

The 1986 JOURNAL—a Continuing Perspective

Many exciting developments have taken place in leprosy in 1986. Research progress is accelerating and better approaches to the management of patients are being sought on several fronts. It again seems appropriate to review the year's progress in leprosy as reflected in the pages of the JOURNAL.

In the March issue, Kvach, *et al.* (1–10*) developed a rapid buoyant density centrifugation procedure using Percoll to isolate and purify *Mycobacterium leprae* from armadillo liver. Temperature-dependent, 2,4-dinitrophenol-sensitive, ATP synthesis occurred in these purified *M. leprae* within minutes. Clofazimine increased the rate of decay of *M. leprae* ATP *in vitro* in direct proportion to drug concentration. Shepard, *et al.* (11–15) reported that all of 73 strains of *M. leprae* tested for dapsone sensitivity in mouse foot pads prior to 1977 were inhibited by 0.0001% w/w dietary dapsone. Almeida, *et al.* (16–20) studied relapses in LL and BL patients who had attained smear negativity on dapsone monotherapy. Regularity of treatment during smear negativity, but not during smear positivity, was associated with lower relapse rates from the fourth year of smear negativity onward. The suggestion is made that beyond the first 3 years of smear negativity sources of bacilli outside the patient may be more responsible for relapse than the patient's own bacilli in a leprosy-endemic area. Huikeshoven and Madarang (21–24) studied a urine spot test for dapsone and concluded that its sensitivity was adequate for the monitoring and management of patient compliance in leprosy control programs. Ponnighaus and Fine (25–37) compared the ability of BCG alone and two different doses of killed *M. leprae*, with or without BCG, to induce skin-test reactivity to soluble antigens of *M. leprae*. All the vaccines caused local ulcers in most subjects, and each induced significant rates of skin-test conversion. Garraud, *et al.* (38–45) studied T-cell subsets and anti-*M. leprae* antibody in leprosy patients. Untreated,

nonreactional lepromatous patients showed moderate decreases in the percentages of OKT3+ (“pan-T”) and OKT4+ (“helper/inducer”) cells with a decrease in the OKT4+ : OKT8+ (“cytotoxic/suppressor”) ratio; these abnormalities disappearing within 9 months of treatment. Erythema nodosum leprosum (ENL) was associated with a transient decrease in the percentage of OKT8+ cells with an increase in the OKT4+ : OKT8+ ratio. Narayanan, *et al.* (46–51) analyzed 24 hr skin reactions in tuberculoid patients to the purified soluble antigen of *M. leprae*, Myl. The predominant lymphocytes in the infiltrates were activated T lymphocytes expressing OKT11, Leu3a, OKT8, and Ia-like antigens. Balybin and Naumov (52–56) studied the relationship between basal or resting lymphocyte cyclic nucleotides and the response of the lymphocytes to PPD and PHA in the lymphocyte blast transformation test. In normal individuals' lymphocytes, higher levels of cyclic GMP were associated with higher levels of responses to PPD. In contrast, with lepromatous leprosy patients' lymphocytes, higher levels of cyclic GMP were associated with lower PPD-induced blast transformation. Chirmule, *et al.* (57–62) administered ICRC antileprosy vaccinations to langur monkeys and found that the majority of them converted their lepromin test after vaccination. Douglas-Jones, *et al.* (63–70) demonstrated that a number of mycobacteria act as polyclonal B-cell mitogens and pointed out the potential difficulties this could create for *in vitro* investigations into specific immune responses to antigens of these bacteria. Band, *et al.* (71–78) failed to demonstrate any *M. leprae*-specific uptake system in Schwann cells using either a rat Schwannoma cell line 33B or rat sciatic nerve-derived Schwann cells. Chandi and Chacko (79–83) injected living *M. leprae* near the site of crushing of rabbit tibial nerves and suggested that trauma may weaken the perineurial barrier and allow the penetration of *M. leprae*-laden phagocytes into the endoneurium of peripheral nerves. Harada and Suzuko (84–87) described a periodic acid-ethanol gelatin methenamine

* Numbers in parentheses refer to page numbers in the INTERNATIONAL JOURNAL OF LEPROSY, Volume 54, 1986.

silver stain for the simultaneous demonstration of *M. leprae* and myelin in peripheral nerves of leprosy patients.

In the Editorial section of the March issue, Hastings (88–108) reviewed the contents of the 1985 JOURNAL.

The Obituary section of the March issue noted the passing of two giants in the field of leprosy, Dr. Robert G. Cochrane (109–119) and Dr. Herbert H. Gass (120–121).

In the Correspondence section, Floch (122–125) discussed the reported shortcomings of dapsone monotherapy and recommended two approaches to the prevention of dapsone resistance, the use of dapsone in doses of 200 mg per day and the implementation of multiple drug therapy. Gelber (125–127) reported a case of acute glomerulonephritis and renal failure in a lepromatous leprosy patient with ENL. Ramadan, *et al.* (127–129) presented two cases from Egypt of epithelioma cuniculatum superimposed on leprotic plantar ulcers. Kazda (129–131) presented evidence that mild sonication of the suspension of viable *M. leprae* used to inoculate armadillos results in a more disseminated infection with higher yields than that following the use of unsonicated inocula. Cree, *et al.* (131–132) described an armadillo that developed sudden respiratory collapse after trans-Atlantic shipment. Shetty and George (133–135) grafted nerves from leprosy patients into immunosuppressed mice and observed their behavior over the next 2 to 6 months. Damavandi and Mehta (135–137) infected endothelial cell cultures with *M. leprae* and found the cells to be phagocytic toward live bacilli, while irradiated bacilli were mainly seen extracellularly. Levy (137–140) reported results of mouse foot pad drug sensitivity testing of *M. leprae* from a patient reported to have clofazimine-resistant disease [IJL 50 (1982) 139–142]. After several passages, the bacilli were found susceptible to 0.001% and resistant to 0.0001% w/w dietary clofazimine.

The News and Notes section of the March issue included the well-deserved Damien-Dutton Award to Dr. John H. Hanks (141–142).

The Book Review section contained reviews of *Histoid Leprosy* by Sehgal and Srivastava and *A Practical Guide to the Di-*

agnosis and Treatment of Leprosy in the Basic Health Unit, 3rd ed., by Wheate and Pearson.

In the Current Literature section of the March issue, Ambrose, *et al.* (149) presented further evidence for the antileprosy activity of deoxyfructose serotinin. Orege and Owili (149) reported a maximum prevalence rate of 7/1000 for dapsone resistance among lepromatous leprosy patients in Kenya. Pareek and Tandon (150) reported a patient with tuberculoid leprosy with an epididymal lesion thought to be due to the disease. Saha, *et al.* (151) found significant elevations in plasma fibrinogen and fibrin degradation products in patients with lepromatous leprosy, especially with ENL, compared to controls and suggested that there is an ongoing occult fibrinolysis during ENL. Abou-Zeid, *et al.* (152) analyzed the antigens of leprosy-derived corynebacteria and found that the cell wall polysaccharide corresponds to the main thermostable cytoplasmic antigen, M₁, and crossreacts with antigen 60 of BCG and antigen 7 of *M. leprae*. Bottasso, *et al.* (152) studied healthy close contacts of lepromatous leprosy patients and found that both the Fernandez and Mitsuda, but not PPD, reactivities decrease with time of exposure. Douglas-Jones and Watson (153) demonstrated genetic control of murine T-cell proliferative responses to *M. leprae*. Izumi, *et al.* (154) demonstrated the presence of *M. leprae*-specific phenolic glycolipid in Formalin-fixed liver tissue from a patient with advanced lepromatous leprosy. Kaplan, *et al.* (154–155) studied *in vitro* T-cell responses in lepromatous leprosy and concluded that some lepromatous patients have low levels of responsiveness to *M. leprae* and that these responses can be enhanced with interleukin-2 (IL-2) or with monocyte depletion. Other lepromatous patients are nonresponsive to *M. leprae* and this nonresponsiveness cannot be reversed with these maneuvers. Lowe, *et al.* (155) adoptively transferred cells from immunized donor mice to sublethally irradiated recipients. *M. leprae*-sensitized, but not BCG-sensitized, cells inhibited the growth of *M. leprae* in the foot pads of recipient mice. Martinez and Sanchez (155) reported two patients with lepromatous leprosy who were treated with

weekly infusions of leukocytes for 12 weeks. One developed a reversal reaction and the other experienced improvement in chronic ENL. Rojas-Espinosa, *et al.* (155–156) demonstrated immune complexes in the wall and periphery of dermal blood vessels in 4 ENL and 4 Lucio phenomenon cases. Swinburne, *et al.* (156) found that a strain of *M. vaccae* was capable of immunizing mice sensitized subcutaneously or orally and speculated that people who become sensitized to *M. vaccae* or certain other environmental mycobacteria might be expected to show some resistance to leprosy. Tausk, *et al.* (156) found reduced numbers of receptors for the C3b fragment of complement on the erythrocytes of lepromatous leprosy patients, a condition which could, in part, result in an impaired ability to correctly process circulating immune complexes. Watson, *et al.* (157) reported that peripheral blood mononuclear cells from 5 of 13 lepromatous leprosy patients failed to produce IL-1 even after stimulation with lipopolysaccharide. Wu, *et al.* (157) presented data indicating that dried blood from the earlobes can be used instead of venous blood for the fluorescent leprosy antibody absorption (FLA-ABS) test. Young, *et al.* (157) developed a simple spot test for the detection of antibodies to the PGL-I antigen of *M. leprae*. Young, *et al.* (157–158) detected PGL-I in the sera of patients with lepromatous leprosy who had received treatment for 1 month or less. There was a marked reduction in circulating PGL-I shortly after the initiation of therapy. Kato (158–159) reported the growth of acid-fast organisms from host-grown *M. leprae* and cultures of "*Mycobacterium X*" cultivated in propane-tetradecane medium. Kato (159) found growth of acid-fast organisms after inoculating propane-tetradecane medium with *M. lepraemurium*. Shetty, *et al.* (159–160) saw demyelination in 3 of 15 mouse nerves when the animals were injected subcutaneously or intraneurally with whole serum or immunoglobulins from leprosy patients. Irgens and Skjaerven (160–161) analyzed secular trends in leprosy in areas of declining incidence and found an increasing age at onset due to a longer incubation period, an increasing male excess, and an increasing fraction of new cases represented by multiba-

cillary leprosy. Neill, *et al.* (161) reported that there were 1835 leprosy cases diagnosed in the United States in the period 1971–1981, only 10% of whom were indigenous. Xu, *et al.* (161–162) presented evidence from family studies that predisposition to lepromatous leprosy is controlled by HLA-linked genes but that HLA-linked genes do not confer susceptibility or resistance to leprosy as a whole. Bourrel (162) pointed out the value of active metacarpophalangeal flexion with simultaneous active extension of the interphalangeal joints as a diagnostic test for the integrity of the intrinsic muscles of the fingers. Kaplan and Gelber (162) compared upper extremity manual muscle testing, sensory testing using monofilaments, and motor and sensory electrophysiological nerve conduction studies in untreated lepromatous patients and found that sensory testing with monofilaments demonstrated the highest number of abnormalities. Hall and Ratledge (163) studied the mycobactins of seven strains of armadillo-derived mycobacteria and found them to be heterogeneous. Mitchison (164) pointed out that the three functions of antituberculosis drugs, a) prevention of the emergence of drug resistance, b) early bactericidal activity, and c) sterilizing activity, may be and often are entirely unrelated. The sterilizing activity of a drug, and not its early bactericidal activity, measures its ability to shorten the duration of treatment.

In the June issue, the Original Articles began with the work of Stanley, *et al.* (231–235) on edema in type 2 reactions. Clinical and histopathological evidence was presented that these episodes of edema can be caused by obstruction of inflow of lymph into regional lymph nodes. Groenen, *et al.* (236–244) studied reactions in patients treated with intensive bactericidal therapy and found type 1 reactions to occur more frequently in multibacillary than in paucibacillary patients. They were more frequent and more severe in regimens containing higher total amounts of rifampin. Clofazimine 100 mg daily prevented type 1 reactions in multibacillary patients and made them less severe. Papaioannou, *et al.* (245–251) found that leprosy patients as a whole had higher levels of exposure to hepatitis B virus than hospital controls without lepro-

sy, but the prevalence of active infection does not differ between leprosy cases and hospital controls. Rathi, *et al.* (252–255) studied taste impairment among leprosy patients by electrogustometry and found over half the cases to show impaired taste sensation. Impairment was most pronounced in lepromatous cases of long duration. Bach, *et al.* (256–267) found elevated IgM antibodies to phenolic glycolipid-I (PGL-I), and IgM and IgG antibodies to whole *M. leprae* in untreated lepromatous leprosy patients. IgM antibodies against PGL-I as well as against whole *M. leprae* declined sharply during the first 2 years of treatment. Tuberculoid patients showed lower frequencies and lower levels of IgM to PGL-I. Narayanan, *et al.* (268–272) prepared single cell suspensions from biopsies of granulomas of leprosy patients and studied their characteristics. Tuberculoid granulomas contained higher numbers of lymphocytes, more activated T cells, and a higher rate of helper to suppressor T lymphocytes than lepromatous granulomas. Gelber, *et al.* (273–283) found the neonatally thymectomized Lewis rat to be superior to the nude rat and to normal mice in detecting low numbers of viable *M. leprae* in patients on chemotherapy. Kohsaka, *et al.* (284–288) showed that thymus transplantation would prevent the growth of *M. leprae* in nude mice and would induce reversal reactions in nude mice already infected with the bacilli. Harris, *et al.* (289–293) found elevated levels of several gangliosides, particularly GM3 gangliosides, in lepromatous armadillo tissue compared to normal tissue. Band, *et al.* (294–299) studied the uptake of *Mycobacterium w* by 33B rat Schwannoma cells and rat peritoneal macrophages, and found the mechanism of phagocytosis to be similar in the two cell types.

In the Editorial section of the June issue we were fortunate to have an elegant review of leprosy and social class in the Middle Ages by Ell (300–305).

The Obituary section noted with great loss the death of Dr. Stanley G. Browne, for many years Secretary/Treasurer and then Secretary of the International Leprosy Association (306–307). The death of Dr. Tetsu Nakayama, Director of the First Research Department, National Institute for Leprosy

Research, Tokyo, was noted with sadness (308).

In the Correspondence section, Beiguelman (309) pointed out that blood-derived macrophages from lepromatous leprosy patients are unable to lyse *M. leprae*. Kato (310–311) proposed a multifactorial medium for cultivation trials for *M. leprae*.

In the News and Notes section of the June issue, the Guangzhou meeting of the Council of the International Leprosy Association on 27 November 1985 was reported (312–314). The inauguration of the China Leprosy Association, the China Leprosy Foundation, the China Leprosy Control and Research Center, and the First International Symposium on Leprosy held in Guangzhou, People's Republic of China, 26–28 November 1985, was noted (316–317). The International Gandhi Award for leprosy for 1986 went to Dr. (Mrs.) Turkan Saylan of Istanbul and Dr. Dharmendra of New Delhi (317).

The Book Review section of the June issue contained reviews of *Heralds of Health; The Saga of Christian Medical Initiatives* by Browne, Davey and Thomson and *Leprosy, Vol. 2* by Dharmendra.

In the Current Literature section, Nebout and Grosset (325–326) discuss past problems and current new strategies in leprosy control work in Francophone Africa. Altes, *et al.* (326) put forth the interesting concept that lymphokine-induced bacteriostasis may protect mycobacteria from at least some antibiotics *in vivo*. Balakrishnan, *et al.* (326) found deoxyfructoserotonin and related liposoluble derivatives as well as a nutrition antileprosy diet effective in suppressing the growth of *M. leprae* in the mouse foot pad. Bhasin, *et al.* (326–327) studied small intestinal function before and after clofazimine treatment in leprosy patients and found no correlation between any abnormalities found or symptomatology and doses of the drug taken. Carayon, *et al.* (327) described a patient with lepromatous leprosy treated for 5 years with Fansil who developed a crossresistance to dapson, verified by mouse foot pad drug sensitivity studies. Cartel, *et al.* (327) found satisfactory acceptance, attendance, and tolerance of daily multidrug therapy for leprosy in Guadeloupe. Castells, *et al.* (327–328) used

thymopentin, the biologically active pentapeptide of the native thymus hormone thymopoietin, to treat 8 chemotherapy-resistant leprosy patients with encouraging results. Cohn, *et al.* (328) reviewed rifampin-induced renal failure. de Wit, *et al.* (328) and George and Balakrishnan (328) compared the paper spot test and the hemagglutination inhibition test in measuring dapsone compliance, and pointed out the advantages of each. Girdhar, *et al.* (328) treated TT/BT patients with less than 5 lesions with dapsone alone for 12 months, dapsone for 12 months plus steroids for the first month, or dapsone for 12 months plus rifampin for the first week. Only about three-fourths of the patients became inactive in a 12-month period. Relapse, after treatment(s) were stopped, was at a rate of 6.3 per 1000 patient months, and there were no differences in the relapse rates among the 3 regimens. Girdhar, *et al.* (328–329) compared two multidrug regimens in lepromatous leprosy, a) rifampin, clofazimine and dapsone and b) rifampin, prothionamide, isoniazid and dapsone, and found both to be effective and neither to be superior to rifampin alone with regard to the rapidity of reaching noninfectivity or the frequency of persisters. Jesudasan, *et al.* (329) suggest that paucibacillary patients who default from treatment are not a serious problem in terms of leprosy control. Katoch, *et al.* (329–330) studied the response of paucibacillary patients to 3 regimens of rifampin plus dapsone and found that 6 months' treatment is insufficient. One year may be adequate. Interesting observations were reported by Millan, *et al.* (330) on 39 lepromatous patients treated 7–9 years earlier with multiple drugs (rifampin, dapsone \pm ethionamide) in various combinations, dosages, intervals, and durations. In all regimens, the patients were treated with dapsone monotherapy for life after the period of combination drug treatment. Seven of the 39 cases showed clinical relapse and 50% of the patients had bacterial index (BI) greater than 2+, suggesting reactivation. The only factor showing a relationship to the positive BI was the regularity of attendance to sulfone monotherapy following the period of multidrug therapy. Pal, *et al.* (331) found the predominant causes of irregularity in attending an

outpatient department and thereby irregular drug treatment were socioeconomic factors. Pankaj, *et al.* (331) reported higher serum levels of rifampin when the drug was given together with probenecid. Sreevatsa, *et al.* (331–332) tested 3 strains of *M. leprae* from patients having dapsone-resistant disease and found that they multiplied in mice fed 0.001% rifampin but not in animals receiving 0.01% rifampin. Vaishnavi, *et al.* (332) found intermediate dapsone resistance (growth in mice fed 0.001% but not in those fed 0.01% dapsone) in 2 of 20 previously untreated bacilliferous patients. Delmonte (333) described a lepromatous patient with ENL who presented with necrotizing lymphadenitis. Kardaun, *et al.* (334) described a borderline tuberculoid leprosy patient who developed nerve abscesses along the line of cutaneous nerves. Three leprosy patients with calcified peripheral nerves were reported by Malaviya, *et al.* (335). Leprosy-specific bone lesions in the finger, termed osteitis leprosa multiplex cystica, were described by Mende, *et al.* (335–336). Nigam, *et al.* (336) found significantly decreased levels of serum calcium and serum magnesium in lepromatous leprosy patients compared to normal controls. Rao, *et al.* (336–337) reported elevated serum copper and reductions in serum zinc, calcium, and magnesium throughout the leprosy spectrum. Samuel, *et al.* (337) reported primary dapsone-resistant borderline leprosy in a 3-year-old child. Shannon, *et al.* (337) described a patient with borderline tuberculoid leprosy who presented with a well-defined sporotrichoid pattern with secondary nodules along draining lymphatic vessels. Suzuki, *et al.* (338) found serum lysozyme to be elevated in lepromatous patients with ENL, and suggested that serum lysozyme might be useful in following treatment and control of ENL. Suzuki, *et al.* (338–339) saw a correlation between circulating immune complexes and anti-*M. leprae* antibody titers in lepromatous leprosy, and suggested that these circulating immune complexes were composed partially of *M. leprae* antigens and anti-*M. leprae* antibodies. Antia, *et al.* (339) demonstrated substantial amounts of non-acid-fast staining bacilli and bacillary antigenic material in peripheral nerves of tuberculoid patients by electron

microscopy and immunoperoxidase staining with anti-BCG antibodies. Antia and Mistry (339–340) found a large number of plasma cells in caseous nerve abscesses. The specificity of the secreted antibodies appeared to be directed against mycobacterial antigens. Britton, *et al.* (340) identified 4 *M. leprae* antigens to which lepromatous patients respond with antibodies. Brown, *et al.* (340–341) presented experimental evidence in support of the theory that exposure to environmental mycobacteria can influence the effectiveness of BCG vaccination. Cho, *et al.* (341) described a simplified serologic test which detected over 90% of untreated lepromatous patients based on a 3,6-di-*O*-methylglucose-containing synthetic antigen. Emmerich and Kaufmann (341–342) established T-cell clones with the T4 phenotype from tuberculoid leprosy patients and tested their antigen reactivity. ICRC bacilli were superior to *M. leprae* and *M. bovis* BCG in stimulating crossreactive T4 clones. Fujiwara, *et al.* (342) described the synthesis of neoglycoconjugates based on the terminal disaccharide of the PGL-I antigen of *M. leprae* for the specific serodiagnosis of leprosy. Gigg, *et al.* (342) described the synthesis of the trisaccharide portion of the PGL-I antigen of *M. leprae*. Haregewoin, *et al.* (342) stimulated lepromatous lymphocytes with *M. leprae* plus IL-2 and found that they could be restimulated with *M. leprae* alone. Some patients' lymphocytes responded better to BCG than to *M. leprae* and some the reverse. Jesudasan, *et al.* (343) found human lepromin in a concentration of 100 million bacilli per ml and armadillo lepromin at a concentration of 40 million bacilli per ml to induce equivalent skin test responses in patients. Kaplan and Cohn (343–344) suggest that the lack of cell-mediated immune responses of lepromatous patients may be due to a low level or lack of *M. leprae*-responsive T cells in the circulation. Klatser, *et al.* (344) described a murine monoclonal antibody, 47-9, which recognized an epitope on the 36 kD protein antigen of *M. leprae*. A competitive inhibition ELISA test based on this monoclonal antibody was positive in 100%, 91%, and 5% of multibacillary leprosy, paucibacillary leprosy, and control sera, respectively. Klatser, *et al.* (344–345) characterized antigenic components of *M. leprae* using an SDS-polyacrylamide gel electrophoresis-immunoperoxidase technique. Kolk, *et al.* (345) produced and characterized 6 monoclonal antibodies to *M. leprae*. Laal, *et al.* (345) studied ENL patients, comparing them to uncomplicated LL patients and found that during the acute phase of the reaction there was significant antigen-induced leukocyte migration inhibition, antigen-induced lymphoproliferation and enhanced antigen-stimulated suppression of mitogen responses as a measure of suppressor cell activity. Intradermal responses to soluble *M. leprae* antigens remained poor, however. Mahadevan (346) reviewed the evidence in support of the concept that the expression of the immune deficiency in lepromatous leprosy results from interaction between the phagocytic cell of susceptible individuals and live *M. leprae* which leads to negative modulation of the immune competence of the susceptible individuals. Mistry, *et al.* (346) measured macrophage Fc receptor expression and monocyte-lymphocyte interaction in the presence of *M. leprae* in family contacts of leprosy patients. Defects in macrophage functions similar to those of borderline and lepromatous patients were seen in 71% of consanguineous contacts and 43% of spouses of index cases. Mobashir, *et al.* (346–347) found histopathologic changes of leprosy in the liver corresponding to the type found in the skin in 38 of 40 patients from across the spectrum of the disease. Mukherjee and Antia (347) showed a special, high rate of adherence of *M. leprae* and not other mycobacteria to Schwann cells *in vitro*. Mukherjee and Antia (347) studied the migration and proliferation of Schwann cells in explant cultures of nerves from leprosy patients. Schwann cells parasitized by *M. leprae* failed to migrate from the explant, attach to the culture surface, and proliferate. Mustafa, *et al.* (347–348) isolated *M. leprae*-specific T-cell clones from *M. leprae*-vaccinated volunteers and used them to screen crude lambda_{gt11} phage lysates of *Escherichia coli* containing individual *M. leprae* antigens. Nearly half of these T-cell clones were stimulated to proliferate by lysates containing an epitope of the 18 kD protein antigen of *M. leprae*. Narayanan, *et al.* (348) used

monoclonal antibodies to demonstrate *M. leprae* antigens on the membranes of lymphocytes and macrophages in both tuberculoid and lepromatous granulomas. Ottenhoff, *et al.* (349) cloned *M. leprae*-reactive T cells of the helper phenotype from a tuberculoid leprosy patient. Half of these clones were almost or completely *M. leprae*-specific while half were widely crossreactive with many other mycobacteria. Four of the six clones proliferated in response to the 36 kD protein of *M. leprae*, each to a different antigenic determinant on that protein, one of which is *M. leprae*-specific. Reitan, *et al.* (349–350) measured antibody levels to an epitope on *M. leprae* antigen 7 defined by a murine monoclonal antibody (038D-C6), and found that they correlated with bacterial load and that levels decreased markedly with treatment in both lepromatous and tuberculoid patients. Samuel, *et al.* (351) vaccinated normal individuals, contacts, and leprosy patients with a mixture of *M. leprae* plus BCG, and then studied their positive leprosin A skin-test sites by enumerating T-cell subsets. The large number of cells infiltrating the positive skin-test sites were of the T-helper-inducer subset. Sharp and Banerjee (351) found equivalent rates of production of H₂O₂ and superoxide in peripheral blood monocytes in response to stimulation with *M. leprae* or phorbol myristate acetate from leprosy patients representing all stages of the disease and healthy controls. Singh, *et al.* (351–352) found evidence of cross immunogenicity between *M. habana* and *M. leprae* in studies of leukocyte migration inhibition in leprosy patients. Singh, *et al.* (352) showed that *M. habana* protected mice against foot pad challenge with *M. leprae*. Young, *et al.* (352) produced an *M. leprae* recombinant DNA expression library. *M. leprae*-specific epitopes recognized by all of 13 monoclonal antibodies tested were produced by recombinant phage in *E. coli*. Dhople and Green (352) measured ATP levels and [³H]-thymidine uptake in *M. leprae* under culture conditions, and found an excellent correlation between the metabolic activity of the bacilli and their viability. Dhople-Hanks and Mahadevan media supported the growth potential of organisms for at least 8 weeks. Kannan, *et al.* (352–353) suggested glyox-

ylate by-pass of the tricarboxylic acid cycle as having a possible role in the physiology of “persisters” in mycobacterial disease. Lee and Colston described (353) adenylate kinase in *M. leprae*, and described (353) the decay of ATP in *M. leprae* upon *in vitro* incubation along with incorporation of phosphate into ATP and other nucleotide materials. Prabhakaran and Harris (353–354) showed that the quinone product of DOPA oxidation undergoes reversible oxidation-reduction and suggested that diphenoloxidase might serve as an alternative respiratory mechanism in *M. leprae*. Saha, *et al.* (354) demonstrated AFB in the gut and excreta of mosquitoes fed on bacilliferous leprosy patients. The bacilli appeared to lose viability after 4 days, but appeared to multiply during the earlier period. Chehl, *et al.* (355) applied *M. leprae* to various sites in nude mice and concluded that the favorite sites of entry of the bacilli were topically on the nasal mucosa and by subcutaneous inoculation. Dhople, *et al.* (355) correlated serum angiotensin-converting enzyme with the extent of lepromatous disease in armadillos. Kohsaka, *et al.* (355–356) inoculated *M. leprae* into rhino mice, which lose the thymus at an early stage, and found them to allow less proliferation of the organism than nude mice. Cartel, *et al.* (357) outlined epidemiologic characteristics of leprosy in Guadeloupe from 1970–1981, including a high frequency of resistance to dapsone. Joseph, *et al.* (358) analyzed leprosy among native-born U.S. citizens from 1932–1981. Thirty percent had a history of contact with the disease, and the average age at diagnosis increased each decade. Pollack, *et al.* (358) found HLA DR2 to be associated with the lepromatous form of leprosy among Filipino patients’ families in Hawaii. Schauf, *et al.* (359) demonstrated an association between HLA DR2 and DQw1 and tuberculoid leprosy in northern Thailand. Beine (359 and 359–360) described modified surgical procedures for claw hands. Kulkarni and Mehta (360) found tarsal disintegration in 3 of 20 cases who had had earlier surgery for foot drop. Palande (361) pointed out the indications for neurolysis as an emergency procedure in leprosy, particularly in acute nerve abscesses. Srinivasan (361) described a technically

simple operative procedure, not requiring postoperative re-education therapy, for paralytic claw fingers. Beck, *et al.* (361–362) found that patients with active pulmonary tuberculosis had an absolute T4 (helper/induced) lymphopenia which seemed to be a reaction to the *M. tuberculosis* infection and not a manifestation of underlying secondary (acquired) immune deficiency. Chitamber, *et al.* (362) used “*Mycobacterium w*” and *M. vaccae* and a variety of radiolabeled precursors to assess the viability and growth of mycobacteria *in vitro* in human monocyte-derived macrophages. Thole, *et al.* (364) cloned *M. bovis* BCG DNA and obtained expression of a crossreacting 64 kD protein antigen.

In the September Original Articles, Douglas-Jones, *et al.* (367–379) examined T-cell antigens of mycobacteria in relation to *M. leprae*. There were genetic differences among mice strains in their T-cell responses to *M. leprae*. The T-cell responsiveness to *M. marinum* was parallel to that to *M. leprae* in these mouse strains. Dedhia, *et al.* (380–382) presented a case report of acute renal failure in a leprosy patient on intermittent rifampin, first once weekly then once monthly. Pieters, *et al.* (383–388) developed a dapsone depot injection which they administered intra-adiposely (subcutaneously) to male and female volunteers. The preparation showed good depot properties and was well tolerated. Kar, *et al.* (389–391) reported a lepromatous leprosy patient who relapsed with bacilli which were resistant to both clofazimine and dapsone as determined by mouse foot pad drug sensitivity testing. The patient was on dapsone monotherapy prior to relapse, and there was no history of the patient ever having received clofazimine. Levine and Saltzman (392–398) administered clofazimine orally to rats and demonstrated selective drug deposition in Peyer’s patches, suggesting that Peyer’s patches are especially susceptible to the toxic effects of the drug. Segasothy, *et al.* (399–402) showed that leprosy patients consume large quantities of analgesics, mainly for neuritic pain. Although the quantities of analgesics were sufficient to cause renal papillary necrosis, no radiologic evidence of renal papillary necrosis was found. Excessive analgesics may contribute to the inter-

stitial nephritis seen in leprosy. Odinsen, *et al.* (403–408) estimated the viability of *M. leprae* by conventional morphological index (MI) and by two fluorescent techniques, fluorescein diacetate (FDA)/ethidium bromide (EB) and rhodamine 123 (R123)/EB. The advantages of the fluorescent methods were pointed out. Katoch and Cox (409–415) outlined an economical approach for the isolation and purification of nucleic acids from mycobacteria which would be especially useful for mycobacteria available in limited quantities, such as *M. leprae*. Khandekar, *et al.* (416–422) constructed a complete genomic library from *M. vaccae* and partial libraries from *M. leprae* and BCG in the plasmid pBR322. Narayanan, *et al.* (423–426) studied sites of DNCB skin reactions in tuberculoid and lepromatous leprosy patients and found no differences in the numbers or distribution of Langerhans’ cells or in the histopathology of the reaction sites despite the fact that the reactions were positive in the tuberculoid patients and negative in the lepromatous cases. Baskin, *et al.* (427–436) skin tested rhesus monkeys with lepromin and found uninoculated control monkeys and those with lepromatous leprosy to be negative while those which had been inoculated with *M. leprae* and had not developed leprosy were positive. The optimum concentration of lepromin A for monkeys appeared to be 1.6×10^9 bacilli/ml. Jeevan, *et al.* (437–445) injected ICRC bacilli and *M. leprae* intravenously, intraperitoneally, and subcutaneously into mice and found that the animals were tolerant to the respective antigens by skin testing. Adoptive transfer of spleen cells from tolerant animals produced suppression in sensitized recipients. *M. leprae*-tolerant mice could be partially converted to immunity by intradermal sensitization with live BCG and two strains of ICRC bacilli. Nomaguchi, *et al.* (446–452) isolated attenuated *M. lepraemurium* from a smooth colony on Ogawa egg-yolk medium. The pathogenicity of the attenuated bacilli was restored partially by adaptation of the bacilli to growth in tissue culture cells and was restored almost completely by passage in mice. After restoration of pathogenicity, the *M. lepraemurium* formed rough colonies on Ogawa egg-yolk medium. Job, *et al.* (453–457)

found 10 (2%) of 494 armadillos killed by automobiles in Louisiana to have disseminated leprosy.

In the Editorial section of the September issue, we were privileged to have the scholarly review by Collins (458–474) dealing with the possible role of *M. avium*-complex infections in contributing to the immunodepression of the acquired immunodeficiency syndrome (AIDS).

In the Correspondence section of the September issue, Sen-Chiew Gan (475–476) used the Draper protocol for armadillo liver to purify *M. leprae* from human skin samples with good results. Rojas-Espinosa, *et al.* (476–479) presented evidence that *M. lepraemurium* infections in mice induce a transitory biochemical activation of their peritoneal cells (mostly macrophages), but despite these changes the murine disease progresses. Ratnam (479–480) lepromin skin tested normal subjects in Singapore and found 70% to be positive. Gelber and Zacharia (480–482) reported an ENL patient who developed bilateral ulnar nerve abscesses.

The News and Notes section of the September issue contained the well-deserved Dr. K. G. Sahu Gold Medal Award to Dr. K. V. Desikan (483). Dr. Wanda Blenska was awarded the Karl Marcinkowski Medal by the Medical Academy of the University of Poznan (484).

In the Current Literature section of the September issue, Barss (487) reported a case of fatal agranulocytosis due to dapsone. Chen, *et al.* (487) described a leprosy patient treated with rifampin 600 mg monthly who developed acute interstitial nephritis with renal failure. Mathur, *et al.* (489) found no evidence that prothionamide affects the pharmacokinetics of simultaneously administered rifampin and dapsone. Mehta, *et al.* (489) showed that clofazimine significantly reduced the absorption of simultaneously administered rifampin. Chung, *et al.* (490) reported low total serum cholesterol and decreased high-density lipoprotein cholesterol in leprosy patients compared with healthy controls. Dash, *et al.* (490) found normal adrenal cortical function in leprosy patients. Kumar and Lakshmanan (490–491) and Walton, *et al.* (491) obtained good results treating uncompli-

cated ulcers in leprosy patients with adhesive zinc tape. Alvarenga, *et al.* (491–492) saw no significant variations in the number of Langerhans' cells (OKT6+) in the various clinical forms of leprosy. Cho, *et al.* (492) described techniques to quantitate phenolic glycolipid-I in body fluids of leprosy patients. Elferink, *et al.* (492) showed that Epstein-Barr virus-transformed lymphoblastoid B-cell lines were able to present *M. leprae* to antigen-reactive T-cell lines and clones in an HLA-DR-restricted fashion. Haanen, *et al.* (492) developed T-cell clones from 3 leprosy patients utilizing Epstein-Barr virus-transformed autologous B cells as antigen-presenting cells. These T-cell clones were HLA class II-restricted in their response to *M. leprae*. Holzer, *et al.* (492–493) found that *M. leprae* failed to stimulate superoxide anion (O_2^-) generation in human blood neutrophils and monocytes and murine peritoneal macrophages. Jacobs, *et al.* (493) constructed genomic libraries of *M. leprae* DNA in the expression vector pYA626. This vector contains a promoter region from a *Streptococcus mutans* gene which is expressed very efficiently in *Escherichia coli*. Several clones complemented a mutation in the citrate synthase gene of *E. coli*, and the complementing DNA was from *M. leprae*. Koster, *et al.* (493–494) studied the ability of different *M. leprae*-sensitized strains of mice to respond to phenolic glycolipid-I in skin tests and in lymphocyte proliferation, and concluded that the cell-mediated responses to the glycolipid are under polygenic control. Modlin, *et al.* (494) found increases in Leu-3a : Leu-2a ratios and increases in IL-2+ cells in skin biopsies of ENL lesions compared to nonreactional lepromatous lesions. Lepromin-induced suppression of ConA responses in peripheral blood mononuclear cells was present in nonreactional lepromatous patients and significantly decreased in patients developing ENL. Dhople, *et al.* (494) showed that armadillos with leprosy have increased serum levels of nicotinamide adenine dinucleotide glycohydrolase, and suggested the possibility of using this assay in monitoring leprosy infections in armadillos. Emori, *et al.* (496) presented evidence that the complex of muramyl dipeptide and branched fatty acids, mostly mycolic acids, is a structure in tu-

bercle bacilli responsible for tubercle formation.

In the Original Articles of the December issue, Converse and Bjune (503–509) assessed natural killer (NK) cells activity in leprosy patients and found that lepromatous leprosy and all untreated, nonreactional patients had lower NK activity than healthy controls. Patients presenting with reversal reactions, on the other hand, had NK activity within the normal range. Pieters and Zuidema (510–516) prepared monoacetyldapsone and studied its pharmacokinetics after intra-adipose injections in normal volunteers. The preparation showed excellent sustained release properties and was well tolerated, making it a promising injection for use every 4 weeks to maintain continuous therapeutic dapsone serum concentrations. Fischer, *et al.* (517–524) measured dapsone compliance among leprosy patients using urinary dapsone/creatinine ratios standardized by dose, ideal body weight, and time since last dose. Significant improvement in compliance occurred when test results were made known to the patients. Jain, *et al.* (525–529) developed devices to grade losses in pain and touch sensations in leprosy patients and found that sensory loss within lesions was not uniform all over the lesion and that it was not necessarily maximum at the center of the lesion. In most lesions sensation improved following chemotherapy. Meeker, *et al.* (530–539) compared results of testing sera from leprosy patients, contacts of leprosy patients, and normal controls by ELISA for IgM antibodies to PGL-I antigen in three different laboratories, each using different methodologies. Agreement on positivity and overall correlations among the techniques were excellent. Kumar and Kaur (540–544) analyzed results of 1000 sets of slit-skin smears from multiple sites on lepromatous leprosy patients and found that, in general, the highest values for bacterial index and for morphological index were from the earlobes. Britton, *et al.* (545–555) raised monoclonal antibodies against *M. leprae* sonicate which recognized two different determinates on related, cell-wall-associated carbohydrate antigens common to *M. leprae*, BCG, and *M. tuberculosis*. The smaller (4.5–6 kD) is possibly a fragment of

the larger (30–40 kD) antigen, and both are significant immunogens in human B-cell responses to *M. leprae*. Truman, *et al.* (556–559) showed that an ELISA for IgM antibodies against the PGL-I antigen of *M. leprae* may be valuable in monitoring the course of experimental infections in armadillos. Saito, *et al.* (560–562), using mouse foot pad infections, demonstrated that ofloxacin, a new quinolone, is bactericidal against *M. leprae* both *in vitro* and *in vivo*. Ji, *et al.* (563–577) extensively evaluated two newer ansamycins, R-76-1 and DL 473, in comparison with rifampin by determining minimum inhibitory concentrations against cultivable mycobacteria *in vitro*, activity *in vivo* in mice infected with *M. lepraemurium*, by the kinetic and proportional bactericidal methods in mice infected with *M. leprae*, and by clinical trial. In general, the newer ansamycins were bactericidal and more potent in many systems than rifampin. Lloyd and Draper (578–583) described a discontinuous Percoll gradient method of purifying *M. leprae* from armadillo liver which are contaminated with a particulate “pigment.” Mori and Kohsaka (584–595), in a series of *in vitro* and *in vivo* experiments, demonstrated that cat leprosy bacilli which had been passaged in mice were identical to murine leprosy bacilli. Ridley and Ridley (596–606) classified and compared concurrent nerve and skin biopsies across the leprosy spectrum. The bacterial load was higher in nerve than in concurrent skin lesions, and in half the cases there was some discrepancy between the histological classification of nerve and skin lesions. Cree, *et al.* (607–613) evaluated skin biopsies from leprosy patients across the spectrum, the biopsies being taken from the center, edge, and adjacent to clinically apparent lesions. Apoptosis, a form of individual cell death in living tissues, seemed to be the mechanism by which epithelioid cells are lost during central healing of tuberculoid lesions. The immigration of monocytes, rather than local mitosis, seemed to be the principal means of maintaining the number of cells in the leprosy lesions. Fine, *et al.* (614–625) reported the results of independent evaluation by three experienced histopathologists of 200 biopsies of individuals suspected of having leprosy. There was more agreement

among the histopathologists with regard to classification of leprosy cases than there was on the diagnosis of the disease itself in these predominantly early cases. In a reprinted article, Grange and Yates (626–631) succinctly reviewed infections caused by opportunistic mycobacteria.

In the Editorial section of the December issue, we were pleased to have a review of host-parasite interrelationships between *M. leprae* and Schwann cells *in vitro* by Mukherjee and Antia (632–638).

The Obituary section noted the tragic loss of Dr. Han Huikeshoven (639–640).

The Correspondence section of the December issue was particularly informative. Hoang Thuy Long, *et al.* (641–644) measured macrophage activation by determining the procoagulant activity of macrophage sonicates. Supernatants from lepromatous or borderline patients' lymphocytes treated with PHA were less active than supernatants from normal control lymphocyte cultures treated with PHA in inducing procoagulant activity. Mathur, *et al.* (644–645) found no apparent effect of cimetidine in eight patients with lepromatous leprosy. Duncan (646) pointed out that there was evidence that *M. leprae* antigens as well as whole *M. leprae* crossed the human placenta but that the eventual clinical manifestations of the disease in early childhood were likely to depend on a number of other factors, such as the timing, dose, and duration of exposure. Rotberg (648–649) advocated the use of the term hanseniasis and amplified on Shakespeare's writings regarding name changes. Kato (649–651) presented examples of medieval art depicting leprosy patients together with the "Ex Libris" of Professor Torshujev. Date (651–653) pointed out some of the writings of Osler on leprosy.

In the News and Notes section of the December issue, the well-deserved Damien-Dutton Award for 1986 to Samuel J. Butcher was noted (654–655). Prof. V. Ramalingaswami was elected a Fellow of the Royal Society of London (655–656). Dr. R. H. Thangaraj was elected President of the Indian Association of Leprologists (656). The XIII International Leprosy Congress to be held at The Hague 11–17 September 1988 was announced (659–660). Dr. Tore Godal assumed the duties of director of the Special

Programme for Research and Training in Tropical Diseases of the World Health Organization (660–661).

The Book Review section contained reviews of *Biochemical Aspects of Leprosy* by Balakrishnan (664), *La Lepre. Manuel Pratique pour les Services de la Lepre sur le Terrain* by Groenen (664–665), *Leprosy* edited by Hastings (665–666), *Annual Report of the Director General 1984–85, Indian Council of Medical Research* by Ramalingaswami (666–669), *Skin Biopsy in Leprosy* (2nd ed.) by Ridley (669–670), and *Leprosy for Medical Practitioners and Paramedical Workers* by Thangaraj and Yawalkar (670).

In the Current Literature section of the December issue, Guillet *et al.* (671) reported two leprosy cases diagnosed at 3 years of age. Almeida and Chacko (672) devised a computerized mathematical model of *M. leprae* population dynamics during multidrug therapy and suggested that multidrug therapy tends to select for resistance to the most powerful drugs used. Anderson (672–673) found that clofazimine enhances and dapsone inhibits the production of prostaglandin E₂ by human neutrophils *in vitro*. Chen, *et al.* (673) found markedly fewer instances of elevations of serum glutamic pyruvate transaminases in leprosy patients given prothionamide and rifampin on different days than in patients receiving these two drugs on the same day. Huikeshoven (674) described an improved, simple urine spot test for monitoring patient compliance to dapsone self-administration. Jagannathan and Mahadevan (674–675) determined minimal inhibitory concentrations of dapsone and rifampin *in vitro* based on the ability of live, but not dead, *M. leprae* to reduce EA-rosetting by infected mouse peritoneal macrophages. Kulkarni and Mishra (675) found that a prodrug of dapsone 4,4'-dibutrylamino-diphenyl sulfone gave therapeutic levels of dapsone for 34 days in rabbits injected intragluteally. Sharma, *et al.* (676) found favorable results with colchicine in the treatment of type 2 reactions (ENL). Wang, *et al.* (677–678) presented evidence that the antileprosy action of R-77-3 [3-(4-cyclopentyl-1-piperazinyl)imino methyl rifamycin Sv] was better than that of rifampin. Waters, *et al.* (677) discontinued treatment in 362 lepromatous

(BL and LL) patients after they had been treated with sulfone therapy for 19–22 years. In a follow-up period of 8–9 years, 25 of these patients relapsed clinically, giving an over-all relapse rate of 8.6% and an average relapse rate of 1.04/100 patient-years of observation. Balybin (678) found low organic iodine levels in the bodies of patients with active lepromatous leprosy, and particularly in those with polyneuritis. Chaturvedi, *et al.* (678–679) reported impaired olfaction in 42% of leprosy patients, most frequent and most severe in lepromatous cases. Deshpande, *et al.* (679) measured alpha-1-antitrypsin levels in leprosy patients across the spectrum and found elevated levels in BL and LL patients. The highest levels were observed in LL patients with ENL. Duncan and Pearson (679) pointed out that complaints of “rheumatism” in pregnant and lactating Ethiopian women with leprosy were frequently associated with relapse, reactions, new nerve enlargements, neuritis, lymphadenopathy, and paresthesias. Furukawa, *et al.* (679) detected anticardiolipin antibodies which crossreact with double-standard DNA in 20% of lepromatous leprosy sera. Kumar, *et al.* (680) found elevated levels of gamma-glutamyl transpeptidase in lepromatous leprosy patients. Murray, *et al.* (680) reported a reduction in suppressor T cells in a patient with lepromatous leprosy in association with an attack of acute anterior uveitis and postulated that acute anterior uveitis could be regarded as an intracellular component of ENL. Parikh, *et al.* (681) reported a borderline tuberculoid patient with involvement of the hairy area of the scalp. Singh, *et al.* (682) reported a case of inoculation leprosy following tattooing. Swamy, *et al.* (683) studied 75 patients with cauliflower growths on trophic ulcers. Malignant changes were seen in only four cases, the remaining 71 cases had pseudoepitheliomatous hyperplasia. Zhang, *et al.* (683) reviewed ophthalmologic findings of 1080 leprosy patients in Guangdong Province in China, and pointed out the importance of correcting lagophthalmos and eyelid ectropion to prevent blindness. Agarwal, *et al.* (684) found that levels of sialic acid removable by neuraminidase from macrophages of bacteriologically positive lepromatous leprosy patients were extremely low

compared to normal or bacteriologically negative lepromatous patients' macrophages. Sialic acid levels were drastically reduced in macrophages from bacteriologically negative lepromatous patients which were allowed to phagocytize *M. leprae*. Band (686) postulated that interleukin-1, a macrophage product that stimulates fibroblast migration, proliferation, and synthetic activity, might be the mediator of neural fibrosis of leprosy. Beck, *et al.* (686) studied skin test reaction sites to “new tuberculin” and leprosin A in tuberculosis and leprosy patients. Selective migration of monocytes/macrophages and to a lesser extent T8 cells seems to be a prominent feature of positive reactions. Birdi, *et al.* (686–687) based on studies of the effects of *M. leprae* on macrophages, suggest that *M. vaccae* is most promising as an immunomodulator in leprosy. Chatterjee, *et al.* (687) described the synthesis of neoglycoproteins suitable for the selective serodiagnosis of leprosy based on the relevant epitopes of native PGL-I. Eustis-Turf, *et al.* (688) detected anti-neural antibodies in the sera of 38% of leprosy patients, all of which reacted with neural intermediate filament proteins. Gill, *et al.* (688) reported good sensitization and no unacceptable side effects in normal, PPD-positive subjects receiving 5×10^7 , 1.5×10^8 , and 5×10^8 killed, armadillo-derived *M. leprae* intradermally. Kaplan, *et al.* (689) found that monocyte-derived macrophages from lepromatous leprosy patients responded normally to recombinant gamma-interferon, phorbol myristate acetate, and intact irradiated *M. leprae* in secreting H_2O_2 . Kingston, *et al.* (689–690) cloned T-cell lines from mice immunized with irradiated *M. leprae*. After a period of *in vitro* stimulation, these lines were found to crossreact with other mycobacteria. Lines established by cloning directly from immune mice appeared more *M. leprae*-specific. Mistry, *et al.* (691) demonstrated abnormal phagocytosis of *M. leprae* by macrophages of lepromatous patients under various conditions. Modlin, *et al.* (691) reported that two T8 clones derived from lepromatous leprosy skin biopsies, in the presence of lepromin, suppressed concanavalin A responses both of peripheral blood mononuclear cells and of T4 clones in an HLA-

D-restricted manner. Additionally, these T8 clones suppressed HLA-D-matched, but not HLA-D-mismatched, antigen-responding T4 clones to *M. leprae* antigens. Murphy, *et al.* (691–692) examined the ultrastructural characteristics of skin biopsies of four patients with ENL and concluded that ENL is compatible with an immune complex-mediated necrotizing vasculitis. Nathan, *et al.* (692) tested the effects of low doses of recombinant interferon-gamma intradermally in six patients with lepromatous leprosy. Local effects of interferon-gamma resembled features of delayed hypersensitivity reactions or tuberculoid leprosy. There was systemic normalization of peripheral blood monocyte production of H₂O₂ in response to phorbolmyristate acetate and *M. leprae*. Nye, *et al.* (693) found that fractions of *M. vaccae* were immunosuppressive when mixed with other mycobacterial antigens and given as skin tests. Some fractions in some groups were suppressive in distant skin-test sites. Ottenhoff, *et al.* (693) cloned a suppressor T cell from a patient with borderline lepromatous leprosy which completely suppressed helper T-cell responses to an *M. leprae*-specific protein with a relative molecular mass of 36,000. Rea, *et al.* (693) studied epidermal keratinocyte Ia expression, Langerhans' cell hyperplasia, and lymphocyte infiltration in skin lesions of leprosy patients across the spectrum. All three changes were well developed in BT and reversal reactions. ENL lesions had the first two but little lymphocytic infiltration. LL skin lesions showed only some Langerhans' cell hyperplasia. Ridel, *et al.* (693–694) found that blood-monocyte-derived macrophages from lepromatous leprosy patients synthesized high levels of prostaglandin E₂ *in vitro* in response to *M. leprae* but not in response to BCG. By blocking the synthesis of prostaglandin E₂ with indomethacin, it could be shown that these lepromatous macrophages were producing normal amounts of interleukin-1. Shankar, *et al.* (694–695) described the characteristics of *M. leprae* and PPD-triggered T-cell lines from tuberculoid and lepromatous patients. In all cases, antigen specificity declined and could not be maintained after 5–8 weeks of continuous culture. Wu, *et al.* (695) found excellent correlations among

serologic tests employing ELISAs with PGL-I, a synthetic antigen with a terminal sugar of PGL-I coupled to bovine gammaglobulin, *M. leprae* itself, and the fluorescent leprosy antibody absorption test (FLA-ABS). Brett, *et al.* (695–696) studied serologic responses of normal individuals, patients with tuberculosis and other mycobacterial diseases, and leprosy patients to synthetic glycoconjugates based on the terminal sugars of the PGL-I antigen of *M. leprae* and concluded that a synthetic conjugate which contains the terminal disaccharide regions of PGL-I may be optimal for the serodiagnosis of leprosy. Hunter, *et al.* (696–697) described a unique glycoconjugate which is one of the dominant immunogens of the leprosy bacillus. Chatterjee and Roy (696) and Kato (697) described media for the cultivation of *M. leprae*.

Dhople (698) reported studies of dapsone pharmacokinetics in armadillos. Dhople, *et al.* (698) cultivated "difficult to isolate" mycobacteria from 6 of 77 *M. leprae*-infected armadillo tissues using massive inocula. Job, *et al.* (699) found that a tuberculoid lepromin response in armadillos was associated with resistance to infection with *M. leprae*. Modlin, *et al.* (699) saw a similar pattern of T-lymphocyte subpopulations and distribution in mangabey monkeys with leprosy as those in humans with lepromatous leprosy. Saito, *et al.* (699) reported that a vaccine consisting of irradiated *M. leprae* and live BCG would protect mice against infection with *M. leprae* if given 4 weeks before challenge but not if given biweekly starting 2 weeks after challenge. Vidyasagar, *et al.* (700) detected changes in the myelinated fiber potentials from the sciatic nerves of mice infected with *M. leprae* as early as 2 months after inoculation.

Deng, *et al.* (701) treated family contacts of newly diagnosed leprosy patients with dapsone for 1 year, and compared the results with the control group of family contacts who were not given dapsone prophylaxis. Over a period of 16 years in the 178 contacts given dapsone, no new patients were seen; while in the 147 untreated contacts, six cases of leprosy developed. Fine, *et al.* (702) pointed out that BCG provides at least 50% protection against leprosy in Malawi, and suggested that BCG is suffi-

ciently effective against leprosy in east and central Africa to be considered an important element in leprosy control in these areas. Lwin, *et al.* (702) reported that the overall protective effect of BCG among children in Burma after 14 years was only about 20%, and that BCG vaccination is not likely to be important for leprosy control in that area. Millan, *et al.* (702–703) found multibacillary leprosy to be more prevalent among Caucasians than among those of non-Caucasian origin in Guadeloupe. Ramu, *et al.* (703) studied healthy contacts of leprosy patients with a battery of tests, and concluded that a competitive inhibition of monoclonal antibody binding to the MY2 determinant of *M. leprae* identifies a preclinical stage of the disease. Truman, *et al.* (704) found positive results in 17 of 182 armadillo sera from the years 1960–1964, testing for IgM antibodies against the PGL-I antigen of *M. leprae*, and concluded that *M. leprae* has been enzootic in Louisiana armadillos at least since 1961.

Ndiaye-Niang, *et al.* (705) performed electromyographic examinations on new leprosy patients, and found that sensory nerves were most frequently involved, abnormalities by nerve conduction velocities being found, in order of frequency, in the sural, posterior tibial, sensory ulnar, sensory median, motor ulnar, lateral popliteal and motor median. Sharangpani, *et al.* (706) advocated exercise in the form of crumbling newspaper with a single hand for rapidly improving hand function following surgery for lumbrical replacement in leprosy patients.

The December issue contained the abstracts of the Twenty-first Joint Leprosy Research Conference of the U.S.–Japan Cooperative Medical Science Program. Mori, *et al.* (718–719) described a method for purification of *M. leprae* from infected armadillo liver which gave good yields of purified bacilli, was rapid and safe, and produced minimum damage to the bacilli without enzyme treatment. Nakamura and Hastings (719) reported enhancement of cord-like formation of *M. leprae* from nude mice *in vitro* in the presence of tyramine. Hirata (719–720) re-examined the pyridine extractability of acid-fastness from leprosy bacilli and found differences in bacilli taken

directly from skin lepromas and those from the nasal mucosa. Franzblau (720–721) evaluated an *in vitro* incubation system and ATP analysis as a rapid primary screen for identifying compounds with anti-*M. leprae* activity. Tsutsumi and Gidoh (721–722) studied the effects of several antileprotic agents on adjuvant arthritis in rats. Gelber (722–723) reported that minocycline was bactericidal against *M. leprae* in mice. Masuoka (723) compared rates of growth of *M. leprae* in different strains of mice. The bacilli grew best in KK mice and least well in C57BL/6 mice. The growth of the organisms was the same in KK-nude mice and C57BL/6 nude mice, indicating that the differences observed in conventional mice were due to cellular immunity involving T lymphocytes. Nakamura and Yogi (723–724) compared the growth of *M. leprae* in SHR and WM nude rats and concluded that the WM nude rat is a “resistant” strain and that the SHR nude rat is highly susceptible. Ito, *et al.* (724) demonstrated the effectiveness of clofazimine against *M. leprae* infections in nude mice. Kohsaka, *et al.* (725) showed that a single thymus transplantation was effective in stopping the growth of *M. leprae* in infected nude mice. Hastings, *et al.* (725–726) showed that macrophages from the foot pads of nude mice infected with *M. leprae* which were heavily parasitized could not be activated by the lymphokines to kill intracellular *Toxoplasma*. Izaki, *et al.* (726–727) demonstrated a serine proteinase-type elastase activity in the bound fraction of hypersensitivity-type murine lepromas in C57BL/6N (resistant) mice. The activity was lower in CBA/N (susceptible) mice in which no granulomatous hypersensitivity developed. Fujiwara and Izumi (727) synthesized the complete trisaccharide of the PGL-I antigen of *M. leprae* and conjugated it to bovine serum albumin (BSA). The conjugates showed excellent serological reactivity. Izumi, *et al.* (727) showed that the natural trisaccharide based on the PGL-I antigen of *M. leprae* coupled to BSA was highly specific for leprosy by serological testing and that its affinity for IgG-class antibody was much higher than the native PGL-I antigen or the natural disaccharide coupled to BSA. Hunter, *et al.* (727–729) showed that the natural trisaccharide coupled to BSA showed

appreciably greater sensitivity and specificity than all other available antigens. The complete structure of lipoarabinomannan (LAM) of *M. leprae* was presented. Abe, *et al.* (729–730) found an association between a percentage of positive FLA-ABS tests in school children and the number of new leprosy cases detected in the districts. The percentage of positive FLA-ABS tests was significantly higher in children with neural symptoms than in those without. Minauchi, *et al.* (730–731) presented evidence for autoantibodies against the peripheral nervous system in the IgG fraction of lepromatous leprosy sera. Matsuo, *et al.* (731) outlined methodology for the immunohistologic staining for beta-glucuronidase of human and possibly of mycobacterial origin in leprosy tissues which have been embedded in paraffin. Maeda, *et al.* (731–732) studied the peripheral blood lymphocyte subsets among leprosy patients. Mohaghepour, *et al.* (732) reported that while fresh CD4+ T cells from most lepromatous leprosy patients were specifically unresponsive to *M. leprae*, following culture in medium alone for 48 hr the same cells responded to *M. leprae* antigens. Recovery of T-cell activity was blocked by the presence of *M. leprae* bacilli in the pre-culture medium. Nomaguchi, *et al.* (732–733) found that injection of PGL-I antigen into mice induced suppression of the ConA and the PHA responses of the spleen cells of these animals. Similar inhibition was seen when the PGL-I was added to these cells *in vitro*. The non-specific suppression of the mitogen responses seemed to be due to an impairment of macrophages. Modlin, *et al.* (733) used a monoclonal antibody directed against the Tal antigen in conjunction with an immunoperoxidase technique to identify activated T cells in frozen sections of leprosy lesions. Approximately 15–20% of the cells stained positively in tuberculoid specimens, lepromin skin tests, and reversal reaction skin lesions. In contrast, <10% of the cells stained positively in lepromatous and lepromatous with ENL lesions. Modlin, *et al.* (733–734) derived T-lymphocyte clones from leprosy skin lesions. T8+ lines from lepromatous lesions exhibited lepromin-induced suppression of ConA responses of normal peripheral blood mononuclear cells;

in contrast, T8+ lines from tuberculoid lesions did not. T4+ clones from tuberculoid lesions but not lepromatous lesions were reactive to lepromin. The T8-cells' suppression was restricted by MHC class II antigens. Cohn and Kaplan (734) discussed macrophage activation in relation to *M. leprae*. Makino, *et al.* (734–735) constructed a genomic library of *M. leprae* with the vector pSN463 which was then transformed into *Streptomyces lividans*. Expression of *M. leprae* protein was obtained in some of these transformants. Anderson, *et al.* (735) predicted the amino acid sequences of epitopes recognized by monoclonal antibodies based on the DNA sequences of subclones of the genes coding for the synthesis of the 65 kD protein of *M. leprae*. Synthetic peptides were synthesized based on these amino acid sequences and tested as inhibitors of serologic reactions between monoclonal antibodies and *M. leprae* sonicate. The peptides prepared by solid-phase peptide synthesis allowed definitive characterization of the epitope sequences for determinants recognized by two monoclonal antibodies. Mehra, *et al.* (735–736) outlined the strategy involved in mapping the various epitopes in the 65 kD protein antigen of *M. leprae* using recombinant DNA. The ability of the strategy to accurately identify antigenic determinants was demonstrated by showing that the predicted synthetic peptides were bound specifically by the respective antibodies.

Once again in 1986 a great deal of information has appeared on the pages of the JOURNAL. From a personal perspective a number of directions seems particularly pertinent.

In the general field of leprosy, two well-known and universally respected figures in the world of leprosy died, Dr. Robert G. Cochrane and Dr. Stanley G. Browne. The First International Symposium on Leprosy in Guangzhou, People's Republic of China, held in November 1985 was noted. The first announcements of the XIII Leprosy Congress in The Hague in 1988 appeared.

In the field of chemotherapy, there was a report that giving prothionamide and rifampin on different days may result in less liver toxicity. Depot preparations of dapsone and monoacetyldapsone have been developed. Several case reports have appeared

of renal failures with intermittent rifampin. A second patient with clofazimine-resistant bacilli, as judged by mouse foot pad sensitivity testing, was reported. Relapse rates in lepromatous leprosy patients treated with 20 years of sulfone monotherapy and then having their treatment discontinued were 8.6% in an 8–9 year follow-up period. Reinfection may be important in causing relapses after chemotherapy is discontinued in patients from endemic areas. Six months' treatment of paucibacillary leprosy patients with rifampin plus dapsone may be insufficient, and one year's treatment may be preferable. A number of promising drugs appeared on the horizon including minocycline, ofloxacin, and three rifampin analogs R-76-1, DL 473, and R-77-3. Whether these drugs offer advantages over currently available drugs remains to be seen, of course.

Clinically, it was reported that over half of leprosy patients have impaired taste sensation and almost half have impaired olfaction. ENL may be associated with occult fibrinolysis. Sensation in skin lesions frequently improves with chemotherapy. The earlobes seem to be the best sites for slit-skin smears overall.

A great deal of newer information is available in the field of immuno-pathology. There are apparent differences in bacterial load and classification between skin lesions and nerve lesions taken from the same individuals. Positive lepromin skin tests are associated with resistance to infection with *M. leprae* in both armadillos and monkeys. ICRC bacilli are reported capable of converting lepromin skin tests in langur monkeys. Macrophages from lepromatous leprosy patients seem to be producing large amounts of prostaglandin E₂ in response to *M. leprae*. Some lepromatous leprosy patients have T cells which can be made to respond to *M. leprae* with preincubation in the absence of antigen, interleukin-2, or with monocyte depletion *in vitro*. Others cannot. Up to 5×10^8 killed armadillo-derived *M. leprae* intradermally appear to be tolerated by normal PPD-positive subjects. Recombinant gamma-interferon has been used intradermally in lepromatous leprosy as immunotherapy. Synthetic neoglycoconjugates based on PGL-I are being synthesized and are being found useful serologically. A new

monoclonal antibody for the detection of activated, antigen-specific, helper T cells, TA1, detected activated helper T cells in a high proportion of the lymphocytes in tuberculoid and reversal reaction skin lesions but not in lepromatous or ENL skin lesions. A number of T-cell lines and T-cell clones have been produced with reactivity to different epitopes of the protein antigens of *M. leprae*. Some of these clones are of the helper/inducer phenotype and others are of the suppressor/cytotoxic phenotype. Based on the determined DNA sequences coding for the 65 kD protein antigen of *M. leprae*, synthetic peptides have been produced which react with specific monoclonal antibodies against two epitopes of the native protein.

Steady progress is being made in the field of microbiology. Measurements of ATP of *M. leprae in vitro* have been refined. Clofazimine and a number of other potential antileprosy drugs have been found to accelerate the rates of decay of ATP of *M. leprae in vitro*. The technique is also being used for cultivation attempts. The bacilli are being maintained for 8 weeks or longer and are maintaining their growth potential in artificial media. A new method for purifying *M. leprae* from armadillo liver tissue eliminates a particulate "pigment." Cat leprosy bacilli have been shown to be identical to murine leprosy bacilli. Lipoarabinomannan has been identified as a major cell-wall antigen of the leprosy bacillus. *M. leprae* rDNA expression libraries are being produced in a number of vectors.

In the field of experimental infections with *M. leprae*, the nasal mucosa seems to be a favored site of entry of *M. leprae* into nude mice. Various serum enzymes and serology have been suggested as a means of following *M. leprae* infections in armadillos. Leprosy has apparently been present in wild armadillos in Louisiana in the U.S.A. at least since 1961.

Patterns in the epidemiology of leprosy in areas of the world where the disease is declining are becoming apparent. BCG is sufficiently protective against leprosy in east and central Africa that it has been advocated as a routine element in leprosy control in those areas. This is not the case in Burma, where its efficacy is much less.

In literature relating to tuberculosis, it has

been pointed out that the sterilizing activity of a drug, and not its early bactericidal activity, is the measure of its ability to shorten a chemotherapeutic regimen.

From the perspective of the 1986 JOURNAL, an explosion of information is occurring, particularly in the field of the immunology of leprosy. The stage is being set

for significant advances in microbiology and chemotherapy. Hopefully this new basic information can be translated quickly and efficiently into better care of leprosy patients and better means to prevent the disease. Much is becoming clearer. Much remains to be learned. I look forward with impatient optimism to 1987.—RCH