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EDITORIALS

Editorial opinions expressed are those of the writers.

The 1989 JOURNAL—A Continuing Perspective

A steady stream of new information about leprosy continued in 1989. As reflected in the pages of the JOURNAL, the highlights of this progress deserve summation, emphasis, and to the extent possible, perspective.

In the Original Articles of the March issue, Mustafa and Qvigstad (1–11)* studied the responses of three CD4+ human T-cell clones raised against *Mycobacterium leprae.* The clones recognized at least 9 different epitopes on *M. leprae,* all recognized in the context of the DR locus. A given recombinant *M. leprae* antigen could mediate both proliferation and cytotoxicity from the same clone, both criteria being HLA-DR restricted. Job, *et al.* (12–19) suggested that 3 patients with single, nodular subpolar lepromatous skin lesions represent cases of inoculation lepromas. Kohli, *et al.* (20–23) found elevated urine levels of renal brush-border enzymes in newly diagnosed, uncomplicated lepromatous leprosy patients, implying preclinical renal tubular damage. Sinha, *et al.* (24–32) measured antibodies to an epitope on the 35-kDa antigen of *M. leprae* and to phenolic glycolipid-I (PGL-I) in lepromatous patients and found wide individual variations in treated as well as untreated patients. Ganapati, *et al.* (33–37) vaccinated children with BCG alone, BCG + killed *M. vaccae,* and BCG + killed *M. leprae.* Only BCG + killed *M. vaccae* significantly enhanced skin-test responsiveness to leprosin A. Stanford, *et al.* (38–44) presented additional evidence that vaccination with killed *M. vaccae* enhanced skin-test reactivity to leprosin A. Ghazi Saidi, *et al.* (45–53) found BCG + killed *M. vaccae* to be superior to BCG alone in villages with leprosy cases in inducing skin-test reactivity to leprosin A. Silva, *et al.* (54–64) found that the normal membrane of *M. leprae* is similar to other mycobacteria and is asymmetrical ultrastructurally. Abnormal, symmetrical membranes appear to result from freezing and primary fixation with aldehydes. Liu, *et al.* (65–72) described the peripheral nerve lesions in experimentally infected armadillos. Bacilli were found inside axons of unmyelinated nerve fibers and inside lymphatics.

In the Editorial section, Ramos, *et al.* (73–81) hypothesized that the immunologic spectrum of leprosy reflects a balance in T-helper cell populations activated by *M. leprae* and the lymphokines they produce. Hastings (81–102) reviewed the 1988 JOURNAL. Pfaltzgraff (103–109) inaugurated

* Numbers in parentheses refer to page numbers in the INTERNATIONAL JOURNAL OF LEPROSY, Volume 57, 1989.

the Clinical Notes section with a masterful discussion of the clinical management of leprosy reactions.

In the Correspondence section, Mistry and Antia (110–112) raised several questions regarding the interpretation of results from preliminary vaccine trials which were answered by Gill, *et al.* (112–113). McDougall (114) expressed caution in taking biopsies of peripheral nerves, while Jacob and Mathai (114–115) felt a somewhat more aggressive approach was justified. Ishaque (115–116) outlined the reasons that *M. leprae* is probably a microaerophilic organism.

The Obituary section noted the death of Ma Haide (George Hatem) of the People's Republic of China—a remarkable personality whose leadership in leprosy control will be felt well into the next century.

In the Current Literature section of the March issue, Ellard, *et al.* (128) found that approximately 75% of the prescribed daily clofazimine and dapsone doses were being taken by multibacillary (MB) patients treated with the World Health Organization (WHO) multidrug therapy (MDT). There was a marked correlation between self-administration of the two drugs. Noncompliant MB patients were therefore likely to be receiving only monthly doses of rifampin and clofazimine. Kar, *et al.* (129) and Pavithran (130) felt that 6 months of WHO MDT therapy may be inadequate for at least some paucibacillary (PB) cases. Nigam, *et al.* (130) reported a patient with rifampin-induced uterine bleeding. Zeis and Anderson (132) showed that the antiproliferative activity of clofazimine is due to its pro-oxidative and prostaglandin synthesis enhancing effects on human mononuclear leukocytes.

Ghorpade, *et al.* (133) reported a case of tuberculoid leprosy involving the hairy occipital area of the scalp. Guillet, *et al.* (133) observed that leukocyte alkaline phosphatase (LAP) activity progressively decreased from tuberculoid to lepromatous leprosy. Although likely epiphenomena, the LAP score might have predictive value for the evolution of indeterminate leprosy. Ramachandran and Seshadri (135) suggested that a trial of steroids may be useful to distinguish between relapse and reversal reactions. Sirumban, *et al.* (135–136) confirmed the validity of presently used combinations correct diagnosis of leprosy, especially the combination of a skin patch with loss or impairment of sensation. Soni (136) described a leprosy patient with excessive rhinorrhea in response to taste stimuli thought to be due to misdirection of regenerating nerve fibers following recovery from a facial nerve paralysis. Soni (136) emphasized the involvement of the paranasal sinuses in lepromatous leprosy.

Anderson, *et al.* (136) described two HLA-DR2-restricted, *M. leprae*-specific, helper T-cell clones derived from a tuberculoid leprosy patient which were activated both by a defined, *M. leprae*-specific epitope of the 65-kDa protein of *M. leprae* and a defined peptide of the HLA-DR2 chain itself. Bhatki, *et al.* (136–137) and Chirmule, *et al.* (137) described a 1,000,000 molecular weight glycolipoprotein from ICRC bacilli with a variety of immunologic properties which suggest it may be of value as a "subunit" antileprosy vaccine. Desai, *et al.* (137) detected lymph node mononuclear cells from lepromatous leprosy patients which responded significantly to viable *M. leprae.* Neill and Klebanoff (139) found that PGL-I and deacylated PGL-I from *M. leprae* could prevent bacterial killing by phagocytes, probably by acting as OH· scavengers. This could play a role in the intracellular survival of *M. leprae.* Sibley, *et al.* (140) showed that lipoarabinomannan (LAM) is a potent inhibitor of interferon-gamma-mediated macrophage activation, and thus may also play a role in the intracellular survival of *M. leprae.* Steinhoff and Kaufmann (141) found that *M. leprae*-specific CD8+ T lymphocytes could lyse *M. leprae*-infected, interferon-gamma-stimulated Schwann cells *in vitro.* The Schwann cells expressed class I, but not class II gene products of the major histocompatibility complex (MHC) after stimulation with interferon-gamma. van Schooten, *et al.* (141–142) studied the epitopes recognized by 38 *M. leprae*-reactive T-cell clones from two tuberculoid leprosy patients. Eight appeared to be *M. leprae*-specific, one of the specific epitopes being on the 36-kDa and the other specific epitopes being on the 65-kDa antigen of *M. leprae.*

Dhople and Osborne (142) found a mycobactin-like substance in chloroform extracts of Percoll gradient-purified, but not

in more crude preparations of, *M. leprae* from armadillo liver.

Moreno and Silveira (143) showed enhanced yields from *M. leprae*-infected mouse foot pads if the popliteal lymph nodes were removed 3 weeks before foot-pad inoculation.

Bhatki (144) reported that present survey methods to detect new leprosy cases in Bombay are not cost effective. Health education is a much more effective and efficient approach. Burgess, *et al.* (144) found that ELISAs for detecting antibodies to the PGL-I antigen of *M. leprae* were not able to detect a high proportion of PB leprosy patients without unacceptable loss in specificity. This limits the predictive value of these serologic tests in areas where a large number of the leprosy cases are PB cases. Chen (145) made the interesting observation that in Sarawak, Malaysia, leprosy and tuberculosis were significantly more common among longhouse dwellers with more extensive social contact than among single-house dwellers. Jesudasan, *et al.* (145–146) point out that MDT campaigns can cause dramatic falls in prevalence during the first 5 years as a result of discharge of cases during screening and shortening of the duration of treatment. Any impact of MDT on actual disease transmission will be much more gradual and will be reflected in declines in incidence rates and case detection rates. West, *et al.* (147) reported leprosy in six isolated residents of northern Louisiana, U.S.A., an area which previously has been free of indigenous leprosy.

Maurice, *et al.* (149) reported a patient with hairy cell leukemia who developed a disseminated *M. avium–M. intracellulare* infection. The mycobacterial infection responded dramatically to erythromycin. Uttley and Collins (151) found antagonism between ciprofloxacin and rifampin *in vitro* against *M. tuberculosis.*

The Congress Supplement of the March issue consisted of the transactions of the XIII International Leprosy Congress at The Hague, The Netherlands, and contained a wealth of information. Of particular interest were the careful summaries of the 13 Workshop Committees (275–302) outlining the current state of knowledge. A great deal of new information was contained in the 670 abstracts of the papers presented at the Congress.

In the June issue Original Articles, Katoch, *et al.* (451–457) reported their results with a slightly modified WHO treatment regimen in highly bacilliferous patients with treatment continuing until skin-smear negativity. By measurement of bacterial ATP, 16% of the patients appeared to harbor viable bacilli after 2 years of treatment and 5% after 3 years. After 4 years of treatment, 42% of the patients had become smear negative. Katoch, *et al.* (458–464) updated their results in PB patients treated with WHO MDT for 6 months vs WHO MDT for 6 months followed by 6 more months of dapsone 100 mg daily. Relapse rates were considerably higher with only 6 months' treatment. Abel, *et al.* (465–471) presented evidence for a gene controlling susceptibility to leprosy per se and a gene controlling susceptibility to nonlepromatous leprosy which might be different. Girdhar, *et al.* (472–475) reported two infants, one 4 months old with a healthy mother and one 2 months old with a mother with skin-smear-negative BT disease, both with histologically confirmed indeterminate leprosy. Max and Shepard (476–482) analyzed the losses in productivity due to leprosy deformities. Marolia and Mahadevan (483–491) found that macrophages from normal individuals produce reactive oxygen intermediates *in vitro* in response to live *M. leprae* and reduce their viability, and that macrophages from bacteriologically negative lepromatous leprosy patients did not. A delipidified cell-wall preparation of *M. leprae,* when added to mononuclear cell cultures from lepromatous patients, could induce the promotion of a soluble factor which, when added to lepromatous macrophages, could cause them to behave normally in response to challenge with live *M. leprae.* Rangdaeng, *et al.* (492–498) analyzed the cellular contents of blisters induced by suction over leprosy lesions over 4-day periods. Mononuclear cells predominated. The T helper: suppressor ratio was higher in BT than in BL and LL lesions at 48 hr. Patnaik, *et al.* (499–505) studied liver function tests and liver biopsies in leprosy patients in reaction. A full range of acute exudative changes were found and a spectrum of lesions evolving

into epithelioid cell granulomas were encountered. Mukherjee, *et al.* (506–510) found dermal lymphatic vessels both within and surrounding granulomatous areas in lepromatous lesions but only along the edges of the granulomas in tuberculoid cases. In lepromatous disease, the lymphatic lining cells contained lipid droplets, lysosomes, and numerous pinocytic vesicles. Both lymphocytes and histiocytes were seen transversing the walls of lymphatic vessels in both lepromatous and tuberculoid disease. Bacilli were rare in lymphatic endothelial cells compared to blood capillary endothelial cells.

In the Editorial section of the June issue, Birdi and Antia (511–525) masterfully reviewed the current knowledge of the macrophage in leprosy. In the Clinical Notes section, Pannikar, *et al.* (526–528) discuss the problems in differentiating relapse from late reversal reaction. Grosset and Ji (529–530) outline the criteria for controlled clinical trials to evaluate the anti-*M. leprae* effects of drugs. In State-of-the-Art Lectures from the XIII Leprosy Congress, Job (532–539) reviewed nerve damage in leprosy and Becx-Bleuminck (540–551) discussed the operational aspects of MDT, especially under field conditions.

The Obituary section included tributes to Zerihun Desta of Ethiopia (552) and Vilhelm Møller-Christensen of Denmark (553).

In the Correspondence section, Li and de Vries (554–556) tested the hypothesis that DQw1 molecules are the product of an HLA-DQw1-associated immune suppression gene which is responsible for the development of lepromatous leprosy. An *in vitro* lymphoproliferative response to *M. leprae* was seen in only 1 of 18 lepromatous leprosy patients when the cells were treated with a monoclonal antibody against a nonpolymorphic determinant of HLA-DQ. The response was not seen with monoclonal antibodies to HLA class I, DR, DQw3 or DQw1. Since only 1 of 18 lepromatous patients' cells responded in this fashion, it is unlikely that an HLA-DQw1-associated immune suppression gene explains the association between HLA-DQw1 and lepromatous leprosy. Waters (556–557) discussed the interpretation of publications on controlled clinical trials.

In the Current Literature section of the June issue Franzblau and Hastings (566) found anti-*M. leprae* activity with macrolides *in vitro,* with clarithromycin showing bactericidal activity in mice. Franzblau and O'Sullivan (566–567) reported structure-activity relationship in a series of phenazines against *M. leprae in vitro.* Girdhar, *et al.* (567) found that at most only 55% of patients were compliant in self-administering dapsone. Grugni, *et al.* (567) recommended that at least 12 months of MDT be given to PB patients.

Chatterjee, *et al.* (569) found that 76% of BL/LL patients had bacillemia with good correlation with the bacterial index (BI) of slit-skin smears. Janssen, *et al.* (591) reported two additional leprosy patients with positive HIV, one a bacteriologic relapse of lepromatous disease and one with a probable reversal reaction. Unfortunately, one can only expect that such cases will increase. Kumar, *et al.* (571–572) reported a significant and consistent elevation in high-density lipoprotein cholesterol in lepromatous patients. Ndiaye, *et al.* (572) pointed out that leprosy patients have difficulty maintaining adequate oral hygiene. Razack, *et al.* (572) presented an interesting case of multicentric reticulohistiocytosis simulating lepromatous leprosy. Singh and Choudhary (573) detected PGL-I antigenuria in 67% of PB and 100% of MB leprosy cases using a dot-ELISA. Yebra Sotillo, *et al.* (574) detected vascular calcifications and periosteal reactions in distal extremities of leprosy patients using soft X-rays.

Bach and Launois (574) reviewed the immune deficiency of lepromatous leprosy and concluded that there is probably an active suppression of IL-2-producing T cells by both suppressor-T cells and macrophages. Booth, *et al.* (575) described the use of a recombinant yeast expression vector to synthesize and secrete the 18-kDa antigenic protein of *M. leprae.* Cherayil and Young (575) cloned and sequenced a 28-kDa antigenic protein of *M. leprae.* Cree, *et al.* (575–576) studied secretory IgA anti-*M. leprae* antibodies in saliva and found lower levels among patients and their household contacts than among hospital contacts, suggesting that the mucosal immune response might be protective. Cree, *et al.* (576) studied a number of ELISAs and concluded that

none had more than 55% sensitivity at 95% specificity and that none were suitable for serodiagnostic use. Duggan, *et al.* (576–577) prepared human monoclonal antibodies using peripheral blood lymphocytes from a lepromatous leprosy patient and showed that there were crossreactions between a number of autoantigens and *M. leprae.* Antigenic mimicry may account for the expression of autoantibodies in leprosy patients. Kaplan, *et al.* (577–578) described the kinetics of positive tuberculin skin test responses in lepromatous patients. Karanth, *et al.* (578) demonstrated changes in cutaneous innervation patterns in leprosy patients with antibodies to neural markers, neurofilaments, neuropeptides, etc., by immunocytochemistry. Liu, *et al.* (578) showed that 6–18 months' chemotherapy markedly reduced endothelial bacillation and vasculitis in lepromatous (BL, BL/LL, and LL) patients. Moudgil, *et al.* (579) developed human B-cell lines from untreated lepromatous patients and showed that antibodies produced by these cell lines were specific for *M. leprae.* Muthukkaruppan, *et al.* (579) presented evidence that T-cell activation is impaired in lepromatous leprosy due to modulation of the CD2 receptor specifically by *M. leprae.* Rama, *et al.* (580) discussed the antigenic similarity of *M. habana* to *M. leprae* in serologic testing.

Clark-Curtiss and Docherty (583) described a 2.2 kilobase *M. leprae* DNA probe (pYA1065) which is specific for *M. leprae* and which can detect DNA equivalent to 4 $\times 10^3$ *M. leprae* in dot-blot hybridizations. Garsia, *et al.* (583–584) and Nerland, *et al.* (585) describe homologies between the *M. leprae* 70-kDa and 18-kDa proteins, respectively, with eucaryotic heat-shock proteins. Jagannathan, *et al.* (584) found a correlation between *M. leprae* viability by mouse foot pad and the *in vitro* macrophage Fc receptor assay. Nagesha, *et al.* (584–585) concluded that Petroff's method of concentration was superior to other methods in detecting and quantitating bacillemia in lepromatous patients.

Frankel (587) reported that only 8% of the 30–50 new cases of leprosy diagnosed per year in Hawaii occur in patients born in Hawaii. Radhakrishna, *et al.* (588) presented a mathematical study of the implications of an antileprosy vaccine trial in a population partially protected against leprosy by previous BCG vaccinations.

Bhattacharya, *et al.* (589) found various mycobacteria, including *M. tuberculosis,* to be sensitive to amoxycillin combined with clavulanic acid. Ha, *et al.* (590) produced pulmonary infections in mice with *M. lepraemurium.* Mehta and Khuller (592–593) protected mice against challenges with *M. tuberculosis* H37Rv by prior immunization with mycobacterial mannophosphoinositides complexed to methylated bovine serum albumin. The same authors (593) measured antibodies to mannophosphoinositides by ELISA and found the ELISA to be highly sensitive and highly specific for tuberculosis in general, except that antibodies to mannosides were also formed in lepromatous as well as tuberculoid leprosy patients. Sherman, *et al.* (594–595), with minor modifications, found commercially available DNA probes to be reliable in rapidly identifying *M. tuberculosis* complex, *M. avium* and *M. intracellulare.* Swartz, *et al.* (595–596) showed that peripheral blood mononuclear cells phagocytized *M. avium* and *M. chelonei* more than *M. tuberculosis, M. kansasii, M. fortuitum* and *M. gordonae* because the former, but not the latter, activate the alternative pathway of complement.

The September Original Articles section begins with an analysis of relapses in MB leprosy treated continuously with dapsone monotherapy by Kurz, *et al.* (599–606). There were 243 relapses observed in a total of 18, 941 person-years of observation, giving a crude relapse rate of 12.8 per 1000 person-years (95% confidence interval of 11.2 to 14.4 per 1000). Regularity of treatment during both bacteriologic positivity and bacteriologic negativity was associated with lower relapse rates. Regular treatment reduced relapses even after 7 years of bacteriologic negativity. Grosset, *et al.* (607–614) reported 22 mouse-foot-pad documented, rifampin-resistant MB cases among 39 patients who had relapsed after some period of treatment with rifampin, almost always as monotherapy. Katoch, *et al.* (615–621) analyzed the viability of bacterial populations from MB patients by ATP content, morphological index (MI), and fluorescein diacetate-ethidium bromide (FDA-EB) staining. ATP correlated with the MI but not with FDA-EB. Viable bacilli could be

detected by ATP, but not by MI, in some patients after 3 years of MDT. Li, *et al.* (622–627) treated 80 MB patients with MDT for 24–27 months. The patients improved clinically and bacteriologically both during treatment and for up to 33 months after treatment was discontinued. Tomioka, *et al.* (628–632) tested the *in vitro* microbicidal activity of a H_2O_2-Fe-mediated halogenation system for 60 minutes on *M. leprae* as measured by FDA-EB staining. The system did not affect the proportion of *M. leprae* staining green by FDA-EB but did seem to augment the decrease in green-staining organisms associated with *in vitro* exposure to clofazimine, dapsone, and ofloxacin. Yandava, *et al.* (633–640) studied *in vitro* responses of peripheral blood mononuclear cells from leprosy patients to pokeweed mitogen and Formalin-treated *Staphylococcus aureus* Cowan I. Lymphoproliferation was highest in lepromatous patients' cells. Spontaneous secretion of immunoglobulins was enhanced in cells from borderline and lepromatous patients. Herrera and Rojas-Espinosa (641–646) showed that the bulk of the lactate dehydrogenase that increases in the serum of mice infected with *M. lepraemurium* derives from the liver and corresponds to isozyme V. Sundar Rao, *et al.* (647–651) found an overall incidence of new cases among household contacts of leprosy patients of 4 per 1000 person-years at risk. Contacts of MB and PB cases had relative risks of 3–6 and 2–4 times the risk of leprosy in the general population, respectively. Khanolkar, *et al.* (652–658) used five monoclonal antibodies directed against antigens of *M. leprae* to study sections from biopsies from leprosy patients. All five antibodies stained tissues with a BI of 3+ or more. Staining occurred in macrophages but was not associated with individual bacilli. Job, *et al.* (659–670) demonstrated *M. leprae* in armadillo hepatocytes, Kupffer's cells, striated muscle cells, adrenal cortical and adrenal medullary cells, endothelial cells, and macrophages. The unique parasitism of parenchymal cells by *M. leprae* and the possible processing and presentation of *M. leprae* antigens by those cells may be related to aberrant immune responses to leprosy.

The Editorial section of the September issue contained the masterful review of immunological tools in leprosy control which was based on a State-of-the-Art Lecture at the XIII International Leprosy Congress by Fine (671–686). The practical values of immunogenetic tests, skin tests, and serologic tests for case prediction seem limited. BCG vaccination for tuberculosis control is undoubtedly reducing the number of leprosy cases. There is a clear need for the development and transfer of new immunologic technology from the laboratory to the field.

In the Correspondence section, Agrewala, *et al.* (687–690) demonstrated anti-dapsone antibodies in the globulin fractions of sera from high proportions of leprosy patients, the lowest (13%) among TT/BT and the highest (63%) in pure neuritic patients. Ghaswala, *et al.* (690–692) were unable to show differences in the binding of serum antibody to human peripheral nerve sonicate between normal healthy individuals and leprosy patients in an ELISA. Kato (693–694) commented critically on leprosy vaccination strategies. Thomas, *et al.* (695) presented a case of histoid leprosy occurring in association with multiple neurofibromatosis.

The Obituary section of the September issue noted with deep sadness the losses of Dr. Melville Christian of India and Professor Juan C. Gatti of Argentina.

The News and Notes section reported the presentation of the JALMA Trust Fund Oration Award in India to Professor V. N. Sehgal.

In the Current Literature section Balakrishnan, *et al.* (707) documented the hemolytic effects of dapsone. Ekambaram and Rao (708) described the dramatic reduction in caseload in North Arcot District, Tamil Nadu, in South India after patients complete MDT and are released from control. Hazra, *et al.* (708) reported 5 of 90 tuberculoid patients who showed reactivation of lesions 3–8 months after stopping 6 months of WHO MDT.

Meeran (709) found 33% of new leprosy patients in rural Zambia to be positive for HIV antibody compared to 50% of suspected tuberculosis patients, 11% of blood donors, and 5% of surgical patients. There thus appears to be an association between leprosy and HIV infection similar to the known association between tuberculosis and HIV infection. Mohan, *et al.* (710) reported 6 cases of the histoid variety of lepromatous

leprosy in children less than 12 years of age. Pavithran (711) described an interesting lepromatous patient who developed patches of vitiligo after each bout of ENL. The depigmented macules persisted after regression of the leprosy on chemotherapy.

Brennan (712) reviewed recent developments in defining the cell-wall carbohydrate and proteins of *M. leprae*. Desai, *et al.* (712–713) presented evidence that the ability of macrophages to kill *M. leprae* may be of greater importance than lymphocyte-mediated activation for protection against *M. leprae* infection. de Vries (713) showed that T cells from individuals with different HLA class II molecules react to different mycobacterial antigens, indicating that HLA class II molecules are the products of immune response (Ir) genes for mycobacteria. These genetically controlled differences in antimycobacterial T-cell reactivity may explain the association of certain HLA class II alleles with different clinical courses of mycobacterial infections and may have implication for vaccine development. Hunter, *et al.* (713) described the isolation and characterization of a highly immunogenic cell-wall-associated protein of *M. leprae*. Kalyanasundaram, *et al.* (714) found increases in CD4+ (helper/inducer) lymphocytes in ENL reactions. Kaplan, *et al.* (714) injected recombinant human interleukin-2 (IL-2) into the skin of bacteriologically positive lepromatous patients. Local reversal reactions resulted with local reductions in bacilli by approximately two logs. Lamb, *et al.* (714) reviewed the approaches to defining potentially pathogenic and protective T-cell epitopes in mycobacteria. Mehra, *et al.* (715) characterized cell-wall protein antigens of *M. leprae* using human T-cell clones. Greatest T-cell reactivity was seen against proteins of 7, 16, and 28 kDa M_r. Ramu (715) presented evidence that the late lepromin (Mitsuda) reaction may be an index of protective immunity; whereas the early lepromin reaction (Fernandez), which indicates delayed hypersensitivity, is not. Sasiain, *et al.* (715–716) found that the ability of *M. leprae* to induce suppressor activity *in vitro* was lower in lepromatous leprosy patients compared to tuberculoid and borderline cases. Sehgal, *et al.* (716) showed that C3 and factor B decreased and C3d increased during ENL, while C1q and C4 were unaffected. This indicates that the alternative but not the classical pathway of complement is involved in ENL. None of the complement components changed during type 1 reactions. Silva and Foss (717) found that peripheral blood mononuclear cells from some lepromatous leprosy patients were unable to produce tumor necrosis factor spontaneously or in response to potent stimulation *in vitro*. Tuberculoid cells either produced tumor necrosis factor spontaneously or did so in response to stimulation. Tuberculoid patients had high plasma levels of tumor necrosis factor in contrast to low plasma levels in lepromatous and in normal individuals. Singh, *et al.* (717) found that *M. habana* (*M. simiae*) was as effective as killed *M. leprae* in protecting mice against foot-pad infection with viable *M. leprae*. *M. vaccae* was ineffective and BCG was partially effective. Thole, *et al.* (717–781) provided a detailed analysis of B-cell and T-cell epitopes on the 65-kDa protein of BCG using recombinant antigens, a variety of T-cell clones, and monoclonal antibodies. The data suggested that the products of different HLA class II loci and alleles present different parts of the 65-kDa protein to the immune system. These techniques are capable of exactly defining epitopes relevant for the development of specific diagnostic tests or vaccines. Vachula, *et al.* (718) found less superoxide anion produced by peripheral blood monocytes stimulated by *M. leprae* when the cells were pretreated with PGL-I. This suggests that PGL-I is a modulator of phagocytic cell function. Wu, *et al.* (718–719) found a *M. smegmatis*-based ELISA to be reliable for the detection of antibody in leprosy.

Doherty, *et al.* (719) described an *M. leprae*-specific epitope on the 18-kDa protein of the bacillus. Grosskinsky, *et al.* (719–720) found an *M. leprae*-specific repetitive DNA sequence greater than 15-fold per genome equivalent. Wheeler (720) showed that *M. leprae* can synthesize pyrimidine *de novo* and suggested that the lack of pyrimidine synthetic activity in whole *M. leprae* could be due to strong feedback inhibition. Pyrimidines are incorporated as bases or nucleosides but not as nucleotides. Overall pyrimidine scavenging occurs at a slower rate and appears to be less important than purine

scavenging. Zainuddin, *et al.* (721) found two vectors based on *Escherichia coli* plasmids capable of being replicated in *M. smegmatis*. Nakamura and Yogi (721) showed that the genetic background of nude mice influenced the severity of infection with *M. leprae*.

Bagshawe, *et al.* (722) describe characteristics of a village in Papua New Guinea with an exceptionally high prevalence of clinical leprosy. Inherited factors seem to influence susceptibility. Chu, *et al.* (723) showed that sulfone treatment of MB patients reduced attack ratios in their descendants tenfold from 3.94 to 0.35 per 1000 person-years. Martinez, *et al.* (724) described a nine-banded armadillo in northeastern Argentina with natural leprosy. The acid-fast bacilli (AFB) were identified as *M. leprae* by the pyridine extraction, DOPA-oxidase, noncultivability, mouse-foot-pad growth pattern, and lepromin responses.

Birke, *et al.* (725) showed that stiffness of the metatarsophalangeal joint of the great toe with limited extension was associated with plantar ulceration of the great toe. Zheng, *et al.* (726) surveyed deformity and disability among leprosy patients and pointed out that bacteriologically arrested disease is not synonymous with the arrest of disability.

Dhandayuthapani, *et al.* (728) tested four rapid-growing and four slow-growing mycobacteria and found that each species had a distinct isoenzyme pattern for lactic dehydrogenase. Fine, *et al.* (728) pointed out the difficulties in reading the presence or absence of BCG scars in a population. Kaufmann (729) presented evidence that both CD4+ and CD8+ T lymphocytes are involved in protection against tuberculosis. Murphy, *et al.* (729) reported the successful treatment of two BCG vaccination abscesses with erythromycin. Parenti (730) felt that three classes of drugs are promising as new treatments for tuberculosis: spiropiperidyl rifamycins, the fluoroquinolones, and combinations of β-lactam agents and β-lactamase inhibitors. Ratcliffe (731) described two patients in whom amoebic disease was unmasked by corticosteroids. Vogelsang, *et al.* (732) reported that thalidomide is useful in graft-versus-host disease. Wong, *et al.* (732–733) showed that the addition of clavulanic acid to amoxycillin greatly improves its *in vitro* activity against *M. tuberculosis* and *M. bovis*. Youle, *et al.* (733) reported rapid healing of mouth ulcers in seven patients positive for HIV antibody after starting thalidomide.

In the Original Articles of the December issue, Chanteau, *et al.* (735–743) quantitated circulating PGL-I antigen and IgM anti-PGL-I antibodies in MB and PB patients before and during MDT. All MB patients were positive for PGL-I antigen (50–5000 ng/ml) and 96% were positive for antibody (titers 1000–64,000). Almost 90% of the antigen was cleared after 1 month's treatment, while antibody titers remained stable. Correlations could not be demonstrated between the number of bacilli in skin biopsies and either antigenemia or antibody titer. Gelber, *et al.* (744–751) measured antibodies to PGL-I and lipoarabinomannan (LAM) in 90 leprosy patients before and during chemotherapy. Ninety-one percent of untreated lepromatous patients had antibodies to both antigens and optical densities tended to fall in both ELISAs over the years of treatment, but with considerable variation. The utility of monitoring the rate of fall in serum antibodies appears limited clinically. Sampattavanich, *et al.* (752–765) surveyed 3014 household contacts of leprosy patients and compared them with 566 villagers from an endemic area and 605 from a nonendemic area in Thailand. FLA-ABS and Dharmendra lepromin positivities were significantly higher in household contacts than in the villagers. The FLA-ABS test showed a significant correlation with suspicious dermal and neural signs. Hasan, *et al.* (766–776) developed quantitative ELISAs for IgM and IgG antibodies to *M. leprae* soluble sonicate antigen and to the disaccharide synthetic epitope of PGL-I. Lepromatous (LL/BL) patients had 10- to 100-fold higher IgM antibodies to both antigens compared to controls. Mullins and Basten (777–787) found that the enhanced proliferation response by peripheral blood mononuclear cells to antigen following preincubation was an *in vitro* phenomenon dependent upon the culture conditions employed and was not specific to leprosy. The T-cell hyporesponsiveness in lepromatous leprosy to *M. leprae* does not appear to be on the basis of

receptor blockade. Mutis, *et al.* (788–793) used T-cell lines and T-cell clones to show that a peptidoglycan-protein complex purified from the cell wall of *M. leprae* contains most, if not all, of the antigens which stimulate *M. leprae*-reactive T cells in association with relevant HLA class II molecules, including some or all of the immunogenic portions of the 65-kDa protein of *M. leprae.* Desforges, *et al.* (794–800) measured IgM anti-PGL-I antibodies in MB patients (100% positive), PB patients (21% positive), household contacts (10%–14% positive), and controls of the same ethnic group (3%–4% positive). Seropositivity was more common in the younger household contacts. Lord, *et al.* (801–809) studied skin test responses to a series of tuberculins in close contacts of MB patients. The rate of acquisition of leprosin A positivity is associated with age and closeness of contact with MB leprosy. Positivity to leprosin A is not solely the effect of the degree of contact with the disease, however, and must also have a genetic or environmental element. *M. leprae* shows high infectivity yet causes comparatively low incidence of disease. Cartel, *et al.* (810–816) gave 25 mg/kg of rifampin to almost 6000 individuals living in the Southern Marquesas, individuals originally from these islands, and members of families from these islands in French Polynesia. About 5% of the population was seropositive for IgM antibodies against PGL-I. Nomaguchi, *et al.* (817–824) described the production and purification of recombinant 65-kDa protein of *M. leprae.* The recombinant 65-kDa protein was not protective for mice challenged in the foot pad with viable *M. leprae,* but it did result in high antibody levels.

The Editorial section began with Ell's (825–833) scholarly examination of two European descriptions of leprosy: that of Theodoric of Cervia who lived from 1205 to 1298 and that of Fracastorius who lived from 1478 to 1553. Many of the unusual claims made about leprosy can be validated in light of current knowledge. Watson (834–843) summarized the deliberations of the First Vaccilep Workshop held in Anandaban, Nepal, in March 1989. The participants reviewed recent progress in the immunology of leprosy and discussed future strategies for vaccine development. In the Clinical Notes section, Matthews (844–846) described the successful application of a health education model to obtain early and regular treatment of leprosy patients. In a State-of-the-Art Lecture from the XIII Leprosy Congress, Valencia (847–863) reviewed research on the social dimensions of leprosy.

In the Correspondence section, Prof. Rotberg (864–866) reviewed the "N-Factor/Hansen-anergic fringe" hypothesis for hanseniasis which he postulated in Brazil in 1937. Malkovsky, *et al.* (866–867) were not able to find evidence that human immunodeficiency virus type 1 (HIV-1) and *M. leprae* shared common antigenic determinants. Saha, *et al.* (867–870) reported that a large number of patients showed a sudden increase in serum ferritin levels at the onset of type 2 reactions and had an accelerated fall at the time of remission of the reaction. During type 1 reactions only a minority of patients had elevated serum ferritin but half of them did at remission. Ganguly, *et al.* (870–872) found elevated levels of soluble IL-2 receptors in the sera of all types of leprosy patients. Yamagami, *et al.* (873–874) noted that macrophages cultured from patients with progressive stages of leprosy formed aggregates *in vitro,* while macrophages from patients with quiescent leprosy were dispersed. Bapat (874–879) used discontinuous density gradient centrifugation to separate ICRC and GMC strains of acid-fast bacilli isolated from leprosy patients into two populations, a "light" fraction and a "heavy" fraction. Both fractions were acid fast. The "light" fraction but not the "heavy" fraction lost acidfastness after pyridine extraction, oxidized D-DOPA, was catalase negative, aryl-sulfatase positive, tellurite reduction negative, contained more PGL-I and did not grow on Lowenstein-Jensen medium. The author suggests that the "light" bacilli are similar to *M. leprae* and the "heavy" bacilli are *M. avium-intracellulare.* Rojas-Espinosa, *et al.* (879–882) saw no important histopathological changes in the kidneys of *M. lepraemurium*-infected mice despite marked deposition of both IgG and IgM in the glomeruli.

The tragic loss of Dr. C. M. E. Matthews (883) was noted.

The News and Notes section included Dr.

Joseph A. Ponniah becoming the new Director of the Schieffelin Leprosy Research and Training Centre in Karigiri, and Dr. Claire Vellut (884) receiving a well-deserved Honorary Doctorate from Louvain University.

In the Current Literature section of the December issue Turk and Rees (890) reviewed the implications of human immunodeficiency virus (HIV) infections on leprosy.

Choudhury, *et al.* (893) found that deoxyfructoserotonin and rifampin, but not dapsone, inhibited the attachment and/or uptake of *M. leprae* with cultured Schwann cells *in vitro.* Mester de Parajd, *et al.* (893–894) pointed out the value of deoxyfructoserotonin in the treatment of leprosy. van Brakel, *et al.* (894) have seen 22 relapsed patients out of 927 who have completed WHO MDT.

Arora, *et al.* (894) found cutaneous lesions of leprosy on male genitalia in 2.9% of the cases. Arora, *et al.* (894–895) saw palmar and/or plantar lesions in 18 of 500 patients examined. The lesions were usually macular, in TT, BT and BB cases, frequently associated with type 1 reactions, and usually were an extension of a patch from a surrounding area. Atkin, *et al.* (895) noted that many leprosy patients have arthritis. Nilsen, *et al.* (895–896) reported 8 patients who had paucibacillary leprosy of the skin and simultaneous multibacillary leprosy in nerve biopsies. Such cases raise questions as to the appropriate treatment regimen.

Boddingius and Dijkman (913) described an immunogold labeling method for demonstrating *M. leprae*-specific PGL-I antigen in glutaraldehyde-osmium-fixed and araldite-embedded lesions. Chanteau, *et al.* (897) found that anti-PGL-I antibody tests have poor predictive value in following household contacts of leprosy patients. *M. leprae* infection occurs frequently but is rarely followed by overt disease. Cho, *et al.* (897–898) had similar experiences, and both suggested the possible value of following PGL-I antigenemia for the early results of chemotherapy. Desforges, *et al.* (899) and Douglas, *et al.* (899) found reductions in IgM anti-PGL-I antibodies in leprosy patients under effective chemotherapy. Huerre, *et al.* (899–900) demonstrated PGL-I antigen in skin biopsies immunohistologically using an anti-PGL-I monoclonal antibody in 7 of 19 indeterminate cases. Janis, *et al.* (900) studied the role of gamma/delta T cells in the immune response to *M. tuberculosis.* The number of gamma/delta T cells increased greatly in draining lymph nodes of mice immunized with *M. tuberculosis*; a large proportion of them were activated *in vivo*; they responded to *M. tuberculosis in vitro*; but in contrast to *M. tuberculosis*-specific alpha/beta cells, the response of the gamma/delta T cells to *M. tuberculosis* did not require major histocompatibility complex class II recognition. The gamma/delta T cells may play a distinct role in generating a primary immune response to mycobacteria. Kaufmann, *et al.* (900) pointed out that CD8+ cells participate in the immune response to *M. leprae,* produce interferon-gamma, and lyse Schwann cells as well as macrophages presenting *M. leprae* antigens. Kaur, *et al.* (900–901) reported elevated levels of lymphocytotoxic antibodies in untreated leprosy patients of all types with a decrease after treatment. Ranade and Mahadevan (903–904) pointed out the possibility of using delipidified cell walls of *M. leprae* in an ELISA as a specific serodiagnostic reagent for lepromatous leprosy and as a means of monitoring the effectiveness of chemotherapy in lepromatous patients. Silva and Foss (904–905) reproduced some aspects of the histopathologic lesions of leprosy *in vivo* using a glycolipid fraction of human *M. leprae* containing trehalose and mycolic acids. Torgal-Garcia, *et al.* (905) showed a sensitivity and specificity of a PGL-I-based ELISA to be 91.7 and 91.8 in MB and 35.0 and 91.7 in PB leprosy patients, confirming the limited value of PGL-I-based serology in case finding in areas with high incidences of PB cases.

Bharadwaj, *et al.* (905–906) found *M. leprae* synthesis of ATP to be better at pH 6.0 to 6.5 and at 30°–33°C incubation in modified Dubos and Sauton's media than at higher pH or temperatures. Gicquel, *et al.* (906–907) and Jacobs, *et al.* (907) described techniques to introduce foreign DNA into mycobacteria. Katoch, *et al.* (907) used ribosomal RNA to identify restriction fragments of DNA containing ribosomal RNA gene sequences. Characteristic patterns were

found with several cultivable mycobacteria and *M. leprae*. Lugosi, *et al.* (907–908) introduced and found stable expression of foreign DNA in BCG on a plasmid vector. Nakamura and Kohsaka (908) lyophilized *M. leprae* and showed 2 to 3 logs loss of viability but sufficient remaining viability so that multiplication occurred in nude mouse foot pads with more than 10^5 bacilli. Vishnevetsky, *et al.* (909) used primary explant cultures of *M. leprae*-infected lepromas as a means of testing antileprosy activity of drugs. Williams and Gillis (909) found that restriction fragment length polymorphism (RFLP) analyses of chromosomal DNA of *M. leprae* from a variety of sources were all identical, suggesting possible homogeneity among members of the species.

Vishnevetsky, *et al.* (910) reported enhanced multiplication and the development of disseminated disease in *M. leprae*-inoculated CBA mice with an induced deficiency of their mononuclear phagocyte system.

Brown, *et al.* (913) found elevated serum levels of soluble IL-2 receptors in all 20 tuberculosis patients prior to treatment and in a majority of patients after as much as 3 months of treatment. Levels of soluble IL-2 receptors may distinguish active cell-mediated immune responses from immunologic memory. David, *et al.* (914) described rapid incorporation of ^{3}H-methyl methionine radioactivity on the surface lipids of *M. avium*. Gorzynski, *et al.* (915–916) found temafloxacin, ofloxacin, ciprofloxacin, and clarithromycin active against *M. tuberculosis in vitro*. Mukhopadhyay, *et al.* (918) reported selective delivery of methotrexate coupled to maleylated bovine serum albumin to macrophages via "scavenger" mechanisms with selective killing of intracellular leishmania. Nikolayan, *et al.* (918) suggested that HLA-DR2 was a risk factor for the development of tuberculosis and that its presence could indicate an unfavorable outcome of the disease.

From a personal perspective some trends can be identified. The historical aspects of leprosy as described by European authorities in the 13th and 16th centuries provided a fascinating glimpse into medicine in those times. In contrast, HIV infections today threaten our most scientific approaches to the control of mycobacterial diseases.

Multidrug therapy (MDT) continues to be the mainstay of treatment. Compliance remains less than ideal. Increasingly, 6 months of MDT for paucibacillary patients is being reported as inadequate with 12 months' treatment giving better results. Results with MDT for multibacillary cases continue to be satisfactory in general, although it is not clear how many patients are receiving MDT until bacteriologic negativity and how many are being treated for only 2 years. Obviously, when patients are being removed from caseloads as they complete MDT, these caseloads fall, and since most cases are paucibacillary these caseloads can fall dramatically. If prevalence is redefined as active caseload rather than total known active and inactive cases, as it was in the past, the impression can be given that MDT has resulted in dramatic falls in disease prevalence. More sophisticated techniques are being used to monitor the metabolic status of *M. leprae* and to follow the effects of drugs on these metabolic pathways *in vivo* and *in vitro*. The fluoroquinolones, minocycline, and clarithromycin show promise *in vitro* and in mouse foot pad infections and are being tested clinically. Deoxyfructoserotonin continues to be of interest. In multibacillary patients beginning chemotherapy, PGL-I antigenemia seems to disappear at about the same time as bacillemia disappears. Antibodies to PGL-I and to LAM tend to fall over time with chemotherapy but with sufficient variability to make questionable the value of serial serologies in following an individual patient.

In the clinical sciences, evidence was presented that uncomplicated lepromatous patients have subtle renal tubular damage. A tuberculoid patient was described with a lesion involving the hairy scalp. Two infants, 2 months old and 4 months old, were reported with indeterminate leprosy, raising a number of questions about the mode of transmission and incubation period of the disease. Differentiating relapse from late reversal reaction in treated paucibacillary patients continues to be a problem. Leprosy patients are being reported with positive HIV serologies at higher rates than the general population. An interesting case of histoid leprosy occurring in association with multiple neurofibromatosis was reported.

Abrupt changes in serum ferritin occur in association with ENL reactions.

Much emphasis continues on the immunology of leprosy. CD4+ human T-cell clones recognize multiple epitopes on *M. leprae,* all in the context of the DR locus. More evidence is accumulating for genetic susceptibility to leprosy per se and to susceptibility to nonlepromatous leprosy. We are reminded that the "N-Factor/Hansen anergic fringe" hypothesis predicted such findings in 1937. HLA class II molecules seem to be products of immune response genes for mycobacteria. The association between HLA-DQw1 and lepromatous leprosy does not seem to be due to an HLA-DQw1-associated immune suppression gene. The role of gamma/delta T cells, which respond to antigen but do not require MHC class II recognition, awaits further definition in leprosy. BCG plus killed *M. vaccae,* more than either component alone, enhances skin-test reactivity to leprosin A in humans. Both PGL-I and LAM inhibit bacterial killing by macrophages. *M. leprae*-infected, interferon-gamma-stimulated Schwann cells can be lysed by *M. leprae*-specific CD8+ T lymphocytes. At reasonable specificities, existing serologic tests seem to lack sufficient sensitivities to be suitable for serodiagnostic use in PB cases. Quantitative ELISAs have been developed for leprosy serology. Several laboratories are cloning and sequencing proteins of *M. leprae* and defining B-cell and T-cell epitopes. Cell-wall carbohydrate and protein antigens are being defined. Crossreactions between *M. leprae* antigens and autoantigens may account for autoantibodies in lepromatous patients. Parasitism of parenchymal cells by *M. leprae* may be related to aberrant immune responses in the disease.

In microbiology, confirmed cultivation of *M. leprae* remains elusive. More is being learned of the metabolism of the organism and newer methods of following its metabolism have been put to use. It is probably microaerophilic and may contain a mycobactin-like substance. More sensitive methods for detecting *M. leprae* are being developed, such as PGL-I antigen detection, DNA probing, and polymerase chain reactions (PCR) based on *M. leprae*-specific DNA segments. There are numerous homologies between *M. leprae* proteins on the one hand and eucaryotic heat-shock proteins on the other, perhaps confirming the antigenic mimickry demonstrated immunologically. The organism is capable of synthesizing pyrimidines *de novo* but does not do so, scavenging them instead, perhaps due to feedback inhibition *in vivo.* The suggestion was made that ICRC bacilli may be a mixture of two populations, *M. leprae* and *M. avium-intracellulare.* By restriction fragment length polymorphism (RFLP) analyses of chromosomal DNA, all *M. leprae* isolates appear identical.

In experimental infections, enhanced yields of *M. leprae* can be obtained from foot pad infections in normal mice by removing the popliteal lymph nodes prior to inoculation. Enhanced multiplication with dissemination was reported in mice with an induced deficiency of their mononuclear phagocyte system.

In epidemiology and prevention, health education was found in one location to be the most cost-effective means of detecting new cases. The true measure of the effectiveness of MDT on disease transmission will be gradual and will be reflected in declines in incidence rates and case detection rates, and not in changes in caseloads. A nine-banded armadillo with natural leprosy was described in northeastern Argentina, raising the possibility of the natural disease existing in nine-banded armadillos throughout South and Central America as well as in parts of North America. Single-dose rifampin chemoprophylaxis has been given to an island population in French Polynesia in a novel approach to interrupt transmission.

In other mycobacterial diseases, a number of findings are of interest to leprosy workers. Antagonism between ciprofloxacin and rifampin *in vitro* against *M. tuberculosis* could prove significant in *M. leprae* infections. Mycobacterial species which directly activate the alternative pathway of complement (which *M. leprae* seems to do both *in vitro* and in ENL patients) are phagocytized more readily than those species which do not. As in leprosy, there is interest in newer chemotherapeutic agents in other mycobacterial diseases, particularly beta-lactam agents in combination with beta-lac-

tamase inhibitors, macrolides, and fluoroquinolones.

Clearly, 1989 was a productive year and much more new information is now available. As in every year, there is never enough information. Compared to present resources and present information, are there better drugs or better drug combinations or better durations of treatment? Are there better ways to diagnose and follow patients or better means to prevent or reverse neuritis? Do we know enough to produce a better vaccine? Do we know enough about *M. leprae* to make new attempts at cultivation so that we can then learn how to prevent or reverse its attack on peripheral nerves, its persistence despite chemotherapy, etc., etc., etc.? There is so much to be done. I look forward with impatient optimism to 1990.—RCH