanine (an inhibitor of mycoside-C biosynthesis) significantly enhanced the susceptibility of the organism to other drugs.

From a personal perspective, in chemotherapy there seem to be more hypersensitivity reactions to dapsone in MDT regimens than were seen with dapsone monotherapy. The suggestion has been made, based on mouse foot pad data, that dapsone may interfere with the bactericidal activity of rifampin. In general, results continue to be good with WHO MDT. Pefloxacin and ofloxacin are bactericidal. The rate of resolution of lepromatous leprosy is independent of the drug regimen used so long as the drug or drugs are active against the patient's bacilli.

In the clinical sciences, it is clear that it is difficult to differentiate relapses and late reversal reactions in PB patients after treatment is discontinued. New neurologic findings may more likely be due to nerve scarring than to renewed bacterial multiplication after MDT. Bacillemia is very frequent in patients and contacts, and the proportions which are positive compare favorably with antigen detection, serologies, and even skin smears. A hand-held, thermal-sensibility testing device is very useful in diagnosing leprosy under field conditions.

In immunopathology, there has been extensive mapping of both T-cell and B-cell epitopes on various proteins of *M. leprae.* Using pools of patients' sera, at least 22 new antigenic determinants have been identified. The technologies for producing subunit antileprosy vaccines in BCG and *Salmonella typhimurium* are now developed, but it is not clear which T-cell epitopes of *M. leprae* are protective. There seems to be no consistent pattern in T-cell reactivities to fractions of *M. leprae* in patients and contacts. HLA-DR genes control T-cell responses to *M. leprae* epitopes. Additional

complexities arise in that *M. leprae* seems inherently immunosuppressive by virtue of its PGL and LAM. *M. leprae*-specific suppressor-T cells arise in some patients. Cytotoxic, CD4+, MHC class II-restricted T cells and cytotoxic, CD8+, MHC class I-restricted T cells both occur, and both can lyse cells with *M. leprae* antigens on their surface. Schwann cells seem able to function as antigen-presenting cells. *M. leprae* enter monocytes through complement receptors and fix complement by the alternative pathway. *M. leprae* enter somatic cells and exist free in the cytoplasm. There seem to be crossreactivities between mycobacterial HSP and human cells, particularly human activated mononuclear phagocytes. Thus, subunit vaccines will need to a) be protective for all subjects, including those destined to develop lepromatous disease; b) be capable of immunizing individuals with a variety of HLA-DR-restriction patterns; c) not generate cytotoxic-T cells harmful to incidental *M. leprae* antigen-presenting cells, such as Schwann cells or somatic cells; and d) not generate T cells crossreactive between mycobacterial HSP and human self-antigens capable of causing autoimmunity. In short, the technology now exists to produce a subunit antileprosy vaccine, but there is little information upon which a decision can be made as to which subunit(s) should be included. A vaccination trial based on ICRC bacilli, *Mycobacterium w.*, and *M. leprae* and BCG, and perhaps others has been initiated in India.

There continues to be interest in leprosy serology. In general, serologies are positive in the majority of MB patients, negative in most PB patients, and positive in 15%–30% of contacts of leprosy patients. Usually there is a relatively weak, but statistically significant correlation between the serologic test results and measures of the bacterial load of the patient.

There is increasing evidence that ENL is on the basis of DTH mechanisms and involves T cells.

In microbiology, a number of probes have been developed which are specific for *M. leprae*. PCRs specific for *M. leprae* with sensitivities approaching the detection of one organism have been developed by several groups. Various *in vitro* metabolic assays have been used to test drug effects on *M. leprae*, and these appear to be predictive for *in vivo* effects. More basic biochemistry of *M. leprae* is becoming known.

In experimental infections, work continues on developing monkeys as leprosy models. There is extensive natural armadillo leprosy in the southern U.S.A. as measured by serology with PGL-I.

In epidemiology, IgM anti-PGL-I antibody determinations have not been found useful in Papua New Guinea, Zaire, nor in French Polynesia, in detecting leprosy cases. BCG gave 48% protection overall against leprosy in Karimuri, and was most effective in children and in preventing BT leprosy. There are disturbing increases in the transmission of leprosy in Brazil since 1969.

In rehabilitation, the prevention of disability and deformity is an accepted part of leprosy control services.

In other mycobacterial diseases, there is considerable interest in mycobacterial HSP in the context of autoimmune disease in which there are shared epitopes with human antigens.

A great deal of new information was published in 1990. In some cases, new information can readily be applied. New antileprosy drugs, new means of detecting and identifying *M. leprae*, and the use of a handheld thermal-sensibility tester come to mind. In other cases, new information casts some doubt on what we thought we knew. The difficulties in differentiating relapses from reversal reactions and limitations on the value of serologic testing might be examples. Finally, and perhaps most commonly, new information reveals the depth of our ignorance about so many aspects of the disease. The complexities of *M. leprae*'s antigenic make up, the enormous complexities of the immune response to the organism, and *M. leprae*'s noncultivability, transmission, and survival mechanisms in its hosts point out how much more we need to learn. I look forward with impatient optimism to 1991.—RCH