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EDITORIALS

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The 1985 JOURNAL—a Continuing Perspective

The year 1985 was an exciting one for leprosy. New findings and new possibilities for better care of patients appeared in abundance. The JOURNAL completed its 53rd year of publication in 1985, having taken final note of the magnificent New Delhi Congress in 1984 and now looking forward to the upcoming Congress at The Hague in 1988. It again seems appropriate to review the progress that has been made in our understanding of leprosy as reflected in the pages of the JOURNAL.

In the March issue, Meyers, *et al.* (1–14)* carefully documented the landmark finding of naturally acquired leprosy in a "sooty" mangabey monkey, a finding offering the promise of a much-needed primate model for leprosy. Cartel, *et al.* (15–18) found a 16.5% incidence of hepatotoxicity among patients treated with daily 5 mg/kg prothionamide, 10 mg/kg rifampin, and 400 mg dapsone, and concluded that thioamide should not be used in combination with rifampin unless the daily dose is 5 mg/kg and liver function is monitored monthly. Jesudasan and Christian (19–21) studied 51 relapsed patients among a group of 1701 paucibacillary cases in whom treatment with dapsone monotherapy had been discontinued. Lepromin-negative paucibacillary cases were 2.4 times more likely to relapse than lepromin-positive paucibacillary patients, and 11 of 29 lepromin-negative paucibacillary cases relapsed with multibacillary disease compared with 0 of 18 in the lepromin-positive group. The advisability of uniform, short-course chemotherapeutic regimens being applied to paucibacillary cases without regard to their lepromin reactivity requires evaluation. Rook (22–27) found no evidence of antibodies to rifampin in sera from 239 leprosy patients being treated with the drug. Chiewsilp, *et al.* (28–32) pointed out the necessity for carefully selected control populations in studying serum immunoglobulin class variations in leprosy patients. Sinha, *et al.* (33–38) applied a competitive inhibition assay to estimate antibody levels to the species-specific antigenic epitope of *Mycobacterium leprae* designated as MY2a (recognized by a murine monoclonal antibody designated as MLO4). The test results satisfied the requirements expected of a leprosy-specific serodiagnostic test. Of considerable interest, 13 (46%) of 28 healthy household contacts of multibacillary leprosy patients were

* Numbers in parentheses refer to page numbers in the INTERNATIONAL JOURNAL OF LEPROSY, Volume 53, 1985.

antibody positive, while none of 15 similar contacts of paucibacillary cases was positive. Narayanan, *et al.* (39–44) ingeniously prepared single cell suspensions from tuberculoid and lepromatous leprosy granulomas with collagenase and quantitated viable lymphocytes, E-rosetting cells, and cells staining for nonspecific esterase. Lymphocytes were abundant from tuberculoid granulomas, a higher percentage rosetted with sheep erythrocytes, and most showed the presence of esterase as dots in the cytoplasm compared to those from lepromatous granulomas. "Large cells" (epithelioid cells and macrophages) from both types of granulomas were similar in that most were esterase positive and peroxidase positive, but those from tuberculoid granulomas were non-adherent to plastic while those from lepromatous granulomas were. Datta, *et al.* (45–51) analyzed the patterns of methyl mycolates of various mycobacteria by thin-layer chromatography and found that *M. leprae*-derived methyl mycolates are alpha- and keto-derivates and not methoxy or dicarboxy compounds. This pattern distinguishes *M. leprae* from a variety of other mycobacteria which have been isolated from leprosy lesions. Nakamura (52–55) demonstrated that virulence of *M. lepraemurium* can be maintained for 30 years if the bacilli are lyophilized in the proper suspension. There is clearly a need to apply these principles to *M. leprae.* Xu, *et al.* (56–63) meticulously analyzed HLA haplotype distributions among siblings in families with leprosy and concluded that HLA-linked genes do not seem to confer susceptibility or resistance to leprosy per se. On the other hand, predisposition to lepromatous leprosy does seem to be controlled by HLA-linked genes. In view of other studies, it can be postulated that there are at least four different HLA-linked genes which control leprosy type, one each for LL, BL, BT, and TT disease. Burchard and Bierther (64–69) carefully studied macrophages and lymphocytes in the skin of lepromatous and borderline leprosy patients by electron microscopy, describing how macrophages are activated and phagocytose *M. leprae* in lepromatous leprosy, and the differentiation of macrophages into epithelioid cells and giant cells in borderline disease. They further (70–74) studied small dermal blood vessels in untreated lepromatous patients and emphasized the important role of these vessels in the multiplication and spread of the bacilli from both pericytes and endothelial cells. Fukunishi (75–78) showed with electron microscopy that *M. leprae*-infected nude mice developed peripheral nerve lesions with the same fundamental pathological features as those in armadillos and humans with lepromatous leprosy. Li, *et al.* (79–85) summarized the highly successful comprehensive leprosy control program in Shandong Province of the People's Republic of China since 1955, and demonstrated the epidemiologic similarities of the disease in this area with findings in other countries in which leprosy is disappearing.

In the Editorial section of the March issue, we were fortunate to have the prize-winning LEPRA essay by Strickland (86–100). The author brilliantly reviewed the immunologic deficiencies of leprosy and tuberculosis, and logically considered the various possible mechanisms of immunosuppression and immunodeficiency capable of influencing the infections. Hastings (101–112) reviewed the contents of the 1984 JOURNAL.

The Correspondence section of the March issue was both lively and informative. Arora, *et al.* (113–114) confirmed several earlier studies which were unable to demonstrate any effect of levamisole on the cell-mediated immune response of lepromatous patients to *M. leprae.* Lyons, *et al.* (114–115) made the very interesting observation that typical Langerhans' giant cells can be found in the lesions of otherwise typical borderline lepromatous to subpolar lepromatous cases if they have rapidly downgraded. Neelan and Reddy (115–116) and Grosset, *et al.* (118–120) critically evaluated the series of papers by Almeida, *et al.* which appeared in the September 1983 issue of the JOURNAL, pointing out areas of disagreement. Almeida and Chacko (116–118 and 120–121) amplified their published findings and defended their point of view.

The News and Notes section of the March issue noted the well-deserved Padma Shri award by the President of India to Dr. H. Srinivasan (123). The sanatorium of Fontilles (Alicante, Spain) celebrated its 75th

anniversary (125). The Robert Cochrane Fund for Leprosy was established (128).

In the Current Literature section of the March issue, an interesting review of the attitudes of medieval Islamic society toward leprosy patients was provided by Dols (132). Anderson analyzed the immunopharmacology of antileprosy agents (133). Cottenot, *et al.* (133) described two additional cases of lepromatous leprosy clinically resistant to rifampin. Ji, *et al.* (134) emphasized the hepatotoxicity of prothionamide, particularly in combination with rifampin. Jopling, *et al.* (134–135) continued to follow up 116 multibacillary leprosy patients treated with multiple drugs for 5–89 months in Malta beginning in 1972, and who have been followed since without chemotherapy. No signs of clinical relapse have been found, but 36 of these patients had positive skin smears and 10 of the 36 had solidly staining bacilli in their smears. Pitchenick (135–136) suggested that former patients who had been models of compliance with drug therapy be recruited to help administer chemotherapy in the hope that they would improve compliance. Sarojini and Mshana (136) reported that colchicine in doses of 1.5 to 2.0 mg daily was dramatically effective in controlling erythema nodosum leprosum (ENL), and that a maintenance dose of 1 mg daily prevented recurrences. On the other hand, Stanley, *et al.* (136) found that colchicine, 2 mg daily, clearly had little or no benefit in ENL. Chen, *et al.* (136) reported a case of ENL regularly accompanied by purpura. Furukawa, *et al.* (137–138) sought correlations between circulating immune complexes and anti-ssDNA antibodies in the sera of lepromatous leprosy and systemic lupus erythematosus (SLE) patients and found that the two were not associated in lepromatous leprosy but were significantly associated in SLE. The authors concluded that the reasons for these serological abnormalities in lepromatous leprosy are completely different from those in SLE. Brett, *et al.* (139) did not find any effect of the phenolic glycolipid antigen of *M. leprae* on a variety of cell-mediated immune responses and delayed-type hypersensitivity responses to *M. leprae* in mice. Cho, *et al.* (139–140) reported comparable results in sero-reactivity using the native phenolic glycolipid antigen of *M. leprae* and a synthetic glycoconjugate based on the 3,6-di-*O*-methyl-β-D-glucopyranosyl epitope. Ferluga, *et al.* (140) suggested that lepromatous leprosy might develop as a result of chronic suppression of specific cell-mediated immunity by anti-idiotypic antibodies and idiotypic-restricted suppressor lymphocytes. Fliess, *et al.* (140) showed a close relationship between cell-mediated immune responses to *M. leprae* and those to *M. marinum* among leprosy patients and healthy subjects, and suggested that this might be on the basis of crossreactivity between the two organisms. Haregewoin, *et al.* (141) provided evidence that the unresponsiveness of many cases of lepromatous leprosy in their peripheral blood mononuclear cells to *M. leprae* was on the basis of a deficiency in interleukin-2 production. Khande, *et al.* (142) analyzed the lipids in the skin of lepromatous leprosy patients. Six distinct phosphatidyl inosito mannosides were identified in infected tissue, a triacyl dimannoside being most prominent quantitatively. Narayanan, *et al.* (143–144) found normal numbers of T6+ Ia+ Langerhans' cells in the epidermis in all types of leprosy patients, but noted a high proportion of these cells in the mononuclear infiltrate surrounding the epithelioid cells in the dermal granulomas of tuberculoid patients, gradually decreasing across the leprosy spectrum to a virtual absence in the dermis in polar lepromatous disease. Olcen, *et al.* (144) detected precipitating antibodies directed against *M. leprae* antigens 5, 6 and 7 in the concentrated urine of 50% of lepromatous patients by crossed immunoelectrophoresis. Ninety percent of these patients had higher levels of anti-*M. leprae* antibodies in their urine than did controls. Salgame, *et al.* (144) found that lysates of lepromatous macrophages induced membrane changes in normal macrophages. Fine (147) made a detailed analysis of the similarities and differences in the epidemiology of leprosy and tuberculosis. Ottenhoff, *et al.* (148), in a population study, found a significant increase in the frequency of the HLA specificity LB-E12 (MB1, DC1, MT1) among lepromatous leprosy patients compared to healthy controls in Venezuela. Aronson, *et al.* (148) reported sensory peripheral neuropathy developing in 3 of 4 patients with

prurigo nodularis who had been treated with thalidomide. Garcia Montelongo, *et al.* (150) found that clofazimine 200 mg daily was beneficial in 35 of 45 patients with "chronic" lupus erythematosus. Goren, *et al.* (150–151) compared the virulence for guinea pigs and various cultural and biochemical patterns in *M. tuberculosis* strains isolated from India and strains isolated from the West. A number of differences were noted between the Indian and Western strains, and the authors postulate that these patterns might be due to parallel evolution occurring among organisms widely separated geographically. Guitierrez-Rodriguez (151) found thalidomide useful in treating rheumatoid arthritis. Neva, *et al.* (151–152) reported that local heat treatment was effective in lesions of diffuse cutaneous leishmaniasis.

The March issue included the abstracts of papers presented at the First U.S. Hansen's Disease Conference held at Carville in August 1984. Schauf, *et al.* (163) confirmed results obtained in other countries in finding that tuberculoid leprosy was associated with HLA-DR2 in Thailand. Cynamon, *et al.* (165) found that the combination of ampicillin plus sulbactam enhanced the *in vitro* activity of ampicillin some fourfold against *M. tuberculosis,* indicating that at least some mycobacteria have a functional β-lactamase which, if inhibited by sulbactam, might result in useful susceptibility of the organisms to β-lactam antibiotics. Harris and Prabhakaran (165) detected malonyl-CoA decarboxylase activity in *M. leprae* and suggested that it could result from the reverse reaction of an avidin-sensitive acetyl-CoA carboxylase. Shannon, *et al.* (165–166) showed that thalidomide enhanced humoral immune responses of mice to the T-independent antigen, DNP-Ficoll, implying that the drug's immunosuppressive activity in response to T-dependent antigens is on the basis of a site of action involving helper T cells, and not B cells or macrophages. Skinsnes, *et al.* (167–168) presented results of detailed numerical taxonomic and immunologic studies on 36 leprosy-derived mycobacterial isolates and 17 members of the *M. avium-intracellulare-scrofulaceum* complex (MAIS). Martin, *et al.* (169) demonstrated a progressive decrease in mitogen-induced lymphocyte blastogenic responses of *M. leprae*-infected mangabey monkeys as the disease progressed. Decreases in lymphocyte blastogenic responses to mitogens were associated with increases in the percentage of OKT8+ lymphocytes. Kvach, *et al.* (169–170) described a new technique for rapidly purifying *M. leprae* from armadillo liver using Percoll buoyant density centrifugation. The bacilli had ATP levels similar to cultivable mycobacteria and died, as measured by ATP, exponentially under defined conditions. Clofazimine accelerated the rate of ATP decay in a dose-responsive fashion. Jacobs, *et al.* (170) demonstrated the expression of polypeptides from recombinant *M. leprae* DNA cloned into the cosmid vector pHC79 and the plasmid vector pYA626. Imaeda and Portaels (170–171) found little homology between DNA from *M. leprae* and that from leprosy-derived corynebacteria or leprosy-derived mycobacteria, suggesting that the presence of these organisms in leprosy tissues may not be directly related to the disease. Gelber (171–172) reported a number of experiments testing compounds for antimicrobial activity against *M. leprae* in mouse foot pad infections. Active compounds included dapsone, rifampin, cycloserine, the combination of bromidoprim with low levels of dapsone, minocycline, cephradine, and the combination of amoxicillin and clavulanic acid. Inactive compounds were beta alanyl and glycyl derivatives of hydroxamic acid, trimethoprim combined with low levels of dapsone, doxycycline, erythromycin, cefoxitin, cefamandole, cefotoxamine, moxalactam, and cephradine. Gelber, *et al.* (172–173) found the neonatally thymectomized Lewis rat model to be useful in detecting viable *M. leprae* after the initiation of chemotherapy in previously untreated lepromatous leprosy patients. Navalkar and Ibegbu (173) studied the antigens of *M. leprae* by isoelectric focusing and chromatofocusing separations. Patterns obtained with *M. leprae* were different from those of other mycobacteria and differences were seen between untreated and autoclaved *M. leprae* preparations. Humphres and Winters (174–175) used Lewis rats to study enhanced cell-mediated immunity after intradermal vacci-

nation with *M. leprae* and antigen-specific tolerance following intravenous or intraperitoneal administration of *M. leprae* at high doses. Truman, *et al.* (175) found serologic reactivity against the phenolic glycolipid I (PGL-I) antigen of *M. leprae* in samples taken from armadillos between the years 1960 and 1964, before the first experimental inoculations of armadillo with *M. leprae* in 1968. Baskin, *et al.* (175–176) presented necropsy findings in a mangabey monkey with experimental leprosy. Malaty, *et al.* (176) described the histopathologic changes in the eye of the same mangabey monkey. Long, *et al.* (176–177) described an interesting, specific, glucose oxidase immunoenzyme stain for the identification of *M. leprae* in tissue. Krotoski and McCormick (177–178) utilized an indirect immunofluorescence technique to demonstrate antigens of *M. leprae* in infected armadillo liver and to demonstrate differences among lepromatous patients in the patterns of antigens which they recognized. Mohagheghpour, *et al.* (178) described the production of two human monoclonal antibodies to *M. leprae.* Gillis, *et al.* (178) developed a competitive antibody binding assay to detect human serum antibody to a unique epitope on the 68KD protein antigen of *M. leprae.* Job, *et al.* (179–180) found that purified PGL-I elicited positive late skin test responses in lepromin-positive armadillos and negative responses in lepromin-negative armadillos. Mehra, *et al.* (180) found that the PGL-I antigen was as effective as integral *M. leprae* in inducing suppression of lymphocyte proliferation in ConA. Douglas, *et al.* (180–181) showed that serum antibody levels to the PGL-I antigen and to whole *M. leprae* fell over time in patients under effective chemotherapy. Modlin, *et al.* (181–182) characterized the cellular infiltrates in the granulomas of tuberculoid leprosy, lepromatous leprosy (LL), localized cutaneous leishmaniasis, and diffuse cutaneous leishmaniasis. In tuberculoid granulomas, interleukin-2 (IL-2) producing cells and suppressor/cytotoxic T cells were both found in the mantle surrounding the granuloma, while helper/inducer cells and IL-2 receptor cells were distributed throughout the granuloma. In LL, localized cutaneous leishmaniasis, and diffuse cutaneous leishmaniasis, all cells were distributed throughout the granuloma. IL-2-producing cells were rare in LL and diffuse cutaneous leishmaniasis but were an order of magnitude greater in tuberculoid leprosy and localized leishmaniasis. IL-2 receptor cells were present in all four disorders. The data suggest that the *M. leprae*-specific failure of cell-mediated immunity in lepromatous patients is secondary to reduced, probably inhibited, IL-2 production. Miller, *et al.* (182–183) found few autoantibodies among their leprosy patients in Seattle, Washington, U.S.A. An interesting observation was that the erythrocyte sedimentation rate was moderately elevated during acute ENL reactions, but in all patients tested during acute reversal reactions the erythrocyte sedimentation rate was extremely low. Schuller-Levis, *et al.* (183–184) showed a significant loss of chemotactic activity in monocytes in response to lymphocyte-derived chemotactic factor in active LL patients but not in inactive LL cases. Tausk, *et al.* (184) demonstrated fewer C3b receptors on erythrocytes from LL patients than those on erythrocytes from normal individuals or tuberculoid leprosy patients. Since immune complexes bind to erythrocytes and are delivered to the liver where they are apparently removed by local macrophages, this reduced number of C3b receptors on erythrocytes from LL patients could have a bearing on the ability of LL patients to inactivate or clear immune complexes from the circulation. Campbell, *et al.* (184–185) found that many plasma samples from all types of leprosy patients contained an inhibitor of monocyte leukotaxis.

The Original Articles of the June issue began with the very interesting paper by Warndorff van Diepen and Mengistu (189–197). Lepromatous leprosy patients on dapsone monotherapy were divided into four groups. The first group continued on dapsone monotherapy, the second received supplemental thiacetazone and isoniazid for 12 months, the third group received daily thiacetazone and daily isoniazid for 12 months plus rifampin daily during months 1 and 7, and the fourth group received rifampin as above but no thiacetazone or isoniazid. Supplemental thiacetazone and isoniazid had no significant effect on either

the overall relapse rate or the incidence of dapsone-resistant leprosy. Rifampin, on the other hand, significantly lowered relapse rates and only a single case of dapsone resistance was detected in those groups receiving rifampin. Of considerable interest, the average annual relapse rate in the control group receiving dapsone monotherapy over the five-year follow-up period appeared to be 2.3%, and the incidence of dapsone-resistant leprosy in this group was 0.7% per year. The apparent decrease in both relapse rates and incidence of dapsone-resistant leprosy in this area compared to earlier reports may well be related to the re-introduction of full-dosage dapsone therapy, uninterrupted during reactions. Bera and Sen (198–200) found that supplemental levamisole accelerated the fall in bacterial indices in BL and LL patients treated with dapsone. Moncada, *et al.* (201–205) found statistically significant increases in percentages of helper T cells in 3 ENL patients after receiving thalidomide in doses of 300 mg per day. Jain, *et al.* (206–210) devised an apparatus to measure the "minimum temperature felt as hot" on the skin surface and used it to assess the degree of sensory loss in leprosy skin lesions. Andreoli, *et al.* (211–217) measured circulating antibody levels to the PGL-I antigen of *M. leprae* and soluble *M. leprae* antigens before, during, and following ENL episodes in 12 patients. During ENL, there was a fall in circulating IgM-class antibody levels to the PGL-I antigen but no apparent changes in IgM, IgG, and IgA antibody levels to a soluble antigenic extract from purified *M. leprae* suspensions. de la Barrera, *et al.* (218–224) showed normal antibody-dependent cellular cytotoxicity and normal total and normal alternative pathway complement activity in LL patients in the presence of elevated circulating immune complexes. Heat inactivation of the LL sera resulted in the sera inhibiting the antibody-dependent cellular cytotoxicity of normal mononuclear leukocytes. This inhibition, in turn, could be reversed with fresh normal human serum, suggesting that complement prevents the inhibition of antibody-dependent cellular cytotoxicity by the immune complexes present in lepromatous sera. Heat-inactivated LL sera containing immune complexes were able to activate and fix 74–80% of total complement activity and 40–50% of alternative pathway complement activity. It would seem that compensatory mechanisms exist in LL patients which are able to modify the potentially harmful effects of circulating immune complexes. Wright, *et al.* (225–232) showed that Vietnamese LL patients had significantly raised levels of serum IgG, IgA, IgM, and IgE, while borderline tuberculoid (BT) leprosy patients had only increased IgG in comparison with local controls. The IgG_2 subclass was not increased in the leprosy patients, but the other subclasses of IgG were increased. Vaishnavi, *et al.* (233–237) found that infection with *M. leprae* resulted in a decreased bactericidal activity of peritoneal macrophages toward *Staphylococcus aureus* in both normal and thymectomized-irradiated mice. In general, phagocytic activity was not impaired in these cells. Haimanot, *et al.* (238–246) studied tissue muramidase activity in neural and skin tissues from leprosy patients. A saccular pattern of distribution of the enzyme was noted in the majority of lepromatous tissues and a granular pattern at the tuberculoid end of the leprosy spectrum. The muramidase-positive cells in peripheral nerves were probably derived from blood monocytes since Schwann cells and axons did not show muramidase activity. Fukunishi (247–250) illustrated *M. leprae* cells dividing by transverse fission inside the phagolysosomes of lepra cells of nude mice and armadillos. Bahlinger, *et al.* (251–254) suggested that leprosy patients experience psychosocial stresses which have many characteristics in common with those experienced by all patients with chronic illnesses. These similarities may allow the application of psychosocial techniques developed for patients with other chronic illnesses to be applied to leprosy patients. Coleman and Madrigal (255–257) explored the psychosocial ramification of sensory loss in leprosy. Rojas-Espinosa, *et al.* (258–261) used levels of serum lactic dehydrogenase, glutamate-pyruvate transaminase, and glutamate-oxalacetate transaminase to monitor the progression of *M. lepraemurium* infections in mice. Rojas-Espinosa, *et al.* (262–268) also found these serum enzyme levels to be useful in following the progression of

M. leprae infections in armadillos. Baskin, *et al.* (269–277) documented necropsy findings in a mangabey monkey that died 46 months after an inoculation with *M. leprae* and that had developed generalized lepromatous leprosy. The necropsy findings were very similar to those seen in untreated human LL patients.

In the Editorial section of the June issue, Lagrange and Stach (278–288) presented their views on a strategy for the control of leprosy. Based on the observation that mononuclear phagocytic cells from LL patients, but not tuberculoid leprosy patients, can inherently inhibit the growth of intracellular BCG, the authors postulate that LL patients correspond to naturally resistant animal models. In mice there is an autosomal dominant gene on chromosome 1, the BCG gene, which is phenotypically expressed on mononuclear phagocytic cells and functions to prevent the multiplication of BCG in these cells. Mice which are classified as resistant based on presence of the BCG gene do not develop additional resistance or acquire resistance to BCG after immunization. Naturally sensitive mice, lacking the BCG gene, can respond with acquired resistance to infection after immunization. If naturally resistant humans, corresponding to mice with the BCG gene, constitute the true primary nonreactive subjects who develop LL after exposure to *M. leprae,* then they can be identified by means of testing the ability of their macrophages to inhibit the growth of BCG. Thus, paradoxically, individuals whose macrophages can inhibit the growth of BCG would be those individuals incapable of developing acquired resistance to leprosy. If operationally feasible, these individuals could be identified, if the hypothesis is correct, by a series of serological testing, lepromin and tuberculin skin testing, and testing for the ability of their mononuclear phagocytes to inhibit the growth of BCG *in vitro.* Once identified, these individuals with true primary nonreactivity to *M. leprae* would require continuous chemotherapy.

The second editorial in the June issue was a magnificent review of the history of leprosy in China by Skinsnes and Chang (289–307).

The deaths of two giants in leprosy research, Professor Mitsugu Nishiura and Dr. Charles C. Shepard, were noted (308–310) in the June issue.

In the Correspondence section of the June issue, Gelber (311–312) presented a most unusual nodular lepromatous patient with typical clinical features but only exceedingly rare acid-fast bacilli in a biopsy of his skin. Imkamp (313–317) reviewed the treatment of reactions in leprosy and offered standardized schemes of corticosteroid treatment for these complications.

In the Current Literature section of the June issue, Manchester (326) explained the decline in leprosy in medieval England as being fundamentally due to an increased population density. Increased population densities would favor the transmission of pulmonary tuberculosis; the survivors of the primary infections with *M. tuberculosis* (mostly young children) would be relatively immune to leprosy thereafter, therefore leprosy would decline. Anderson (327) found that dapsone inhibited and clofazimine enhanced both the spontaneous and induced release of prostaglandin E_2 from human neutrophils *in vitro.* This could be related to the immunostimulating and immunosuppressive properties of dapsone and clofazimine, respectively. Bhatia, *et al.* (327) reviewed their experience with dapsone-resistant *M. leprae* as detected in mouse foot pad infections in Chingalpattu, South India, since 1974. There were 23 primary dapsone-resistant isolates, 16 (70%) of which were mild or low level and only 1 (4%) of which was fully resistant or resistant to high levels of dapsone in the mouse diet. In contrast, of 76 secondary resistant isolates, 69 (91%) were at a high level and none were at a low level. Foucauld, *et al.* (327–328) reported a case of aplastic anemia felt to be due to dapsone. In mouse foot pad infections, Gelber, *et al.* (328) found kanamycin, streptomycin, and amikacin to have bactericidal activity against *M. leprae* with lesser activity with gentamicin and tobramycin. Gonzalez Vazquez (328) pointed out the two possible mechanisms by which a leprosy patient being treated with sulfones can have the disease recur; a) through relapse with endogenous bacilli which have developed sulfone resistance or b) re-infection with exogenous sulfone-resistant organisms. Joshi,

et al. (328–329) found no evidence that dapsone induces the metabolism of oral contraceptives. Mester de Parajd and Garnier (329) fed mice with a dietary supplement rich in tryptophan, unsaturated fatty acids and glucose, and found inhibition of the multiplication of *M. leprae* in conventional foot pad infections. The effectiveness of this diet was thought to be due to increased biosynthesis of deoxyfructo-serotonin in the mice which, in turn, inhibited the multiplication of the bacilli. Niwa, *et al.* (330) found that clofazimine increased the generation of $OH\cdot$, decreased the generation of H_2O_2, and had no effect on superoxide dismutase activity in neutrophils and monocytes from active multibacillary leprosy patients. Pattyn, *et al.* (330) performed a survey among 994 LL patients in Upper Volta, and concluded that at least 7% had secondary dapsone-resistant disease. Schwab, *et al.* (330–331) showed a progressive decrease in serial nerve conduction velocities in rabbits chronically treated with thalidomide. Fleury and Opromolla (331) reviewed 16 cases of carcinoma arising in plantar ulcers in leprosy patients. Hobbs and Hempstead (332) described an interesting case of disseminated coccidioidomycosis whose skin findings resembled those of lepromatous leprosy. Kale, *et al.* (332) found variable degrees of cardiovascular autonomic dysfunction among a group of LL patients including some with reactions. Laing, *et al.* (333) described an LL patient who developed a squamous cell carcinoma at the site of a preceding plantar ulcer. After an amputation, new lesions appeared and leprosy bacilli were found within the squamous cell carcinoma with occasional organisms in the cytoplasm of the neoplastic cells. Roy, *et al.* (334) determined the prevalence of gynecomastia among leprosy patients in South India. The prevalence was higher among lepromatous patients, those with frequent ENL reactions, those patients in whom treatment was delayed after the onset of the disease, and/or those with an overall long duration of the disease. Duncan, *et al.* (336) studied 81 placentae from women with leprosy and found no morphological evidence of infection of the placenta with *M. leprae.* No acid-fast bacilli were seen on light microscopy, although homogenates from 2 out of 7 placentae from women with very active LL contained very small numbers of acid-fast bacilli. Gonzalez-Abreu, *et al.* (336) found that standard lepromin skin testing induced anti-*M. leprae* antibodies by the FLA-ABS test up to 180 days after testing. Khandke, *et al.* (337) found that mononuclear cells from LL patients which were unresponsive to intact *M. leprae, M. leprae* sonicates, *M. leprae* cytoplasm, cell wall or lipid fractions would respond strongly *in vitro* to delipified cell wall fractions of the bacilli. Mehta and Antia (338) described the ultrastructural features of sciatic nerves from armadillos infected with *M. leprae.* Modlin, *et al.* (338) showed that ENL tissue had more numerous cells of the helper-inducer phenotype and fewer of the suppressor-cytotoxic type as compared with nonreactional lepromatous tissues. Nath, *et al.* (339) found that supernatants from 24-hr cultures of monocytes (adherent cells) from borderline and lepromatous patients inhibited IL-2 production by a T-cell line. It is possible that the unresponsiveness associated with lepromatous leprosy is related to the inhibition of IL-2 production by soluble suppressive factors from monocytes. Nath, *et al.* (340) demonstrated heterogeneity among LL patients regarding the presence of *M. leprae*-reactive T cells *in vitro.* Autologous T cells co-cultured with autologous adherent cells showed significant improvement in *M. leprae* antigen-induced lymphoproliferation in 9 of 16 LL patients. Some LL patients responded *in vitro* to exogenous, purified human IL-2 with enhanced lymphoproliferation in response to *M. leprae* antigens. A proportion of clinically similar LL patients remained unresponsive to *M. leprae* antigens despite a variety of manipulations *in vitro.* Ridel, *et al.* (340–341) found the immunogenicity of *M. leprae* to be markedly enhanced in mice if the bacilli were presented after having been incorporated into mouse peritoneal macrophages, as compared to being administered alone. Ridley, *et al.* (341) studies the levels and distribution of lysozyme-positive cells in leprosy lesions throughout the spectrum. Lysozyme proved to be a useful means of following cell turnovers in the lesions. Interestingly, peak numbers of monocytes were seen in the lesions of active LL as well as

those of TT lesions. Schwerer, *et al.* (341) found a linear correlation between serum IgM-class anti-PGL-I antibody levels and the bacterial index in leprosy patients. Antibody levels were significantly lower in patients with ENL as compared to those without ENL, suggesting that IgM-class anti-PGL-I antibodies may be involved in the pathogenesis of ENL. Sharp and Banerjee (341–342) found that macrophages from nude mice were hyperactive as compared to normal mice but that nude mice were unable to control the growth of *M. leprae* in contrast to the limited infection seen in normal mice. Sharp, *et al.* (342) studied the fate of intracellular *M. leprae* in macrophages from nude mice and showed that the bacilli were susceptible to the bactericidal effects of hydrogen peroxide. Clark-Curtiss, *et al.* (344) reviewed their work on the molecular analysis of DNA from *M. leprae,* "*M. lufu,*" and *M. vaccae.* Papa, *et al.* (345–346) used an anti-BCG antigen 60 monoclonal antibody and showed that *M. leprae* and several corynebacteria shared this antigenic determinant. Some of the corynebacteria were isolated from leprosy lesions, but others had no relation with leprosy patients. Portaels, *et al.* (346) studied the lipids of four bacterial strains isolated from the livers of armadillos experimentally infected with *M. leprae,* and concluded that their mycolates and glycolipids clearly differentiated them from *M. leprae.* Ryter, *et al.* (346–347) studied the formation of electron-transparent zones following the phagocytosis of mycobacteria including *M. leprae* by macrophages. The electron-transparent zone formed within 1 hr after ingestion and occurred equally well with heat-killed *M. leprae,* showing that its formation does not require the active participation of the bacillus. Silva, *et al.* (347) reported detailed analyses of individual *M. leprae* by electron microscopy. Degenerating *M. leprae* cells largely predominated in most samples. Wieten, *et al.* (348) described a pyrolysis high-resolution gas chromatographic technique for detecting wax-ester mycolates capable of detecting contamination levels as low as 5% of the total number of acid-fast bacilli in preparations of *M. leprae.* Brett (349) studied macrophage activity in mice infected with *M. lepraemurium* and showed that the most susceptible mouse strain exhibited the highest levels of macrophage activation. Bahmer (354) collected data on the prevalence of leprosy in West Germany. A total of 106 patients were reported by a questionnaire. Most cases were among refugees from South East Asia and from farm workers from southern Europe. A total of 16 cases were Germans. No secondary cases have been reported. Basset (354) reviewed the epidemiology of leprosy in France. In metropolitan France there are about 1000 leprosy patients, most of them from overseas countries. de Lange, *et al.* (355) found significant differences between LL and BT patients with regard to distributions of immunoglobulin haplotypes in Vietnamese leprosy patients. Ganapati, *et al.* (355–356) pointed out the value of an intensive health education program in an urban area in identifying new cases. Jesudasan, *et al.* (356) made a detailed analysis of leprosy incidence rates among household contacts. Household contacts of nonlepromatous patients had a relative risk twice as high as individuals not exposed to leprosy in the same area, while household contacts of lepromatous and borderline lepromatous patients had a relative risk three times as high. The peak age-specific incidence rate among household contacts was between the ages of 5 and 9 years. Jesudasan, *et al.* (356–357) examined the effect that variation in the interval between successive cross-sectional surveys might have on estimates of the incidence rates for leprosy. When the interval between surveys increased from 1 year to 3 years, the estimated incidence rate for leprosy was halved. Ji, *et al.* (357) studied FLA-ABS tests in endemic areas. Rates of subclinical infection ranged from 11.4% to 16.3% and were at least 200 times higher than the cumulative prevalence rate for overt clinical infections. Koffi, *et al.* (357) described impressive declines in the incidence and prevalence of leprosy in the Ivory Coast since 1960. van Eden, *et al.* (358–359) studied HLA haplotype segregation patterns in multi-case families and found that HLA-DR3 was inherited preferentially by children with polar tuberculoid leprosy and HLA-MT1 was inherited preferentially by children with lepromatous leprosy. Balestrino, *et al.* (360) studied enzyme-linked

immunosorbent assays (ELISA) for IgG antibody to *M. tuberculosis* antigen 5 and tuberculin purified protein derivative (PPD) among pulmonary tuberculosis patients and found that the ELISA with antigen 5 had a sensitivity of 81.4% at a serum dilution of 1:40 and a specificity of 93.4% for tuberculosis. Overall, antigen 5 was more accurate than PPD for the diagnosis of tuberculosis using ELISA. Bhargava, *et al.* (360–361) found reduced abilities of patients with intestinal tuberculosis to be sensitized to DNCB compared to normal control subjects. Thalidomide was found to be effective in hyperkeratotic discoid lupus erythematosus by Frías Iniesta, *et al.* (361) and in severe orogenital ulceration by Jenkins, *et al.* (362). Heifets, *et al.* (361–362) found a number of cephalosporins and cephamycins to be promising based on *in vitro* screening against *M. tuberculosis.* Mackett, *et al.* (363) demonstrated the feasibility of incorporating DNA from an infectious agent into the vaccinia genome and inducing protective immunity against that agent after intradermal vaccination with the live recombinant virus.

The Original Articles in the September issue began with an interesting new technique to measure the physiologic state of *M. leprae* by Seydel, *et al.* (365–372). Bacilli isolated from patient biopsies were studied using single cell mass spectrometry by laser microbe mass analysis and by ATP measurements in the same populations of bacilli. Low intracellular sodium to potassium ratios were characteristic of presumably healthy *M. leprae* cells. Under dapsone chemotherapy, the bacilli showed higher sodium to potassium ratios which correlated with a decrease in ATP content. Lamas-Robles, *et al.* (373–377) found that human skin sections were much better substrates to demonstrate the anti-nuclear antibodies present in the sera of LL patients than conventionally used rat liver sections. Sathish, *et al.* (378–384) showed an excellent correlation between standard mouse foot pad dapsone sensitivity determinations and radiometric macrophage assays based on the incorporation of ^{3}H-thymidine into *M. leprae* in macrophage cultures. Longley, *et al.* (385–394) conducted sophisticated studies on the immune cell phenotypes and IL-2 production in naturally occurring leprosy skin lesions. In absolute terms, the number of T suppressor cells (OKT8+) were unchanged across the leprosy spectrum. In lepromatous patients' lesions, the absolute numbers of total T cells (Leu-1+) were decreased. The absolute number of helper T cells (Leu-3+, OKT4+) decreased markedly from tuberculoid to lepromatous lesions. The absolute numbers of Langerhans' cells (OKT6+) a) were higher in tuberculoid than in lepromatous lesions, b) correlated with the percentage of T cells with receptors for IL-2 (Tac+), and c) correlated but less strongly with the percentage of T cells producing IL-2 (DMS-1+). Variability was noted in the lesions of tuberculoid patients with regard to the percentage of T cells producing IL-2 with some overlap with lepromatous lesions in this regard. Samuel, *et al.* (395–403) made a detailed analysis of the cellular infiltrates following the intradermal inoculation of leprosin A. Similar cells were found to infiltrate both positive and negative responses to the skin test antigen. At the lepromatous end of the leprosy spectrum, the infiltrates were largely neutrophils. Dugan, *et al.* (404–409) studied the cellular infiltrates of Mitsuda reactions *in situ.* Interleukin-2 positivity and the epidermal triad of lymphocytic infiltration, Langerhans' cell hyperplasia, and Ia-positive kerotinocytes appeared to be consistent correlates of a delayed-type hypersensitivity response and provided evidence that the 21 to 28 day Mitsuda reaction may be a delayed-type hypersensitivity phenomenon. Teruel, *et al.* (410–411) reported a successful kidney transplantation in a lepromatous patient. The patient experienced a transitory recurrence of the disease which responded to sulfone treatment in spite of the immunosuppression associated with the renal transplantation. Douglas-Jones and Watson (412–420) presented details of a microculture assay for measuring the response of murine T lymphocytes to *M. leprae* antigens, and showed that it was the T lymphocytes that proliferated in response to antigen in the microcultures and that the lymphocyte response varied with the mouse strain used. Nagata, *et al.* (421–427) found no effect of rifampin or dapsone on immunologic responses in mice. Datta, *et al.*

(428–432) studied the protein binding of dapsone, using hen egg white lysozyme. The drug most probably interacts with tryptophan residues through π–π interactions. Hirata (433–440) studied the ultrastructural characteristics of the cell walls and cytoplasmic membranes of *M. lepraemurium* and *M. leprae.* The cytoplasmic membranes of the two organisms seemed to have a similar structure but the fine structure of the cell walls was slightly different. Larsson, *et al.* (441–446) found two long-chain secondary alcohols, 2-octadecanol and 2-eicosanol, by gas chromatography in hydrolysates of *M. avium/intracellulare,* in cultivable, armadillo-derived mycobacteria, and in *M. lepraemurium* but not in purified suspensions of *M. leprae.* The technique is a rapid means of detecting and quantifying contaminating mycobacteria in preparations of *M. leprae.* Fukunishi, *et al.* (447–454) identified PGL-I and phthiocerol dimycocerosate in lepromas from a nine-banded armadillo which had been inoculated with *M. leprae* from a mangabey monkey with naturally acquired leprosy. These lipids were thought to originate from the spherical droplets (peribacillary substance) surrounding *M. leprae* in the tissues. Date, *et al.* (455–460) reported necropsy findings in 133 leprosy patients and showed that renal disease, pyogenic infections, and tuberculosis were the most frequent causes of death. A variety of kidney lesions were encountered and, in many cases, the renal lesions were secondary to infections in other organs. Lechat, *et al.* (461–467) developed a newer version of an epidemiometric model for leprosy which takes into account age- and sex-specific incidence rates according to type of leprosy and which includes more realistic parameters for death rates, population variations, and natural growth rates. The model was used to simulate the effects of various vaccines and drug resistance on the incidence of leprosy in a population.

In the Editorial section of the September issue, Duncan (468–473) reviewed the problem of leprosy in young children in light of recent findings. Huikeshoven (474–480) thoughtfully reviewed the problem of compliance among leprosy patients, arguing that treatment compliance is more important now than ever before.

In the Correspondence section of the September issue, Sebille, *et al.* (481–483) described reductions in motor nerve conduction velocities in the sciatic nerves of mice inoculated into the foot pad with *M. leprae,* and found that rifampin treatment could prevent and, in some cases, reverse this disorder. Caticha-Alfonso (483–484) found no correlation between NADH-methemoglobin reductase activity and hemoglobulin level or reticulocyte rate in leprosy patients on chronic sulfone therapy. Hunter, *et al.* (484–486) provided very valuable, detailed methodology for the purification of PGL-I antigen from *M. leprae* from armadillo and human tissues. Vemuri, *et al.* (487–489) described a procedure for the isolation of PGL-I from human leprosy nodules, and showed that PGL-I from human and infected-armadillo tissues was chemically and immunologically identical.

In the Current Literature section of the September issue, Kumar, *et al.* (493) suggested the feasibility of involving community leaders in providing support for leprosy health education and control programs. Amokhina (493) described a technique for *in vitro* incubation of leprosy granulation tissue which seemed useful in studying the effects of antileprosy drugs. Daneshmend (494) reviewed the relatively rare reports of neurotoxicity of dapsone. Gnenjuk (494) reported the effectiveness of a drug called dimociphon in the treatment of lepromatous leprosy. Jagannathan and Mahadevan (495) found brodimoprim to be synergistic with dapsone in inhibiting the reduction of Fc receptor-bearing macrophages caused by live *M. leprae* after phagocytosis. Juscenko, *et al.* (495) reported preliminary results of experiments using liposomes for the targeted transport of drugs in leprosy. Kadantsev and Kogan (495) found annual relapse rates of 1.3% in recent years among leprosy patients in Russia. Defaulting from treatment played a particularly important part in relapses. Kar and Roy (495) reported a case of reversible acute renal failure at the time of the second and third monthly doses of rifampin in a patient being treated for lepromatous leprosy according to the WHO regimen. Pattyn (496–497) found that 50% of relapses in paucibacillary leprosy occur within 3½ years and 50% of relapses in multibacillary lep-

rosy occur within 2 years after discontinuing treatment. The author feels that it is possible to reduce the duration of treatment of multibacillary leprosy to 1 year, and there are indications that regimens of 6 months' duration may be effective. Reddy and Neelan (497) found that responses to dapsone monotherapy were comparable in cohorts of bacteriologically positive patients being treated in the years 1960–1962 and in those treated from 1968–1970. Samuel, *et al.* (497) found that 7 of 15 isolates of *M. leprae* from previously untreated leprosy patients in Nepal were resistant to 0.01% dapsone in the mouse diet. Samuel, *et al.* (497) found that 29 out of 56 patients suspected of having developed dapsone-resistant leprosy were proved to have secondary dapsone-resistant disease by the mouse foot pad test. Durairaj, *et al.* (498) reported diminished responses in serum cortisol levels after stimulation with ACTH in both reactional and nonreactional patients with lepromatous leprosy of over 10 years' duration. Thus, adrenal corticol reserve was felt to be diminished in both reactional and nonreactional lepromatous leprosy. Gupta, *et al.* (499) reported an interesting case of indeterminate leprosy developing at the site of a dog bite. Gupta, *et al.* (499) found impaired sympathetic respiratory reflexes in 12 of 25 polar lepromatous leprosy patients with and without lepra reaction. Jesudasan and Christian (499) studied 88 paucibacillary leprosy patients and found that 40–75% underwent spontaneous regression within a period of 5 years from detection. Lucht, *et al.* (500) reported a patient with type 1 (reversal) reaction whose condition improved dramatically after 5 plasma exchanges on 5 successive days. Seang Hoo Nah, *et al.* (501) found a correlation between the duration of confirmed untreated lepromatous leprosy and the degree of alveolar bone loss in the anterior maxilla. Gad, *et al.* (502) showed that thalidomide induced a reduction in the percentage and absolute number of T-helper cells in the circulation of healthy subjects. Jeevan and Bapat (502–503) showed that ICRC bacilli were capable of sensitizing mice to lepromin, and this sensitization could be adoptively transferred to syngeneic recipients by sensitized spleen cells. Mathew, *et al.* (503) analyzed the granulomas induced in draining lymph nodes of guinea pigs immunized with BCG and *M. leprae.* The BCG-induced granulomas were well organized and contained epithelioid cells with macrophage-specific antigen on their surface, but no detectable Ia antigen. In *M. leprae*-induced granulomas, there was an absence of organization and an absence of epithelioid cells; the macrophages in the granuloma expressed both macrophage-specific and Ia antigens. Mathur, *et al.* (503) found reduced numbers and ultrastructural morphological changes in Langerhans' cells in the epidermis of lepromatous (LL) cases compared to those in tuberculoid (TT) patients. Modlin, *et al.* (503–504) characterized the cells in human leprosy granulomas *in situ* using a variety of monoclonal antibodies and concluded that the defective cell-mediated immunity in lepromatous leprosy seems to be associated with diminished IL-2 production and disorganization of the granuloma. Narayanan, *et al.* (504) studied T-cell phenotypes in reactional BT patients (reversal or type 1) and found a significant influx of OKT8+ (suppressor/cytotoxic) cells compared to nonreactional BT lesions. In reactional BL lesions (both reversal and ENL), there were increases in pan T cells with a proponderance of the helper/inducer subset. OKT6+ Langerhans' cells were increased in all reactional lesions. Poulter, *et al.* (505) studied macrophages, interdigitating cells, and Langerhans' cells in the dermal infiltrates of BL lesions and found the proportion of cells parasitized by *M. leprae* within each subpopulation was equivalent to the overall proportion of each cell type within the infiltrate. Saha, *et al.* (505) found correlations between various clinical states in leprosy and serum beta-2-microglobulin levels. Umerov, *et al.* (506) found a common antigen in human peripheral nerves and in *M. leprae.* Umerov, *et al.* (506) found that sera from patients with active leprosy exerted myelinotoxic activity in cultures of spinal ganglia which is due to the presence of antibodies against specific mycobacterial antigen which is, in turn, similar to the antigen of human peripheral nerves. Yushin (506) presented evidence for the activation of the mononuclear phagocytic system in lepromatous patients. Mankar, *et al.* (507–508) used the ability of live *M. leprae* to

reduce the number of EA-rosetting macrophages as a means of testing bacterial susceptibility to drugs. Mukherjee, *et al.* (508) found that radiolabeled acetate could be incorporated into the PGL-I antigen of *M. leprae* maintained in a Schwannoma cell line. The synthesis of PGL-I antigen could be inhibited with dapsone and rifampin. Šula and Sulova (509) described a newly isolated phage A1-1 obtained from a laboratory strain of *M. lepraemurium* "Douglas." Talati and Mahadevan (509) found that penicillinase was expressed by *M. leprae* when incubated with penicillin. Live *M. leprae* had demonstrable lipase activity. Hoffenbach, *et al.* (510) saw no evidence of a direct influence of the *Bcg* gene on lymphokine production and antibody secretion in mice infected with *M. lepraemurium.* Juscenko (510) reported an interesting case of an armadillo which developed reversal reaction during the course of an experimental infection. Bharadwaj, *et al.* (510–511) saw higher rates of FLA-ABS positivity among contacts of LL and BL patients than among contacts of nonlepromatous patients. All 11 contact children who have developed the disease to date belonged to a group who were lepromin negative and FLA-ABS positive. Jesudasan, *et al.* (511) reported that the incidence rates remained high even 10 years after treatment was started in a primary case among household contacts. Berreman (512–513) pointed out the effectiveness of a policy of not confronting people with a diagnosis of leprosy in problematic childhood cases, but of asserting instead that leprosy can be prevented if treatment is accepted. Brandsma and Brand (513) studied long-term median nerve function in leprosy patients who originally had had pure ulnar palsy for which they had tendon transfers to correct claw hands. The use of the carpal tunnel as a pathway for tendon grafts did not significantly affect the long-term status of the median nerves in these cases. Shah and Pandit (513) found reconstruction of the heel with a flexor digitorum brevis myocutaneous flap was useful in the management of chronic nonhealing plantar ulcers on the heel in leprosy patients. Horney, *et al.* (514) reported a case of cutaneous inoculation tuberculosis occurring in a tattoo. Wulff, *et al.* (514–515) described predominantly sensory peripheral neuropathy, mainly involving the lower limbs, in 7 patients with prurigo nodularis and 1 with aphthous stomatitis treated with thalidomide.

The Original Articles in the December issue began with the definitive review of leprosy occurring in children one year of age and under by Brubaker, *et al.* (517–523). Leprosy was diagnosed in 91 infants one year of age and under. The source of the infection in at least 43% of the infants was someone other than the mother. The youngest patient was 2–3 months of age. Sommerfelt, *et al.* (524–532) studied leprosy prevalence in South India, and found that leprosy prevalence rates were significantly lower in field areas than in villages, and that there was a significant correlation between the occurrence of malnutrition in young children and the prevalence of leprosy. No significant correlations were found between the occurrence of malnutrition in the general population, the occurrence of poverty or illiteracy and leprosy prevalence rates. Hackel and Beiguelman (533–539) studied chromosomal aberrations in cultures of skin fibroblasts of leprosy patients and found that structural chromosomal abnormalities were associated with treatment with dapsone alone or with combined therapy. Petri, *et al.* (540–545) measured clinical and histological reactions to lepromin in healthy adults with no known contacts with leprosy. Surprisingly, the intensity of the clinically read Mitsuda reaction was not correlated with the intensity of the histological response. Waters and Stanford (546–553) provided a detailed description of a phenomenon termed "giant reactions" to tuberculin. The reaction may occur in up to a fifth of predominantly lepromatous patients during their first 1 to 3 years of chemotherapy. Yoder, *et al.* (554–558) described an unusual patient with documented lepromatous leprosy presenting as a solitary lesion with a high bacterial count. Brown, *et al.* (559–564) saw essentially no enhancement of cell-mediated immunity in patients with lepromatous leprosy being given cimetidine. Wu, *et al.* (565–570) applied an enzyme-linked immunosorbent assay with soluble antigens of *M. leprae* to blood samples collected from earlobes of leprosy pa-

tients and healthy controls. The blood samples were absorbed with *M. vaccae,* BCG, cardiolipin, and lecithin before being tested in the assay. While there were areas of overlap, antibody activity gradually increased from TT to LL. Mukherjee, *et al.* (571–576) described the ultrastructure of leprous phlebitis, demonstrating bacilli in endothelial cells and the release of *M. leprae* into the lumen of veins by exophagocytosis. Bacilli were able to grow and multiply in the endothelial and smooth muscle cells, and the smooth muscle cells showed no evidence of reaction due to the presence of the bacilli in their cytoplasm. Hirata (577–581) described the ultrastructure of *M. leprae* in the nasal mucosa of leprosy patients. Cree, *et al.* (582–586) described a technique to determine the proportion of the dermis occupied by granuloma in histological sections of skin biopsies from leprosy patients by planimetry. Shepard, *et al.* (587–594) carefully studied the structure-activity pattern of a series of substituted thioamides against *M. leprae* and concluded that the structural requirements for antileprosy and antituberculosis activity are probably similar, with ethionamide and prothionamide being found to be most active. Balina, *et al.* (595–599) summarized their experience in the experimental reproduction of leprosy in the seven-banded armadillo (*Dasypus hybridus*). The seven-banded armadillo, unlike the more commonly used nine-banded armadillo, breeds readily in captivity. Mori, *et al.* (600–609) summarized elegant work on the purification and biochemical studies of *M. leprae.* It seemed possible to enrich for solidly staining bacilli by means of density gradient centrifugation. Endogenous respiration was higher in more dense bacilli than in fractions containing less dense bacilli. Cytochrome B_1 was detected but cytochromes A, A_2, and C were not detected. No catalase activity was found and no NAD-peroxidase activity was detected.

The Editorial section of the December issue began with an elegant review of the epidemiologic patterns observed during declining incidence rates of leprosy by Irgens (610–617). In a number of settings, declining incidence rates are associated with increases in mean age at onset. Evidence is presented that these changes in age at onset are not caused by postponement of the infection to a later time in life, but that these older patients represent cases with long incubation periods who become relatively more frequent as time goes on compared to patients with shorter incubation periods becoming ill at the same time. Since lepromatous patients have a longer incubation period than patients with other types of leprosy, when the fraction of new cases with long incubation periods increases, the fraction of the new cases with lepromatous disease also increases. Thus increases in the proportion of lepromatous cases and increases in average age at onset are both associated with decreasing incidence rates.

We were delighted to have the prize-winning essay on monoclonal antibodies and recombinant DNA technology by Seckl as a Guest Editorial in the December issue (618–640). These two powerful technologies have opened vast new areas of research in leprosy and tuberculosis, and we join in the hope that they will hasten the day when "both leprosy and tuberculosis will dwindle into the historical annals of medical literature."

In the Obituary section of the December issue, the death of Dr. James Cecil Pedley was noted with sadness.

The Correspondence section of the December issue began with a description of good results using silastic implants to simulate the contour of the first dorsal interosseous muscle in leprosy patients with loss of this muscle mass by Zacharia and Gelber (643–644). Pavithran (645–646) described a patient who developed generalized exfoliative dermatitis after being treated with clofazimine who showed a recurrence of the exfoliative dermatitis upon rechallenge with the drug. Furukawa, *et al.* (647–648) demonstrated that anti-cardiolipin antibodies in the sera of LL patients have the ability to crossreact with double-stranded DNA. Shankar, *et al.* (649–652) studied the *in vitro* proliferative responses of peripheral blood mononuclear cells to *M. leprae* and PPD in lepromatous leprosy patients, tuberculoid patients, and healthy controls in the presence and absence of supplemental IL-2. The data indicate that a majority of *M. leprae* nonresponders, including all lepromatous patients, a few borderline tu-

berculoid patients, and some healthy subjects not exposed to *M. leprae,* may acquire *in vitro* proliferative response to *M. leprae* upon the addition of IL-2. This capacity seemed to be closely related with the ability of these individuals to develop a proliferative response to PPD, strongly suggesting that the IL-2-induced proliferative response to *M. leprae* is directed against epitopes shared between *M. leprae* and *M. bovis* BCG, the source of the PPD. Shepard and Levy (653–655) commented on earlier suggestions by Humber regarding the technique used for counting *M. leprae.* Humber (656–657) continued to feel that application of a stratified sampling technique would be preferable.

In the News and Notes section of the December issue, Dr. and Mrs. Olaf Skinsnes' return to China (659) was noted. Well-deserved recognition to Dr. Indira Nath (660), Dr. M. G. Deo (660), Baba Amte (660), and Dr. B. R. Chatterjee (660) was recorded. The inauguration of trials of leprosy vaccines in Malawi and Venezuela were noted (660–661).

In the Current Literature section of the December issue, Alvarenga, *et al.* (667–668) described excellent results with the combination of rifampin and Isoprodian in almost 800 patients in Paraguay. Some 126 lepromatous cases have completed therapy and have been observed for 2 years or longer with no sign of relapse. Arora, *et al.* (668) found that levamisole was not effective in ENL. Khalil, *et al.* (669) found that antacids significantly reduced the bioavailability of concomittantly administered rifampin. Levy (669–670) outlined the role of chemotherapy in both the management of an individual patient and in the control of leprosy in the community. Li (670) reported favorable clinical results with a clofazimine (B663) analogue designated B628 in a total of 9 lepromatous patients treated for five months. Mathur, *et al.* (670) found that approximately 45% of orally administered clofazimine was absorbed in single doses of up to 600 mg. Mester de Parajd, *et al.* (670) reviewed the antileprosy potential of deoxyfructo-serotonin and its analogues. Mittal, *et al.* (671) tested the effects of clofazimine and 6 analogues on the viability of *M. leprae* in macrophage cultures as measured by ^{3}H-thymidine incorporation. In general, clofazimine appeared to have a more rapid onset of action and an action at a lower concentration than the other analogues tested. Nair and Mahadevan (671) measured the inhibition of the preferential accumulation of cholesterol ester by macrophages that have ingested live *M. leprae* by dapsone and rifampin as a measure of bacterial drug sensitivity. Pandian, *et al.* (671–672) reviewed results of dapsone monotherapy in nonlepromatous and intermediate leprosy. Relapse rates appeared to remain steady at about 5/1000 for each year following release from control for 7 years. Schroder and Matthiesen (672) administered large doses of thalidomide to rabbits for prolonged periods of time and found that there was a reduction in the thickness of the myelin sheaths in their sural nerves. This was associated with a reduction in sensory conduction velocity. Sharma, *et al.* (672–673) felt that levamisole was useful in shortening the duration of both reversal reactions and ENL. Agrawal and Agrawal (673) found vascular changes in the arteries in the hands and feet of a majority of leprosy patients as measured by percutaneous arteriography. Arora, *et al.* (673) found statististically significant changes in lepromin reactivity following levamisole in a group of borderline leprosy patients. ffytche and McDougall (674) reviewed ocular leprosy, making a distinction between "potentially sight-threatening" lesions and those considered only as "academic." Kiran, *et al.* (674–675) suggested an unsupervised outpatient method of treating recent loss of nerve function in patients with borderline leprosy using a semi-standardized course of corticosteroids. Robertson, *et al.* (675) described an LL patient diagnosed finally on the basis of histopathologic changes in an eye which had been enucleated for bilateral anterior uveitis for which no cause had been found. Foci of inflammation containing *M. leprae* were found in the vitreous extending to the retina at the posterior pole. Wright (677) studied plasma phospholipid essential fatty acids in leprosy patients and found a significant reduction in linoleic acid with an increase in its metabolite, dihomo-gamma-linoleic acid. No difference was found between patients with multibacillary and pau-

cibacillary leprosy and treatment seemed to result in normalization of these measurements. Atlaw, *et al.* (677–678) described their experience in producing human monoclonal antibodies against *M. leprae.* The results suggest that a combination of Epstein-Barr virus transformation and hybridization may be an optimal method in producing human monoclonal antibodies from leprosy patients. Bloom and Mehra (678) reviewed the immunology of leprosy. Collings, *et al.* (678–679) described an interesting technique to quantitate the class II MHC antigens (HLA-DR) expressed by cells within tissue sections. The method was applied to the lesions of tuberculoid and lepromatous leprosy and significant differences in the HLA-DR expression by cells in the infiltrates were observed. Gillis, *et al.* (679) described a 65,000 apparent molecular weight protein associated with cell wall of *M. leprae* which contained at least 1 species-specific and 4 crossreactive antigenic determinants as defined by a variety of monoclonal antibodies. Kundu, *et al.* (679–680) found that corticosteroids could induce a negative lepromin reaction in polar tuberculoid leprosy patients. Levamisole was ineffective in converting lepromin reactivity in polar lepromatous cases. Mehra, *et al.* (680) presented evidence that the PGL-I antigen of *M. leprae* is capable of inducing suppression of mitogenic responses of lepromatous patients' lymphocytes *in vitro* and that the suppressor T cells recognize the specific terminal trisaccharide moiety on this antigen. Mohagheghpour, *et al.* (680–681) studied the ability of LL patients' mononuclear leukocytes to produce IL-1 and IL-2 upon stimulation with *M. leprae* and determined the ability of exogenous IL-1 and IL-2 to reconstitute the responses of these patients *in vitro* to this antigen. Results with IL-1 were comparable in BT and LL patients' cells. On the other hand, T cells of LL patients failed to express receptors for IL-2 or to produce IL-2 in response to *M. leprae* in contrast to cells from BT patients. Recombinant human IL-2 failed to reconstitute the response of LL patients' cells to *M. leprae.* The failure of T cells of LL patients to respond to *M. leprae* may be on the basis of their failure to express receptors for IL-2. Praputpittaya and Ivanyi (681) partially characterized a repeating epitope (MY4b) common to *M. tuberculosis* and *M. leprae.* Ramanthan, *et al.* (681–682) found that sera from BT and LL patients in reaction had markedly decreased abilities to solubilize immune preciptates *in vitro* through the complement system. These changes did not seem to be related to total or alternative pathway hemolytic levels of complement, circulating immune complexes, or serum C3d levels. Tausk, *et al.* (683) found reduced numbers of receptors for C3b on the erythrocytes of LL patients as compared to tuberculoid patients or normal controls. Teuscher, *et al.* (683) studied the responses of inbred strains of mice to *M. leprae* by measuring the resulting antibodies to PGL-I. Antibody levels were controlled by multiple genes and low antibody responses to the PGL-I seemed to be inherited as a dominant trait. Young, *et al.* (684) described the use of a polysulfone membrane as a solid support for chromatography and immunoblotting of the PGL-I antigen of *M. leprae.* There was very little nonspecific background binding and the assays could be carried out with IgM antibodies from human sera. Young, *et al.* (684) described studies characterizing a 28,000 dalton protein antigen of *M. leprae* by monoclonal antibodies. One epitope on molecule appears to be specific for *M. leprae,* one partially specific, and one broadly crossreactive among all mycobacteria. Brennan (685) reviewed the evidence that the phthiocerol-containing lipid capsule of *M. leprae* may be directly responsible for the intracellular survival of the organism. David and Rastogi (685–686) described an interesting system of exposing *M. aurum* to sublethal concentrations of colistin (polymyxin E), resulting in synchronized cell division once the antibiotic was removed. Kato (686) found that extracts of *M. leprae* did not contain mycobactin and speculated that *M. leprae* might be dependent upon secondary mycobacteria present in *M. leprae*-infected tissues to provide it mycobactin for its own multiplication. Katoch, *et al.* (686) studied LDH isoenzyme patterns of mycobacteria and concluded that they could be of identification value at the species level. Minnikin, *et al.* (686–687) identified the free lipids of the leprosy bacillus over the total

polarity range and showed that the patterns were particularly related to those of *M. bovis, M. kansasii,* and *M. marinum.* Minnikin, *et al.* (687) did not find a particularly close relationship between *M. leprae* and *M. gordonae* on the basis of fatty and mycolic acid compositions. Mukherjee and Antia (687) observed a significant multiplication of acid-fast bacilli within the Schwann cell component of organized nerve cultures of dorsal root ganglia from neonatal mice which had been infected with *M. leprae.* Portaels, *et al.* (687–688) reviewed their experience in cultivating mycobacteria from 16 out of 32 samples of tissues from armadillos inoculated with *M. leprae* and in 3 out of 7 samples from noninoculated armadillos held in captivity. *M. avium-intracellulare-scrofulaceum* complex, *M. gordonae, M. terrae,* and new armadillo-derived mycobacteria (ADM) were identified. Wang, *et al.* (689) studied the viability of *M. leprae* in normal saline by the mouse foot pad technique and found that at room temperature for 3 days the viability of the bacilli decreased slightly, and after 2 weeks the viability was lost. At refrigerator temperature viability decreased by 8 days and after 20 days the viability was lost. Ganguly, *et al.* (689–690) found no effect of levamisole on the rate of growth of *M. leprae* in mice. Job, *et al.* (690) studied armadillos which developed disseminated disease after inoculation with *M. leprae* and noted the first lesion occurring at the site of inoculation in 14 of the 16 animals infected intravenously and in 4 of the 4 infected intradermally. Lefford (690) found that *M. lepraemurium* grew equally well in nu/+ (heterozygous, euthymic) mice from a BALB/c background as they did in nu/nu (nude, athymic) littermates, and concluded this was due to the intrinsic genetic susceptibility of both types of mice. Rojas-Espinosa, *et al.* (691) inoculated turtles with *M. lepraemurium* and *M. leprae.* Limited multiplication of *M. lepraemurim* occurred and *M. leprae* persisted for up to 23 months postinoculation but without clear evidence of multiplication. Ferreira, *et al.* (691–692) analyzed the patterns of leprosy incidence by age and type of disease and concluded that these patterns could be explained by the proportions of Mitsuda-positive individuals increasing with age and the number of contagious patients and consequently the "supply" of bacilli capable of causing infections being greater in high-prevalence areas. The conclusions reached to explain these patterns in leprosy epidemiology differ from those outlined by Irgens (610–617). Schlagel, *et al.* (692–693) reported 89 cases of leprosy among active duty U.S. military personnel during the period 1970–1983. Chaise and Sedel (694) measured the carpal tunnel and intraneural pressures in 15 cases of leprous neuritis of the median nerve at the wrist and found markedly increased pressures compared to those at the same location in healthy volunteers. Dickinson and Mitchison (695) found evidence that fludalanine acted synergistically with cycloserine against rapidly growing mycobacterial species. When tested against slowly growing mycobacteria, the combination was no more active than cycloserine alone. Mizuguchi, *et al.* (696–697) described *in vitro* activity of β-lactam antibiotics against strains of *M. avium-intracellulare.* Mookerjee and Pauly (697) presented evidence that purified recombinant human IL-2 can serve as the first signal for T-cell proliferation for lymphocytes of healthy human donors. Perkus, *et al.* (698) inserted coding sequences for the hepatitis B virus surface antigen, the herpes simplex virus glycoprotein D, and the influenza virus hemagglutinin into a single vaccinia virus genome. Rabbits immunized with this polyvalent vaccinia virus recombinant produced antibodies reactive to all 3 authentic foreign antigens. It thus seems feasible that this approach can be used to immunize against multiple pathogens. Young, *et al.* (699) described the recombinant DNA approach used to systematically survey the *M. tuberculosis* genome for sequences that encode specific antigens as detected by monoclonal antibodies.

The December issue contained the abstracts for the Twentieth Joint Leprosy Research Conference of the U.S.–Japan Cooperative Medical Science Program. Nomaguchi, *et al.* (706–707) found in general that exogenous interferon-alpha, -beta or agents which induced the *in vivo* production of interferons did not affect the survival of mice infected with viable *M. lep-*

raemurium. Modlin, *et al.* (707–708) cloned T4 and T8 lymphocytes from tuberculoid and lepromatous skin granulomas and found that lepromin-induced suppressor cells were found only in cells derived from lepromatous granulomas. Kaplan, *et al.* (708–709) found that peripheral blood mononuclear cells from lepromatous patients were heterogeneous in their response to *M. leprae in vitro* as assessed by T-cell proliferation and gamma-interferon release. Exogenous IL-2 had no significant effect on the response of T cells from nonresponder patients, although it was effective on T cells from low-responder patients. Similarly, deletion of monocytes and/or OKT8+ T cells had no effect on the response to *M. leprae* by nonresponder patients. Uyemura, *et al.* (709) evaluated the *in vitro* effect of cyclosporin A on lepromin-induced suppression in the peripheral blood of LL patients and in LL patients with ENL. Lepromin-induced suppression was present in lepromatous leprosy but not in ENL, and cyclosporin A treatment of peripheral blood mononuclear cells from ENL patients restored the lepromin-induced suppression to levels observed in LL patients. These findings may provide evidence that cyclosporin A has potential efficacy in the treatment of ENL. Izaki, *et al.* (709–710) extracted plasminogen activator activity from hypersensitivity-type murine lepromas and extensively characterized the material biochemically. Truman, *et al.* (710–711) estimated antibodies to the PGL-I antigen of *M. leprae* among hospitalized leprosy patients, staff members at a leprosy hospital, and a leprosy-naive population. Antibodies were detected in 12–14% of presumed healthy hospital staff members. Thalidomide significantly decreased specific IgM antibodies to the PGL-I antigen. Jacobs, *et al.* (711–712) described genomic libraries DNA prepared using the plasmid expression vector pYA626. A 46KD polypeptide was produced which complements the *glt*A mutation in the *E. coli* host strain. The expression of *M. leprae* genes in *E. coli* to date seems to depend upon the presence of promotors recognized by the *E. coli* transcription system. Cocito (712) compared the properties of *M. leprae* and leprosy-derived corynebacteria. Hunter, *et al.* (712–713) isolated a family of major carbohydrate-containing macromolecular antigens for *M. leprae,* all of which contain mannose and arabinose. These are highly lipidated, acylated exclusively by 10-methyloctadecoanoate. One of these, designated lipoarabinomannan-B (LAM-B), is the dominant immunogen in *M. leprae.* Miller, *et al.* (713–714) found evidence that antibody to the 14,000 molecular weight antigen of *T. pallidum* which develops in a subset of leprosy patients is the most common cause of false-positive FTA-ABS tests in this population. Tsutsumi and Gidoh (714–715) reported on the abilities of various antileprosy drugs to scavenge active oxygen radicals. Abe, *et al.* (715) studied salivary anti-*M. leprae* antibodies using a modified technique for the fluorescent leprosy antibody absorption test. The test was positive in 59% of household contacts, 39% of school children, and 17% of adults in an endemic area. A significant number of individuals showed a positive reaction with saliva but a negative reaction with sera, possibly suggesting subclinical infection through the mucous membrane. Cho, *et al.* (715–716) described the results of serologic testing using a variety of synthesized neoglycoproteins based on the PGL-I antigen of *M. leprae.* The natural terminal disaccharide conjugated to bovine serum albumin via an 8-methylene (octyl) linker arm shows the greatest sensitivity and specificity among these neoglycoprotein antigens to date. Additionally, techniques were described for the estimation of the PGL-I antigen itself from clinical samples with a sensitivity down to 0.5 ng. Buchanan (716–717) summarized analyses of 33 monoclonal antibodies to *M. tuberculosis* done as part of a workshop sponsored by the World Health Organization. Mohagheghpour, *et al.* (717–718) described initial findings in efforts to produce human monoclonal antibodies to *M. leprae* antigens. Gillis (718) described a technique for the affinity purification of a 65KD protein of *M. gordonae* using a monoclonal antibody. Tung, *et al.* (719) quantitated soluble receptors for IL-2 in the sera from a variety of leprosy patients and their contacts. Receptors for IL-2 were greatly elevated in BL patients with reversal reactions but were only slightly elevated in patients with ENL. Nakamura and Yogi

(720) found differences in the susceptibility of nude rats for the growth of *M. leprae,* depending upon the genetic background of the animals. Chehl, *et al.* (720–721) studied the adoptive transfer of cell-mediated immunity in *M. leprae*-infected nude mice and concluded that adoptively transferred helper T cells were responsible for inducing reversal reactions in this model. Tung, *et al.* (721–722) found that murine antibody responses to PGL-I antigen exhibited strain variations. Eustis-Turf, *et al.* (722–723) found IgG-type antibody in the sera of 17 of 43 leprosy patients which bound to peripheral nerves at the junction of the axon and the myelin sheath. The positive sera reacted with a protein band migrating at approximately 50KD prepared from an intermediate filament fraction from human spinal cord. Job, *et al.* (723–724) surveyed for the problems of leprosy among wild armadillos and found a prevalence rate of 3.1% in Louisiana. In 1 animal evidence was presented that the *M. leprae* entered the tissue along with a thorn. Thomas, *et al.* (724–725) presented epidemiologic evidence that both direct and indirect exposure to armadillos appeared to be significant risk factors in the development of lepromatous leprosy. Cohn, *et al.* (725–726) reviewed the role of lymphokines in cell-mediated immunity in leprosy. Goren, *et al.* (726–727) reviewed the functionality of secondary lysosomes in murine resident peritoneal macrophages. Fujiwara, *et al.* (727) described the synthetic methods employed in producing neoglycoconjugates based on the PGL-I antigen of *M. leprae.* Mehra, *et al.* (727–728) provided an overview on the recombinant DNA strategy to isolate genes from *M. leprae* and *M. tuberculosis* that encode for immunologically relevant proteins of these organisms. Recombinant DNA expression libraries containing *M. leprae* and *M. tuberculosis* genomic DNA fragments have been constructed in the bacteriophage vector lambda gt11. These libraries have been screened with monoclonal antibodies directed against many of the major proteins of both bacilli. Recombinant DNA clones producing relevant antigens which react with these antibodies have been isolated. Particular attention is focused on the 65KD antigen gene of *M. leprae* which is being sequenced.

Once again a great deal of progress has been made in our understanding of leprosy in the past year. From a personal perspective a number of developments and directions appear particularly relevant.

In general there seems to be an increasing awareness and interest in the history of leprosy in different parts of the world as evidenced by papers on leprosy in medieval Islam, China, medieval England, etc.

In the field of chemotherapy, the additive hepatotoxicity of daily rifampin and thioamide now appears clear. The lepromin status of paucibacillary patients may be important in their risk for relapse after discontinuation of short-term chemotherapy. Considerable interest has been evident in levamisole as immunotherapy for leprosy, but, in general, disappointing results have been reported from a number of studies. Cimetidine also does not appear to be promising. The status of the multibacillary patients in the Malta Project continues to be followed with interest. There have been no relapses but a number of these patients continue to show acid-fast bacilli in skin smears. Colchicine was reported by some, but not by others, to be effective in ENL. Increasingly, there are reports of thalidomide neuropathy occurring in nonleprosy cases. Rifampin, when given daily for 30 days followed by another 30-day course six months later, significantly prevents relapse in lepromatous patients receiving dapsone monotherapy. The suggestion was made that full-dose dapsone therapy, uninterrupted during reactions, may decrease the incidence of dapsone resistance. It was noted that primary dapsone resistance as measured by mouse foot pad studies is usually of low level; whereas secondary resistance is usually at a high level. Interest has been evident in β-lactam antibiotics, either with or without inhibitors of β-lactamase, as potential chemotherapy for *M. leprae.* Experimental and clinical interest has been expressed in clofazimine analogues.

Clinically, there have been reports of possible respiratory and cardiovascular autonomic dysfunction in leprosy patients. A new apparatus has been described for testing sensation to heat. A large necropsy series emphasizing renal disease in leprosy patients has appeared. "Giant reactions" to tuberculin have been described. It has been

re-emphasized that as many as 75% of true paucibacillary leprosy patients undergo spontaneous regression within five years of detection without chemotherapy.

Our knowledge in the field of immunology is expanding rapidly. Serologic studies with specific antigens of *M. leprae* continue to point to rather frequent infection in relation to overt disease. Overt disease seems clearly to be more common in individuals with a positive antibody test and a negative lepromin skin test. Salivary antibodies to *M. leprae* have been described and appear to be common. A significant number of individuals in endemic areas show antibodies in saliva but not in blood, and this may suggest that subclinical infection is occurring via mucous membranes. The nature of the failure of cell-mediated immunity in lepromatous leprosy to *M. leprae* continues to be the subject of intense interest. This failure seems to be associated with decreased, possibly inhibited, IL-2 production within the granuloma of lepromatous leprosy. This inhibition could come from macrophages. T cells are being cloned from leprous skin granulomas and analyzed functionally. IL-2 restores specific responsiveness of peripheral blood mononuclear cells from some but not all LL patients *in vitro*. The suggestion has been made that this may be related to crossreactions to other mycobacteria to which these individuals are sensitive. The infiltrates of reactional skin lesions are being analyzed for T subsets. ENL lesions seem to be associated with increases in helper T cells and functional assays show a loss of suppression in ENL over what is normally observed in nonreactional lepromatous leprosy. It has been reported that reversal reactions in BT lesions are associated with increases in suppressor T cells, while those in BL patients are associated with increases in helper T cells. Emphasis continues on lipid antigens of *M. leprae*. The PGL-I antigen of *M. leprae* seems to have little if any activity in cell-mediated immunity or delayed-type hypersensitivity reactions to *M. leprae* in mice but was able, in one study, to elicit a positive late skin reaction in a lepromin-positive armadillo. Anti-PGL-I antibody levels of the IgM type clearly seem to fall with chemotherapy and are related to the bacterial index in outpatients. The suggestions have been made that the IgM-class antibody to the PGL-I antigen is involved in ENL and that thalidomide preferentially reduces this antibody. A number of synthetic antigens based on the PGL-I have been produced and a number of methods developed for detecting the PGL-I antigen in biologic samples. Lipoarabinomannan-B has been isolated from *M. leprae* and is apparently a major immunogen of the bacillus. Two groups have produced human monoclonal antibodies to *M. leprae*. Two groups have suggested that there are shared antigens between *M. leprae* and human peripheral nerve tissue. Antibodies and antigens of *M. leprae* have been demonstrated in the urine of LL patients. An interesting report showed that the intensity of clinically read Mitsuda skin reactions was not correlated with the histologic intensity of the response in normal individuals. Field antileprosy vaccine trials have been initiated in Malawi, India, and Venezuela.

In the microbiology of leprosy, work continues in defining the chemical composition, particularly the lipid composition, of *M. leprae*. Improved rapid isolation techniques for the bacilli have been reported and more sophisticated estimates of its viability described with measurements of ATP, radiometric assays, single cell spectrometry with laser microbe mass analysis, etc. Recombinant *M. leprae* DNA is being expressed and the stage is being set for complete DNA mapping of a number of important antigens of the bacillus.

In experimental infections, a primate model for the disease seems to be available in the mangabey monkey. Infections in seven-banded armadillos have been more fully described. Antibodies to the PGL-I antigen have been found in serum samples from armadillos taken in 1960–1964, implying that the natural infection in armadillos existed prior to the first experimental inoculations of these animals with *M. leprae*. A spontaneous reversal reaction has been described in an armadillo infected with *M. leprae*.

In the field of epidemiology, genetic studies are suggesting that HLA-linked genes control for leprosy type although not for susceptibility or resistance to the disease per se. Epidemiologic patterns of leprosy as it declines in a population now seem to be

clearer. A new refined epidemiometric model of leprosy has been described. Emphasis has been placed on leprosy in infants and young children as well as the possible placental transmission of the disease to the fetus *in utero.*

In the field of rehabilitation, a possible mouse model for progressive leprous neuropathy has been described. Marked increases in intraneural pressure were measured in leprous neuritis.

From the perspective of the 1985 JOURNAL, a great many of the promises of 1984 now appear to be bearing fruit. A revolution has occurred and is now under way in our understanding of leprosy at a basic level. As never before, we are being challenged to use this new information as rapidly, efficiently, and wisely as possible to improve the care of leprosy patients and to, hopefully, prevent the disease altogether in future generations. This is indeed an exciting time for leprosy workers. I look forward with impatient optimism to 1986.—RCH