The 1980 JOURNAL—A Perspective in Leprosy

At the end of the first full year of publication of the JOURNAL from Carville, it seems appropriate to reflect on the contents of Volume 48. As the official organ of the International Leprosy Association, the JOURNAL hopefully provides an international overview of the leprosy field and, as such, may reflect both the areas of progress which we have all enjoyed and areas of frustration which touch every leprosy worker. More commonly perhaps, the JOURNAL reflects our probing into the seemingly endless array of questions besetting leprosy and indeed all of medicine, and the answers to our probing seem mystifying, controversial in their interpretation, and all too often so far outside our immediate fields of interest that they seem barely worthy of our attention. Ideally, all leprosy workers, from the sophisticated biomedical scientist to the overworked paramedical field worker, are working for the same thing, the control and eventual eradication of leprosy, and, in the interim, the care of its victims. As reflected in the pages of the JOURNAL, what new information to help accomplish this task is available to us at the end of 1980 which was not available to us a year ago?

In the original articles of the March issue of the JOURNAL Kazda, *et al.* (1–6)* implied the revolutionary concept that viable *M. leprae* might exist and presumably propagate in sphagnum and moss vegetation, in short, outside humans and even outside animals. Their findings were intriguing and hold vast implications for the epidemiology of leprosy and efforts at leprosy control. The key question is whether or not these noncultivable acid-fast bacilli which multiply in mouse foot pads are actually *M. leprae*. Hopefully, we will learn more about this in the not too distant future. Pattyn and Portaels (7–14) reported results of sophisticated cultures and careful *in vitro* testing of three different strains of *M. lepraemurium*, confirming their identity to each other and providing authoritative proofs of their differences from all other known mycobacteria. Wheeler and Draper (15–17) pointed out that the technique of counterstaining acid-fast preparations with soluble blue instead of methylene blue increased the intensity of non-bacterial components in preparations of *M. leprae*, a most useful technique for workers involved in bacterial purification. Seydel, *et al.* (18–29) elegantly demonstrated that dapsone acts as a synthetase inhibitor in the folate synthesizing enzyme system of *E. coli* and probably acts that way in *M. leprae*. Bjune (30–40) meticulously examined the responses of 157 BT patients in the lymphocyte stimulation test and pointed out the complexities which must be considered in interpreting such results. Chandi, *et al.* (41–47) shared their clinical and histopathological observations on 30 cases of "nerve abscesses" in leprosy, and arguing that the vast majority of the cases are not true abscesses, proposed the new term "segmental necrotizing granulomatous neuritis of leprosy." Mukherjee, *et al.* (48–50) lucidly described leprous phlebitis occurring in lepromatous cases and pointed out that the condition is not as rare as was previously thought. Lechat, *et al.* (51–61) proposed a simplified information system for leprosy (OMSLEP), provided detailed forms for such recordkeeping, and explained the ability of such a system to permit evaluation of leprosy control efforts.

In a guest editorial, Convit, *et al.* (62–65) succinctly summarized their exciting clinical observations on the use of a mixture of heat-killed *M. leprae* and viable BCG, commented on the implications of their findings regarding the basic immunologic defect in leprosy, and advocated this vaccination procedure for leprosy-susceptible individuals in endemic areas. In a Letter to the Editor, Skinsnes (71–73) provided glimpses into leprosy work in mainland China.

The current literature section of the March issue noted an authoritative clinical article by Pernambuco, *et al.* (90) on the arthritis of erythema nodosum leprosum. Alonso, *et al.* (92) reported an interesting serological test for anti-*M. leprae* antibod-

* Numbers in parentheses refer to page numbers of the INTERNATIONAL JOURNAL OF LEPROSY, Volume 48.

ies of the IgG and IgM class using peroxidase labeled antisera and measuring bound enzyme activity. The stimulating article by Convit, *et al.* (93) detailing their observations on Mitsuda-negative patients with indeterminate leprosy, bacteriologically negative lepromatous leprosy patients, and Mitsuda-negative contacts treated with a mixture of autoclaved armadillo-derived *M. leprae* and living BCG was noted. Lai A. Fat, *et al.* (93–94) showed with a sophisticated *in vitro* skin culture system that IgG is produced locally in the skin lesions of leprosy patients, particularly in lepromatous cases. Mehra, *et al.* (94) reported that lepromatous leprosy patients but generally not tuberculoid cases had suppressor cells in their circulation, that these cells were activated by lepromin *in vitro,* and that these cells were of two types, adherent cells and T lymphocytes bearing Fc receptors for IgG (the so-called Tγ cells). Stoner (94) put forth the thought provoking hypothesis that immunologic unresponsiveness in lepromatous leprosy might be due to a continuous leakage of bacilli into the circulation from a primary focus of intraneural infection. Wager, *et al.* (95) concluded that the platelet aggregation test is a sensitive indicator of IgG complexes in lepromatous leprosy, and its discriminatory power seems better than that of other tests for immune complexes in leprosy. Wall, *et al.* (95–96) demonstrated cell-mediated autoimmunity to testes in lepromatous leprosy patients, particularly those with testicular disease, and suggested that such an autoimmune mechanism might account for other manifestations of the disease, particularly some of the neurological manifestations. Kawaguchi, *et al.* (96–97) reported their very interesting observations that *M. lepraemurium,* cultivated *in vitro,* produced typical disease when inoculated into various strains of mice; that rough and smooth strains of *M. lepraemurium* could be separated during *in vitro* growth; and that the smooth forms of the bacillus seemed to have a lower pathogenicity than the rough strain, at least in some strains of mice. Lagrange (97–98) reported detailed immunopathologic studies in C57BL/6 and C3H mice with different capacities to develop cell-mediated immunity to *M. lepraemurium.* Rea, *et al.* (98) found elevations in serum angiotensin-converting enzyme in armadillos with disseminated leprosy and suggested this test as a means of evaluating armadillos for clinical leprosy. Leiker (100, 100–101) definitively reviewed the epidemiology of leprosy in the Netherlands from 1945–1975, concluded that leprosy behaves for practical purposes as a noncontagious disease in the Netherlands, and lucidly discussed the most likely reasons for this phenomenon. Two articles, one by Bourgeois-Droin, *et al.* (87) in leprosy and another by Erickson, *et al.* (104) in Goodpasture's syndrome brought up the concept of treating severe erythema nodosum leprosum or Lucio's phenomenon with plasma exchange or plasmapheresis.

The June issue of the 1980 JOURNAL began with an authoritative original article by Abe, *et al.* (109–119) detailing the methodology of their fluorescent leprosy antibody absorption test, providing convincing evidence of its specificity, illustrating its usefulness together with lepromin skin-testing in following household contacts, and providing dramatic evidence that subclinical infections with *M. leprae* may be 200-fold more common in endemic areas than clinically apparent infections. Rea and Levan (120–125) suggest that anergy in leprosy may be a teleologically beneficial phenomenon to minimize the severity of hypersensitivity reactions and together with Bjune (30–40) bring up a perhaps somewhat clearer way of thinking about the immunology of leprosy, i.e., immune phenomena connected with resistance to infection with *M. leprae* or immunity on the one hand and immune phenomena connected with reactional or hypersensitivity responses to antigens of *M. leprae* on the other. Bechelli, *et al.* (126–134) reported definitive large-scale comparisons between armadillo lepromin and human lepromin in human subjects. Ridley and Ridley (135–139) reported detailed light and electron microscopic studies of a histoid leprosy lesion and concluded that the main cell type in the histoid nodule is a young, not well differentiated cell of the mononuclear phagocyte series; stimulated as regards proliferation but without enhancement of functional activation. Daver, *et al.* (140–148) and Dastur and Daver (149–158) reported elegant, detailed inves-

tigations of striated muscle in leprosy. Myopathic changes were demonstrated in lepromatous cases, and for the first time histochemical studies of striated muscle were performed in leprosy. Ultrastructural observations suggested that vascular lesions might be responsible for the myopathic changes, and the possible involvement of anti-muscle autoantibodies was suggested. Rojas-Espinosa, *et al.* (159–166) reported factors present in the serum of lepromatous leprosy patients which interfere with the ability of neutrophils and monocytes to phagocytize *M. lepraemurium* and suggested that such impairments in phagocytic function *in vivo* might help to explain the depressed overall inflammatory responses seen in lepromatous patients. In a series of papers by Mahadevan and Antia (167–171), Salgame, *et al.* (172–177), Birdi, *et al.* (178–182), Mukherjee, *et al.* (183–188) and Mukherjee, *et al.* (189–192), the effects of *M. leprae* on the biochemistry of its host cells were investigated. Viable but not autoclaved *M. leprae* reduced protein synthesis in lepromatous but not normal or tuberculoid macrophages *in vitro*. Lysates of lepromatous macrophages depressed protein synthesis in normal macrophages exposed to *M. leprae in vitro* and also interfered with *in vitro* lymphocyte blast transformation in response to *M. leprae*. Lepromatous macrophages showed decreased Fc receptors and a reduced ability to interact with lymphocytes after exposure to *M. leprae*. These observations led to the conclusion that lepromatous macrophages are defective and are unable to process antigens of *M. leprae* and initiate cell-mediated immunity. Schwann cells were infected with *M. leprae in vitro* and showed a lack of DNA synthesis, an inability to interact with axons and an inability to synthesize myelin. These observations suggested that a biochemical effect of *M. leprae* on Schwann cells may account for the defective myelinization seen clinically in leprosy patients.

In a guest editorial commemorating the tenth anniversary of the Armauer Hansen Research Institute, Harboe (193–205) provided the readership of the JOURNAL with an elegant review of the immunology of leprosy, pointing out and meticulously documenting the quite revolutionary changes which have come about in our understanding during the last decade, and sharing a wealth of insights and perspectives into past work and future directions.

In the current literature section of the June issue, Colston, *et al.* (222) reported that temporary exposure of *M. leprae* in mouse foot pad infections to ethionamide or thiacetazone can result in prolonged bacteriostasis but that efficacy is rapidly lost as the interval between doses is increased. Girdhar and Desikan (223) reported good clinical results with giving dapsone 100 mg daily combined with rifampin on a schedule of two 900 mg doses on successive days at monthly intervals for three months. Huikeshoven, *et al.* (223) reported preliminary experiments leading to a simple and sensitive ELISA inhibition technique for the quantitation of sulfones in body fluids. Barton (226) and Barton and McDougall (226) carefully demonstrated that the mucosa of the paranasal sinuses, particularly the maxillary antra, is involved in lepromatous leprosy and speculate that the large surface area of the paranasal sinuses may contribute to the large numbers of bacilli that are disseminated from the nose into the environment. Jopling, *et al.* (228) studied two dapsone treated lepromatous patients and suggested that the dorsum of the fingers is a favorable site for persister bacilli because it is cool and nerve bundles are more superficial than in most other areas. Noussitou (228–229) reviewed tuberculoid leprosy and cogently argued for studies of the long-term effectiveness of short-term chemotherapeutic trials for these cases. Pursley, *et al.* (229) suggested that some cases of Lucio's phenomenon may be caused by vascular damage due to direct invasion of *M. leprae* and not necessarily by leukocytoclastic vasculitis. Campinchi, *et al.* (230) provided very interesting observations which suggested intraocular antibody formation in leprosy patients who have enlarged corneal nerves. Mori and Kohsaka (232–233) cultivated seven strains of *M. lepraemurium in vitro*, isolated INH and rifampin-resistant strains, and reproduced murine leprosy when these *in vitro* grown organisms were inoculated into mice. Stevens (233) suggested that *M. leprae* and some other noncultivable microorganisms probably evolved in a time (600 million

years ago) when ambient oxygen tensions were on the order of 5–10 mm Hg and predicted that vigorous *in vitro* growth in pure culture will await the development of techniques which can maintain these low oxygen tensions at the microbial cell wall. Lagrange and Hurtrel (233–234) in studies of the BCG vaccination on murine leprosy in C57BL/6 and C3H mice concluded that higher natural resistance to pathogens and cross-reactive immunization with related microorganisms can interfere with the artificial immunization when living microorganisms are used. Bloom (239–240) reviewed an amazing variety of techniques utilized by parasites to evade destruction by the host's immune system and thereby chronically persist. The Tuberculosis Prevention Trial in Madras (242) reported the shocking finding that there was no evidence of a protective effect of BCG vaccination against tuberculosis in a study of 260,000 individuals followed for 7½ years.

In an original article in the September issue, Stoner, *et al.* (247–253) described an interesting technique utilizing crossed immunoelectrophoresis with intermediate gel to quantitate antibodies in patients' sera reacting with mycobacterial ribonucleoprotein. Ths antigen, common to most mycobacteria and numerous nocardia species, corresponds to the β precipitinogen of Navalkar, antigen no. 1 of *M. smegmatis*, and antigen no. 5 of *M. leprae*. Masuda and Scheinberg (254–259) studied *in vitro* peripheral blood monocyte function in leprosy patients, utilizing a variety of sophisticated techniques, and found that both tuberculoid and lepromatous monocytes showed evidence of being already stimulated *in vivo*. Monocytes from both tuberculoid and lepromatous patients showed diminished *in vitro* chemotactic activity and plasma from leprosy patients, particularly lepromatous patients, inhibited the chemotaxis of normal monocytes. Bjorvatn and Kronvall (260–266) analyzed different strains and species of nocardia for antigenic relatedness to *M. leprae* antigen no. 21, utilizing crossed immunoelectrophoresis and a lepromatous leprosy serum pool. *N. caviae*, but not four other nocardia species, shared antigen no. 21 determinants with mycobacteria. Fieldsteel and Levy (267–276) reported meticulous long-term experiments utilizing neonatally thymectomized rats as models for microbial persistence in lepromatous leprosy. In these animals, various regimens of dapsone and rifampin were capable of reducing the proportion of viable *M. leprae* below that which could be detected by passage into normal mice, but viable bacilli were still detectable by passage of larger inocula into neonatally thymectomized rats. Nomaguchi, *et al.* (277–284) cultivated *M. lepraemurium* in a variety of cell lines in tissue culture, pointed out the practical advantages of the agar suspension culture technique, and utilized these techniques to study the effects of drugs on the multiplication of these bacilli *in vitro*. The implications of these studies for the *in vitro* cultivation *M. leprae* are of considerable interest. Rea, *et al.* (285–290) studied detailed histopathology of the spleen from an early case of diffuse nonnodular lepromatous leprosy. Junqueira, *et al.* (291–297) studied nerve biopsies from ten leprosy patients, showed that there was a marked increase in collagen in these nerves, but that the localization of collagen types I and III remains the same as in normal nerves. Mathai, *et al.* (298–302) analyzed in detail the leprosy attack rates among the staff and students of their institution, which cares for large numbers of leprosy patients and for whom no isolation is practiced. They concluded that the staff and students at their institution do not carry any additional risks of acquiring leprosy. Frist (303–308) studied the attitudes of potential employers towards leprosy patients in the Bauru region of Brazil and showed that, while there is certainly employer prejudice towards leprosy patients, this prejudice is neither unique nor by any means insurmountable; the majority of employers are ready to accept the rehabilitated leprosy patient if he can do the job and if the employer can be convinced that he presents no contagion risk to others.

Huang (309–318) editorially provided a concise and orderly review of our knowledge on the mode of transmission of leprosy. This extensive review was the prize-winning essay in leprosy in the 1976 competition set up by the British Leprosy Relief Association and provides all of us with an opportunity to review and rethink our own concepts in light of the perspective

of a writer who has had neither the opportunity to have learned from, nor perhaps the misfortune to be prejudiced by, traditional teachings on this important subject. Rabello (318–321) editorially reviewed the polar concepts of hanseniasis, emphasizing the numerous Latin-American contributions to this very important area and authoritatively explaining the basis for the system of classification utilized by many Latin-American workers. This explanation emphasizes the fundamental importance of the immature (group I, incipient, uncharacteristic, indeterminate) group of patients in our thinking.

In the current literature section of the September issue, reference was made to the authoritative article by Girling and Hitze (344) on the variety of adverse reactions which can occur to rifampin. Saint-André, *et al.* (344–345) reported an interesting pilot study combining immunostimulation with repeated BCG, levamisole, or *N. perflava* lysate injections with chemotherapy in patients with various types of leprosy. Barton, *et al.* (345–346) reported an interesting case of documented borderline-tuberculoid leprosy, who developed a documented histoid leproma in the nose. McAdam (347–348) studied secondary amyloidosis in Papua New Guinea and found that lepromatous leprosy patients who developed amyloidosis were those who had recurrent ENL reactions. During these reactions there was elevation of the serum protein (SAA) related to the amyloid fibril protein (AA) and the height of the acute SAA response correlated with the severity of the inflammatory response. Colchicine, which is effective in preventing amyloid formation, apparently acts at a lysosomal level, does not prevent SAA elevations, and did not abolish the ENL reactions. Pacin and Fliess (348) reported elevations in SGOT and SGPT in tuberculoid and lepromatous patients with reactions. Antia, *et al.* (350–351) reported that early nerve fiber involvement in both tuberculoid and lepromatous leprosy patients consists of involvement of unmyelinated fibers and their Schwann cells, followed by small myelinated, and lastly by large myelinated fibers. Segmental demyelination occurs early and definite and typical nerve changes can be demonstrated not only in clinically uninvolved nerves in early leprosy patients but also in contacts of leprosy patients. Closs, *et al.* (350) showed that about 20 antigenic components of *M. leprae* could be demonstrated in crossed immunoelectrophoresis, utilizing rabbit antisera, and that lepromatous leprosy patients had antibodies against seven of these antigens all of which are widely cross-reactive with other mycobacteria. Melsom, *et al.* (352) found elevations of IgA in cord blood from babies delivered from mothers with active lepromatous leprosy, when compared to a control group and a group in which the mothers had tuberculoid leprosy. They suggested that this could indicate transfer of *M. leprae* or *M. leprae* antigens across the placenta into the fetus during pregnancy in lepromatous patients. Nath, *et al.* (352) reported that Con A pretreatment of lymphocytes *in vitro* generated suppressive activity which inhibited mitogen-induced transformation of autologous lymphocytes. Tuberculoid cases showed enhanced suppression while lepromatous patients showed a decrease in suppressive activity when compared to normals. Of interest, this loss of suppressive activity in lepromatous cases was restored during ENL. Rotberg (353–354) reviewed his theory of the N-Factor/Anergic Margin as it has become accepted in resistance and susceptibility to hanseniasis. Davey (357–358) reviewed newer information on the transmission of leprosy and the implications of this newer information in leprosy control efforts. Irgens (358–359) summarized monumental work on the epidemiology of leprosy in Norway over the span of a century. An interim report by Noordeen, *et al.* showed that DADDS was an effective agent in the chemoprophylaxis of leprosy. Terencio de las Aguas (361–362) reviewed the epidemiology of leprosy in Europe and pointed out the potential new problem of leprosy in Europe secondary to imported cases. Mahfouz, *et al.* (363) reported an interesting immunofluorescence test for antibodies in tuberculosis, utilizing polymerized old tuberculin, which could perhaps be adapted to leprosy work.

In the December issue, Shepard, *et al.* (371–381) reported meticulous and extensive studies in mice immunized with *M. leprae*. Heat-killed, intact *M. leprae* in a

dose of about 1×10^7 bacilli administered intradermally were found to be effective in immunizing these animals. The short term trypsin procedure, purification by the two phase polymer procedure, and irradiation in the doses used were not harmful, but a trypsin-chymotrypsin digestion step was sometimes harmful to the immunogenicity of the bacilli in these systems. Brennan and Barrow (382–387) provided interesting evidence that lipid antigens of *M. leprae* may be species-specific and suggested that mycosides of the A, B, or G variety are possible candidates for the role of specific antigens on the surface of *M. leprae*. Navalkar, *et al.* (388–396) performed detailed antigenic analyses of *M. vaccae* and showed that *M. vaccae* shares a number of antigens with both typical and atypical mycobacteria. It was not possible to demonstrate any particularly close relationship between *M. vaccae* and *M. leprae* in these systems and thus no evidence to suggest the use of *M. vaccae* as a possible antileprosy vaccine source. Balraj, *et al.* (397–401) methodically and carefully searched for patients with secondary dapsone resistant leprosy in their control area in South India and found an alarming crude prevalence rate of 2.3% of cases (33 of 1431 patients examined). These findings, confirmed by mouse foot pad testing, are particularly alarming in view of the well known excellence of the control work in this area for many years. Collins, *et al.* (402–407) clearly demonstrated that the Gomori silver methenamine staining method detected higher numbers of *M. leprae* (and *M. tuberculosis*) in smears of suspensions of heat-killed bacilli than the auramine method and the Ziehl-Neelsen method. Okada, *et al.* (408–413) provided evidence that Spurr's resin mixture was the most suitable embedding material for electron microscopic studies of lepromata and that dimethylformamide or dimethylsulfoxide was superior to propylene oxide as a substituter in preserving the ultrafine structures of leprosy bacilli. Leiniger, *et al.* (414–421) described detailed postmortem examinations of a young male chimpanzee with a naturally acquired disease that was similar to disseminated leprosy in man. The histopathologic features of the disease and the microbiological and antigenic properties of the acid-fast bacilli in the tissue of this animal indicate that *M. leprae* or an organism indistinguishable from it was the causative organism. Saoji, *et al.* (422–425) found an increased frequency of serum haptoglobin phenotype 0-0 in leprosy patients compared to normal controls. These authors (426–430) studied LDH isoenzymes in the skin of leprosy patients and provided exciting evidence that viable *M. leprae* contain isoenzymes of LDH which differ from those of the host and which can be relatively easily demonstrated in skin biopsy tissues. Kumar and Verghese (431–434) conducted an epidemiologic study of the prevalence of psychiatric disturbances among leprosy patients and found that leprosy patients, particularly long-term patients and those with physical deformity, are about one and one-half times more likely to develop psychiatric problems than normal individuals. The most common psychiatric problem encountered was depression.

In a timely guest editorial, Goihman-Yahr (435–439) reviewed the immunology of leprosy as it relates to the clinical and histologic features of the disease, the possibilities of vaccine development, the pathogenesis of reactional states, and the possibilities of immunologic contributions to the earlier diagnosis of leprosy.

In a Letter to the Editor, Warndorff (441–442) pointed out the practical pitfalls of arithmetically averaging BIs, a logarithmic expression, and of arithmetically averaging MIs when some sites show too few bacilli for accurate estimations of the percentage which stain solidly.

The current literature section of the December issue noted Rotberg's (460) well reasoned explanation for the strategy for control of hanseniasis (Phase III), which was inaugurated by the Brazilian Ministry of Health in 1976. Professor Rotberg explained the view that Phase I (compulsory isolation of patients) and Phase II (case finding, ambulatory treatment, integration, patient and public education, and attempted social rehabilitation) have failed. Phase III is based on the concepts that the worst aspect of the disease is social and psychological; removal of these psychosocial factors opens the way to more effective medical measures, and the psychosocial factor is in-

extricably bound to the term "lepra" or its equivalents. Das, *et al.* (462) reported the novel finding of immune complexes in the circulation of some leprosy patients containing dapsone and antidapsone antibodies. No evidence was found to suggest that these complexes play a role in ENL, however. The controversial report by Griciute and Tomatis (463) dealing with the possible carcinogenicity of dapsone in mice and rats was noted. Ji, *et al.* (463) provided insights into the sophisticated investigations being performed in China in leprosy research. Using Shepard's kinetic method in mouse foot pad infections with *M. leprae*, two Chinese herb medicines, diethyldithiocarbamate, and Antabuse® were inactive. Clindamycin, dapsone, B663, B628, rifampin, "phenylthiozole rifamycin," and prothionamide showed bactericidal activities. Duncan (465–466) found that babies of mothers with leprosy, particularly lepromatous leprosy, weighed less at birth, had smaller placentas, and grew more slowly than babies from healthy mothers. Ishihara (466) made the interesting clinical observation that calcium deposits can occur in the skin in longstanding lepromatous patients and speculated that this dystrophic *calcinosis cutis* probably occurred in tissues damaged by prolonged lepromatous lesions or repeated ENL. Lynch and Johnston (467) pointed out that 87% of presumably healthy British soldiers had palpable greater auricular nerves and that in 39% these nerves were both palpable and visible. They conclude that palpable greater auricular nerves *per se* are of limited significance. Wirawan, *et al.* (468) found coagulation abnormalities in most ENL patients, and these abnormalities return to normal after the episode of ENL. The scholarly review of immune reactions in leprosy by Bjune (469–470) was noted. Han, *et al.* (471) reported impaired mixed lymphocyte reactions in patients with active lepromatous leprosy and demonstrated that cells from these patients were impaired both in their ability to stimulate and to respond in this system. Active lepromatous patients had a plasma factor which could depress the reaction of normal cells. Hirschberg and Bergh (471), using mixing experiments *in vitro*, reported that macrophages from low responding (presumably lepromatous) patients could not effectively interact with lymphocytes from high responding (presumably tuberculoid) patients or high responding normal individuals to induce them to respond to *M. leprae*. Conversely, T-cells from low responding patients could respond to *M. leprae* antigens *in vitro* in the presence of macrophages from high responding patients or high responding individuals. The authors point out that a genetic macrophage defect, acquired macrophage defects due to the disease state, or the existence of suppressor macrophages in lepromatous patients could all explain these experimental findings. McGee, *et al.* (471–472) demonstrated that typical hypersensitivity granulomas (macrophage, epithelioid cell, giant cell granulomas surrounded by lymphocytes such as tuberculoid leprosy lesions) were dependent on antigen being presented in insoluble form in a sensitized animal. Melsom and Duncan (472) showed that antibodies against *M. leprae* antigen no. 7 consisted of both IgG and IgM classes in lepromatous leprosy patients. No IgM antibodies against *M. leprae* antigen no. 7 were detected in several cord sera from babies born of mothers with active lepromatous leprosy. Rea and Terasaki (473) were not able to demonstrate statistically significant differences in the frequencies of 16 HLA-A, 23 HLA-B, 5 HLA-C or 6 HLA-DR locus antigens in 57 Mexican leprosy patients compared to 174 Mexicans without leprosy. Singh and Nath (473–474) found significant reductions in a subpopulation of T-cells with receptors for the Fc portion of IgG (Tγ, regulator or suppressor T-cells) in bacillary positive lepromatous patients and normal levels of these cells in tuberculoid patients. They conclude that these regulator T-cells are observed when cellular immune responses are good (e.g., tuberculoid leprosy) but are lost in those patients showing a failure of cellular responses and the presence of irrelevant antibodies (e.g., lepromatous leprosy). Colston and Hilson (475) showed that 10% of *M. leprae* survived slow freezing and remained viable during storage in liquid nitrogen and during subsequent thawing. Wang and Huang (475) demonstrated the ability of ultraviolet light and natural sunlight to rapidly kill *M. leprae* in

suspensions. Martínez Domínguez, *et al.* (477) reported the detailed epidemiologic data available on leprosy in the Singu area of Upper Burma and pointed out the unique value of this information for future control activities. van Eden, *et al.* (478) reported additional data confirming their earlier findings that there is a preferential inheritance of HLA-DR2 by siblings affected with tuberculoid leprosy but not by healthy siblings nor by siblings affected with lepromatous leprosy. Tandon, *et al.* (480) described an enzyme-linked immunosorbent assay (ELISA) for the detection of PPD antibodies in tuberculosis patients, the principles of which might be applicable to leprosy.

The December issue included abstracts of the Fifteenth Joint Leprosy Research Conference of the U.S.-Japan Cooperative Medical Science Program held at Kagoshima, Japan. Nakamura and Yogi (490) observed massive growth of *M. leprae* inoculated into the upper lip of nude mice. Hastings, *et al.* (490–491) reconfirmed earlier workers' observations that *M. leprae* multiply well in nude mice. Fieldsteel, *et al.* (491–492) found that the congenitally athymic nude rat shows a more uniform and a more rapid and extensive dissemination of infection with *M. leprae* than neonatally thymectomized normal rats. Nakamura and Yogi (492) did not find evidence of dissemination or enhanced multiplication of *M. leprae* in congenitally asplenic mice. Shepard (492–493) critically reviewed statistical methods employed in evaluating results of mouse foot pad infections with *M. leprae*. Nishiura, *et al.* (493–494) extensively studied 4 nine-banded armadillos from Louisiana with a naturally-acquired leprosy-like disease. All four armadillos had lesions typical of those seen in experimental leprosy, but the mycobacteria in one animal did not produce typical foamy structures in nude mice and did not stain typically in the FLA-ABS test. Fukunishi, *et al.* (494) showed that the ultrastructural features in experimental armadillo leprosy lesions are quite similar to those of *M. leprae* in human lepra cells or nude mouse leprosy lesions. Kusaka, *et al.* (494–495) isolated and analyzed mycolic acids from *M. leprae* from infected nude mice, from armadillos with experimental leprosy, and from armadillos with naturally-acquired leprosy-like disease. Meyers, *et al.* (495–496) presented detailed findings consistent with naturally-acquired, borderline lepromatous to subpolar lepromatous leprosy in an adult female mangabey monkey. Tsutsumi and Gidoh (496) described a high performance liquid chromatographic method for the simultaneous analysis of dapsone, rifampin, clofazimine, and their major metabolites. Kohsaka, *et al.* (496–497) reported results suggesting that dapsone was not effective against the *M. leprae* used to infect their nude mice. Morrison, *et al.* (497–498) reported detailed structure activity relationships of a series of 2-acetylpyridine thiosemicarbazones utilizing inhibition of *in vitro* multiplication of *M. smegmatis*, ATCC 607, and *in vivo* multiplication of *M. leprae* in the mouse foot pad. Jacobson and Hastings (498) reported that approximately 20% of newly diagnosed leprosy patients at Carville harbor bacilli which can multiply in mice fed low concentrations of dapsone but that with one exception, those patients treated with dapsone monotherapy have generally shown a satisfactory clinical and bacteriologic response to date. Nakata and Ito (498–499) were not able to show any effects of dapsone or rifampin on antibody production or delayed-type hypersensitivity responses of mice to sheep erythrocytes. Tsutsumi, *et al.* (499–500) examined the effects of a variety of antileprosy drugs on various animal models of inflammation and cell-mediated and humoral immunity. Koseki, *et al.* (500) extensively correlated clinical and bacteriologic findings in their leprosy patients with the results of immunologic examinations in an effort to predict relapse. Abe, *et al.* (500–501) utilized the FTA-ABS test to detect subclinical infection with *M. leprae* in three villages in the Miyako Islands, a leprosy hyperendemic area of Japan. Results of the FTA-ABS test were found to be specific and correlated well with subtle clinical findings suggestive of leprosy. Assuming the percentage of positive FTA-ABS tests represents the infection rate, the general population in this area has at least a 15% infection rate, which is approximately 1000 times higher than the incidence rate of clinical leprosy in this area. Nelson, *et al.* (501–502) studied skin test responses to PPD and *Candida albi-*

cans in clinically healthy children of parents with leprosy and found evidence to suggest that these children may have subtle defects in their cell-mediated immunologic responsiveness. Sugiyama, *et al.* (502) reported an elegant analysis of the immunogenetic background of 408 Japanese leprosy patients by HLA and serum protein allotypes. HLA-B7 was significantly high, while BW22, BW54, and CW1 were significantly low in lepromatous patients, HLA-DR2 was significantly high, and DRW9 significantly low in both lepromatous and tuberculoid patients. Mehra, *et al.* (502–503) extended their work on suppressor cells in lepromatous leprosy patients, finding that the *M. leprae*-induced suppressor T cells in their system all belong to the TH_2^+ subset, and that lepromatous patients have elevated levels of I_a^+ T-cells, most of these I_a^+ cells T-cells being found in the TH_2^+ subset. Tokunaga and Nakamura (503) methodically demonstrated that C3H/He mice were low responders to BCG, that their decreased delayed-type hypersensitivity (DTH) responses were related to suppressor T-cells and to a lowered effectiveness of their antigen-containing macrophages in stimulating antigen-primed lymphocytes, and concluded that DTH to BCG is regulated by genes which are not linked to H-2 in these animals. Akiyama and Yamaura (503–504) explained their hypothesis that intracellular parasitism creates autoantigenicity of the infected host cells and that this autosensitization can be detected by the macrophage migration inhibition test (MIT). Liver cell extracts from athymic mice infected with *M. leprae* did not show evidence of these autoantigens by MIT, leading the authors to conclude that *M. leprae* do not behave as intracellular parasites in mice (at least in liver cells). Krahenbuhl, *et al.* (504–505) were not able to show activity with the synthetic adjuvant muramyl dipeptide (MDP) against mouse infections with *M. leprae*, *M. marinum*, or *Listeria monocytogenes* but showed clear protection against *Toxoplasma gondii*. Killed *Corynebacterium parvum*, on the other hand, was active in mouse foot pad infections with *M. leprae* or *M. marinum*. Gillis and Buchanan (505) reported the results of immunodiffusion precipitation reactions between lithium acetate antigenic extracts of 21 species of mycobacteria and a reference serum pool from human leprosy patients, which was absorbed with *M. vaccae*, *M. bovis*, and cardiolipin/lecithin. Clear cross-reactivity was demonstrated between *M. leprae* and both *M. lepraemurium* and *M. bovis* (BCG) in this system. Harada and Kasai (506) described histopathologic changes in leprosy skin lesions utilizing the periodic acid-carbol parasanilin and periodic acid-methenamine silver stains. Okada (506) reported electron microscopic changes in tuberculoid leprosy lesions and proposed the designation of subpolar tuberculoid ((TTs) to describe those patients who have originally had borderline disease and who now show typical TT lesions. Cheng (507) reported the effects of nucleic acid bases on the *in vitro* growth of *M. bovis*, BCG, and *M. lepraemurium*. M. Nakamura (507–508) found that the *in vitro* growth of *M. lepraemurium* was enhanced by dextran (MW 100,000), α-cyclodextrin, lecithin, cholesterol, liposome, and vitamins K_3 and B_{12}. Findings suggestive of possible multiplication of *M. leprae in vitro* were reported when dextran, liposome, vitamin K_3, and vitamin B_{12} were added to the base of the Nakamura system. Nomaguchi, *et al.* (508) reported encouraging results in attempts to cultivate *M. leprae*. In one experiment (out of three) up to 16-fold increases in the number of AFB were observed after 123 days of cultivation in A 31 cells using the agar suspension culture technique.

Clearly then, a great deal of information has appeared in the pages of the JOURNAL during 1980, and much of it has immediate relevance to our work. From a personal perspective, a number of general trends appear among the multitude of new facts available to us. Disappointments and discouragement come from reports of the lack of effectiveness of BCG in tuberculosis and the increasing prevalence of secondary dapsone resistant leprosy. On the other hand, clear progress is being made in a number of areas in microbiology, including attempts to cultivate *M. leprae*. *M. lepraemurium* is now being cultured with regularity and greater and greater degrees of sophistication. *M. leprae* has been found to contain LDH isoenzymes which are differ-

ent from those of the human host. It has become more clear that the methenamine silver staining technique demonstrates more *M. leprae* than routine acid-fast staining. In immunology, progress continues in the development and utilization of serologic tests in leprosy. More and more sophisticated antigenic analysis of *M. leprae* is being reported. Several lines of investigation point to serum factors in lepromatous leprosy patients, which are antiinflammatory and/or immunosuppressive. Mixtures of viable BCG and dead *M. leprae* have shown promise as immunostimulants in leprosy patients and as possible vaccines. Controversies are developing as to the presence of suppressor cells in leprosy patients and interpretations as to their role in the pathogenesis of the disease and their role in the hypersensitivity reactions occurring during the disease. More evidence is accumulating that monocytes and macrophages are defective in lepromatous leprosy. Biochemical effects of viable *M. leprae* on macrophages and Schwann cells have been presented. More information about the association between HLA antigens and leprosy is available. Subclinical infections seem to be much more common than we suspected a year ago. Evidence has appeared that babies of mothers with lepromatous leprosy may be exposed to *M. leprae in utero*. The possibility that *M. leprae* may exist outside an animal host has been put forth. Nonhuman primates with spontaneous leprosy-like disease have been reported. Clearer evidence for the mechanism of action of dapsone has been presented. Emphasis continues to be placed on combination chemotherapy in the treatment of multibacillary cases in an effort to reduce a growing problem secondary dapsone-resistant disease.

In the perspective of the JOURNAL, 1980 was a year of steady progress in a number of areas in leprosy, a year of consolidation and building on past knowledge, a year with a number of intriguing hypotheses and observations, and a year of promise. I look forward with impatient optimism to 1981.

—RCH

The JOURNAL is Late

We apologize for the late appearance of the December 1980 issue (48:4), which was mailed on 12 March 1981, and the present issue which will also appear some three months behind schedule. To some extent this has been due to unavoidable production delays at the printer, but, perhaps more importantly, it has been due to an unusually lengthy December issue (185 pp.), which included the U.S.-Japan Cooperative Medical Science Leprosy Research Conference and the Index for 1980. We are making every effort to accelerate our production schedule (within the limits of available material) and hope to be back on schedule by the December issue. We regret the inconvenience this is creating and appreciate your patience.

—RCH