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IMMUNITY IN LEPROSY : III. CELL MEDIATED IMMUNITY

Understanding the Mechanism of Unresponsiveness

Macrophage/Antigen Presenting Cell

It is known that *M. leprae* is an obligatory parasite and resides inside the macrophages/Schwann cells and produces a granuloma in the host. The claim[253] that macrophages from lepromatous patients are incapable of killing *M. leprae in vitro* was contradicted later[254,255]. While studying the capability of *M. leprae* antigen presentation by the macrophages of LL patients, Hirschberg[256] pointed out that due to the defect in the macrophage presentation of antigen, LL patients are unable to respond to *M. leprae*. Nath *et al*[257] further confirmed this observation in HLA-D matched co-cultured situations. They showed that the macrophages from LL patients inhibited the lymphoproliferation of peripheral blood in *M. leprae* responding individuals. Nath *et al*[257] further showed that lymphocytes of LL patients were capable of undergoing proliferation when macrophages from tuberculoid patients were added in the culture, indicating thereby that antigen reactive T cells are present in the peripheral blood of LL patients. However, a study[258] in HLA-D identical siblings completely negated the role of monocyte population[257] and suggested a T cell defect being responsible for the unresponsiveness. More data are now available[259] indicating that the adherent cells in the peripheral blood of lepromatous individuals having macrophage characteristics, induce a suppressive effect on the antigen induced lymphoproliferation in HLA-D identical tuberculoid patients and healthy contacts. It was further concluded that the suppression induced by these macrophages is due to some soluble factors liberated by these cells[259]. In support of this view, Salgame *et al*[260] had already established that lysates of LL macrophages inhibit protein synthesis of normal macrophages in addition to the inhibition of lymphoproliferation[261]. Recently, the soluble factor was characterised[262] and was found to be heat-stable, indomethacin resistant and of >25 kDa.

It has been shown that the macrophages after phagocytosis of live *M. leprae* downregulate their own Fc receptor expression, biochemical and other functions[263]. In addition, the macrophages of LL patients have been shown to have a selective depression in leucine uptake and exhibited a reduction of Fc receptors only when exposed to *M. leprae*[260]. Mahadevan and Antia[264] proposed that macrophages after phagocytosis of *M. leprae* lose their capacity to process antigen leading to a CMI defect. At the same time it has been noted that Schwann cells after phagocytosis of *M. leprae* lose their capacity to synthesise DNA and are unable to associate themselves with axon thereby inducing a defect in C-fibre function. Recently, Marolia *et al*[265] noted that macrophages from the peripheral blood of patients of paucibacillary and multibacillary leprosy, but not of healthy individuals, are inefficient in killing phagocytosed *M. leprae* due to their inability to produce superoxide (O_2^-) and hydroxyl radicals (OH^-).

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Immune responses are controlled partially by soluble factors liberated by the lymphoreticular system. IL-1 liberated by macrophages, acts upon T cells in the early G1 phase of the cell cycle and prepares the T cells to respond to the subsequent signals. Initial report by Horwitz *et al*[266] of lowered production of cytokine by macrophages of lepromatous patients has been further confirmed and characterised by Watson *et al*[267] while studying the IL-1 production in LPS stimulated monocytes. They noted that 38.5 per cent of BL/LL patients failed to produce IL-1 while TT/BT patients were able to either produce IL-1 in the normal range spontaneously or upon stimulation. Similar findings were also reported in a *M. leprae* stimulated situation[268].

Tumour necrosis factor (TNF-α) is a secretory product of macrophages[269] and activated mononuclear cells of the peripheral blood[270,271]. Higher levels of TNF-α have been seen to be associated with malaria and kala-azar[272]. Using a bioassay higher levels of TNF in serum[273] and higher TNF production by antigen induced mononuclear cells[274] have been noted in tuberculoid patients as compared to patients with various lepromatous forms. However, a higher level of TNF-α in sera of lepromatous patients[275] could be due to the presence of inhibitors in the sera of such patients. The presence of such inhibitors has already been reported in tuberculosis and sarcoidosis[276]. Moreover, the presence of higher number of TNF containing cells[277], higher concentration of TNF mRNA by *in situ* hybridization[278], and PCR amplification[252] in tuberculoid skin lesions than in lepromatous lesions have already been reported. The protective role of TNF can further be explained by the finding of its inhibitory role in mycobacterial multiplication in murine and human macrophages[279]. Moreover, TNF has been recently, shown to enhance the production of nitric oxide in mouse macrophages[280] which in turn have been shown to kill *M. leprae*[280]. Further the finding of high levels of TNF[274] in active ENL patients could explain the clinical manifestations of fever and nerve damage which have been noted by TNF inoculation in mice[281] and by *in vitro* experiments[282,283] respectively.

T Cells

The understanding of suppressor function of a subpopulation of T cells in mice, which regulates the immune response, prompted researchers to work on normal and diseased states of human beings. Investigators engaged in leprosy research also generated data on the T suppressor (OKT8+) cells in leprosy. A preliminary study[284] in an Ethiopian population indicated that *M. leprae* antigens generally suppress the *in vitro* PHA-induced lymphoproliferation in leprosy patients and their household contacts. While working with ConA induced lymphoproliferation in leprosy patients and healthy individuals, Mehra *et al*[285] noted that Dharmendra antigen suppressed the ConA induced proliferation selectively in majority of lepromatous and borderline patients and not in tuberculoid and healthy individuals. These authors further pointed out that the suppression was induced by the generation of the classical T8+ and TH2+ phenotype markers bearing suppressor cells[286,287]. Although these studies demonstrated that suppressor T cells were responsible for the suppression of CMI in lepromatous leprosy, Stoner *et al*[288] could not establish such a role, rather they noted a lack of these cells in most of the Ethiopian patients. Further, from their observations on subclinically infected healthy individuals these workers established that there is an association of suppressor cell activity with resistance to *M. leprae* infection[289]. To prove the role of suppressor cells in leprosy, Nath *et al*[290] have done extensive work in untreated leprosy patients belonging to both hyperendemic and low endemic areas of India. It was noted in a 4-day culture condition that ConA induced suppressor cells selectively suppressed the autologous mitogenic responses of tuberculoid patients. Further, this ConA stimulated lymphoproliferation was suppressed by addition of *M. leprae* antigen in a large number of tuberculoid patients but not in all the lepromatous patients. On the other hand, many of the lepromatous patients showed enhancement in the lymphoproliferative response. However, when the cultures were continued for 6 days the differences in suppression in various groups were abolished and the suppressive effect was noted uniformly in all subjects[291] as earlier noted by Bjune[284]. Earlier studies, where T cell bearing Fc receptors for IgG used to be considered as suppressor T cell subset, also indicated the presence of normal levels of these cells in tuberculoid patients[292] with a reduction in their number in lepromatous patients[293].

The results of these studies on the suppressor cell activity are very divergent in their views. The suppressor cell activity in tuberculoid type of leprosy gains support from only one observation wherein the suppressor cell generation was mostly associated with a strong CMI response[294], which might possibly play a role in the suppression of unwanted antibody production[295]. On the other hand, with the understanding of murine

TH1/TH2 subsets and their biological function[296,297] more evidence is being accumulated to show that TH1 lymphocyte proliferation alongwith IFN-γ secretion are associated with acute stage of the disease whereas TH2 lymphocyte proliferation with increase of IL4 and IL10 are associated with chronic disease[298-300]. Recently, Salgame *et al*[301] categorised the functional subsets of T cells in leprosy. They established that CD4+ cells cloned from tuberculoid patients produced more IFN-γ, whereas those obtained from lepromatous patients produced more IL4. In addition, CD8+ T suppressor clones producing IL4 isolated from lepromatous patients were found to be essential for suppression of *in vitro* responses to antigen in these patients. However, more recently the role of contrasuppressor (Cs) cells for antagonising the suppressor function in leprosy, has also been reported[302]. Cs cells are known to interact with CD4+ cells and render them unresponsive to the signals of CD8+ cells[303]. Cs-like functional activity has also been noted in CD8+ cells in leprosy[302].

T cell unresponsiveness to *M. leprae* stimulation in lepromatous leprosy has also been attributed to the lack of lymphokine production by the immune cells[266,304-307]. Several workers[308-310] have noted T cells in LL patients are incapable of specific antigen stimulated proliferation due to deficiency of IL-2. However, in spite of exogenous supply of IL-2 in about one third of the patients, T cell unresponsiveness could not be corrected[308]. All these studies have also indicated that in most lepromatous leprosy patients, there is no clonal deletion of *M. leprae* specific T cells which was opined earlier by Godal *et al*[171]. This unresponsiveness may be either due to lack of required number of *M. leprae* reactive T cells being circulated[307] or to the presence of monocytes which are liberating suppressive factors[311]. In contrast to the above findings Mohagheghpour *et al*[312] could not find IL-2 deficiency in lepromatous patients; they suggested that the unresponsiveness could be due to the lack of IL-2 receptor on the T cells. An interesting observation[313] recently made relates to CD4+ cells of LL patients which were found to respond to *M. leprae* stimulation after culture for 48 hours in medium alone. They further noted that the recovery of this T cell reactivity was blocked by the presence of *M. leprae* in preculture medium. These authors reasoned the unresponsiveness to be due to the persistence of antigen which renders unresponsive the antigen responsive T cells.

Downregulation of T cell response specially by *M. leprae* modulating the CD2 has been recently postulated by Muthukkaruppan *et al*[188,189]. Using OKT11 and OKT3 monoclonal antibodies they showed that bacilliferous lepromatous leprosy patients while exhibiting low levels of CD2+ cells show normal levels of CD3+ cells. Further, when *M. leprae* (Dharmendra lepromin only) were exposed to the suspension of peripheral blood T lymphocytes obtained from normal healthy individuals, CD2+ cells were reduced in number while the CD3+ cell number remained intact. These observations indicated that *M. leprae* antigens by modulating the E-receptor of T cells, might be inducing the suppression. Contrary to this, Wong *et al*[314] while looking for expression of CD2+ and CD3+ receptors on lymphocytes in lepromatous skin lesions and peripheral blood found that virtually all the CD3+ cells express CD2 in both situations.

Other Factors

Serum/plasma

From time to time, the presence of some unknown factors in the blood plasma/serum of leprosy patients which are capable of inhibiting the *in vitro* growth of autologous lymphocytes have been reported[175,176,315-317]. Bullock and Fasal[170] and others[175,318] described that some LL sera are lymphocytotoxic and these sera also suppress the lymphoproliferation induced by PHA. Later Potts *et al*[316] and Kerr *et al*[317] showed that the inhibition in lymphoproliferation is due to the decrease in number of cells responding to mitogen. On the other hand, Kerr *et al*[317] have recently shown that the putative inhibitory factor(s) is (are) not cytotoxic. The suppression in the proliferative response may be due to an inherent cellular defect or to factors in the serum which inhibit lymphocyte activation. They further characterised[317] the inhibitory factor which was resistant at 60° C for 30 minutes and was denatured at 100° C. A very interesting report[319] is available showing that LL sera bring down some chromosomal aberrations of normal lymphocytes in culture, leading to a lowering in the mitotic index and thus inhibiting lymphoproliferation.

Although the presence of such serum/plasma factors in leprotic patients, has been reported by different workers, these factors need further chemical and structural characterisation to substantiate the findings.

Mycobacterial component

In addition to the isolation from lepromatous lesions, of T-cell clones having suppressor functions[320],

M. leprae soluble products have also been shown to suppress lymphoproliferation to the antigen not only of lepromatous but also of tuberculoid patients[321]. It is also possible that a nonspecific suppressive function by microbial fraction may be responsible for the suppression as noted by Molloy *et al*[322]. Holzer *et al*[323] noted that *M. leprae*, as a whole, fails to stimulate human blood monocytes, neutrophils and murine peritoneal macrophages to generate superoxide anions (respiratory burst). Vachula *et al*[324] pointed out the role played by phenolic glycolipid-I (PGL-I) in blocking the respiratory burst of human macrophages. Recently, Parkash and Sengupta[325] have hypothesised that the failure of oxidative burst exhibited by *M. leprae* phagocytosed macrophages is probably due to the complement mediated entry of *M. leprae* into the monocytes. Such a view has already been favoured by workers using various particulate materials including *Leishmania major* as a pathogen[326-330]. With regard to the PGL-I induced suppressive function by macrophages further evidence has accumulated from the work of Neill and Klebanoff[331] who showed that both purified PGL-I and its deacylated form abolished the antimicrobial effect by blocking the xanthine oxidase system which is essential for the release of OH^-. Blocking effect on the myeloperoxidase-H_2O_2-halide system was also observed using this lipid.

Another cell-wall associated lipid of mycobacterial species, lipoarabinomannan (LAM), which has been shown to inhibit antigen responsiveness of human peripheral blood leucocyte[332] and antigen induced proliferation of CD4+ T cell clones[333], has also been found to block the activation of macrophages without any change in their capability of phagocytosis[334]. The same group of workers further demonstrated[335] that LAM is able to block the activation of mouse macrophages induced by IFN-γ.

M. leprae protein components and 12 kDa protein antigen of *M. leprae* have been shown by Sengupta *et al*[187] to suppress the tuberculin induced DTH response *in vivo* in leprosy patients. However, such a suppression could not be reproduced by Fine *et al*[336]. This discrepancy may be due to the differences in the type of leprosy patients studied and the differences in the genetics of the ethnic group included in these studies.

All the above studies proved beyond doubt that there are several *M. leprae* components which are suppressive for cell immune functions and these components may be playing a major role in the pathogenesis of leprosy.

Antibodies/immune complexes

It is known that entry of *M. leprae* leads to host immune response by production of antibodies and CMI against the pathogen. This is also known that there is an inverse correlation between CMI and *M. leprae* antibody levels in leprosy patients[6,311]. It could be expected that when the protective antigens are capable of eliciting both CMI and antibody in the host, the antibodies can mask the *M. leprae* antigens expressed on the membranes of antigen presenting cells and this could result in the lowering of CMI[337]. Further, preliminary evidence has been provided by Tyagi *et al*[338] to suggest that circulating immune complexes from leprosy patients could suppress the *M. leprae* induced lymphocyte proliferation.

Antigenic Mimicry

M. leprae has been known to have afflicted human beings since biblical time. It is possible that during these many years the organism has adapted to the human host, in a way that it generally does not evoke a strong host immune response. The unresponsiveness of the host is possible if *M. leprae* share or "mimic" some of their antigens with the host tissues. Such a possibility is not far fetched, as it has been reported that human tissues possess proteins which are almost similar to mycobacterial 65 kDa heat shock protein when compared on the basis of their aminoacid sequences[339,340]. Recently, Naafs *et al*[341] have shown that 8 monoclonal antibodies (MAb) against *M. leprae* determinants (12 kDa, 18 kDa and 65 kDa) reacted with dermal determinants. If at all these similarities are founded then these *M. leprae* antigens would be recognised as self and due to the presence of some minor dissimilarities in some sequences from the host proteins, they would evoke an autoimmune reaction. Evidence exists for such a situation in other diseases like Group A streptococcal myocarditis[342], rheumatoid arthritis in *M. tuberculosis* infection[343], myasthenia gravis[344] and neuropathy/cardiomyopathy in Chagas disease[344,345].

An attempt has been made in this review to cover various aspects of studies on the humoral and cellular immunology on which studies have been carried out to understand the disease process. It is known that there are genes for immune responses as well as for immune suppression[346] It has not yet been established whether a genetic mechanism also plays a role in modulating the host immune response. However, a significant association of HLA-DR2[347-352] and HLA-DR3[350] molecules with various types of leprosy has been claimed. The role played by HLA-DR antigens in modulating the immune response to *M. leprae* antigens calls for separate mention.

References:

6. Ridley, D.S. and Jopling, W.H. Classification of leprosy according to immunity: A five-group system. *Int J Lepr 34*: 255, 1966.

170. Bullock, W.E. and Fasal, P. Studies of immune mechanisms in leprosy. III. The role of cellular and humoral factors in impairment of the *in vitro* immune response. *J Immunol 106:* 888, 1971.

171. Godal, T., Myklestad, B., Samuel D.R. and Myrvang, B. Characterisation of the cellular immune defect in lepromatous leprosy: A specific lack of circulating *Mycobacterium leprae*-reacting lymphocytes. *Clin Exp Immunol 9:* 821, 1971.

175. Nelson, D.S., Nelson, M., Thurston, J.M., Waters, M.F.R. and Pearson, J.M.H. Phytohemagglutinin-induced lymphoctye transformation in leprosy. *Clin Exp Immunol 9:* 33, 1971.

176. Wong, P.C., Chan-Teoh, C.H., Wu, S. and Kendall, F.H. Transformation of lymphocytes by phytohemagglutinin in leprosy sera. *Int J Lepr 39:* 7, 1971.

187. Sengupta, U., Sinha, S., Ramu, G., Lamb, J. and Ivanyi, J. Suppression of delayed hypersensitivity skin reactions to tuberculin by *M.leprae* antigens in patients with lepromatous and tuberculoid leprosy. *Clin Exp Immunol 68:* 58, 1987.

188. Muthukkaruppan, V.R. A possible role for E-receptor in immunosuppression. *Indian J Lepr 58:* 389, 1986.

189. Muthukkaruppan, V.R., Chakkalath, H.R. and Malarkannan, S. The classical and alternate pathways of T-cell activation are impaired in leprosy. *Immunol lett 19:* 55, 1988.

252. Yamamura, M., Uyemura, K., Deans, R.J., Weinberg, K., Rea, T.H., Bloom, B.R. and Modlin, R.L. Defining protective responses to pathogens: Cytokine profiles in leprosy lesions. *Science 254:* 277, 1991.

253. Beiguelman, B. Leprosy and genetics. A review of past research with remarks concerning future investigations. *Bull WHO 37:* 461, 1967.

254. Godal, T. and Rees, R.J.W. Fate of *M.leprae* in macrophages of patients with lepromatous or tuberculoid leprosy. *Int J Lepr38:* 439, 1970.

255. Samuel, D.R., Godal, T., Myrvung, B. and Song, Y.K. Behaviour of *M.leprae* in human macrophages *in vitro. Infect Immun 8:* 446, 1973.

256. Hirschberg, H. The role of macrophages in the lymphoproliferative response to *M.leprae in vitro. Clin Exp Immunol 34:* 46, 1978.

257. Nath, I., Van Rood, J.J., Mehra, N.K. and Vaidya, M.C. Natural suppressor cells in human leprosy: The role of HLA-D-identical peripheral lymphocytes and macrophages in the *in vitro* modulation of lymphoproliferative responses. *Clin Exp Immunol 42:* 203, 1980.

258. Stoner, G.L., Mshana, R.N., Touw, J. and Belehu, A. Studies on the defect in CMI in lepromatous leprosy using HLA-D-identical siblings. Absence of circulating suppressor cells and evidence that the defect is in the T-lymphocyte rather than the monocyte population. *Scand J Immnol 15:* 33, 1982.

259. Nath, I. Mechanisms underlying unresponsiveness to *M. leprae:* The role of suppressor T cells and adherent cells in human leprosy. *6th IMMLEP Scientific Working Group Meeting WHO, Geneva,* 1982.

260. Salgame, P.R., Birdi, T.J., Mahadevan, P.R. and Antia, N.H. Role of macrophages in defective cell mediated immunity in lepromatous leprosy. I. Factor(s) from macrophages affecting protein synthesis and lymphocyte transformation. *Int J Lepr 48:* 172, 1980.

261. Salgame, P.R., Mahadevan, P.R. and Antia, N.H. Mechanism of immunosuppression in leprosy: Presence of suppressor factor(s) from macrophages of lepromatous patients. *Infect Immun 40:* 1119, 1983.

262. Satish, M., Bhutani, L.K., Sharma, A.K. and Nath, I. Monocyte-derived soluble suppressor factor (s) in patients with lepromatous leprosy. *Infect Immun 42:* 890, 1983.

263. Birdi. T.J., Salgame, P.R., Mahadevan, P.R. and Antia, N.H. Role of macrophages in defective cell mediated immunity in lepromatous leprosy.II. Macrophage and lymphocyte interaction. *Int J Lepr 48:* 178, 1980.

264. Mahadevan, P.R. and Antia, N.H. Biochemical alterations in cells following phagocytosis of *M.leprae*. The consequence—A basic concept. *Int J Lepr 48:* 167, 1980.

265. Marolia, J., Robinson, P and Mahadevan, P.R. A complex component modulating immune-deficient cells in leprosy patients leading to loss of viability of *Mycobacterium leprae*—A possible vaccine. *Clin Exp Immunol 79:* 7, 1990.

266. Horwitz, M.A., Levis, W.R. and Cohn, Z.A. Defective production of monocyte-activating cytokines in lepromatous leprosy. *J Exp Med 159:* 666, 1984.

267. Watson, S., Bullock,W., Nelson, K., Schauf, V., Gelber, R. and Jacobson, R. Interleukin 1 production by peripheral blood mononuclear cells from leprosy patients. *Infect Immun 45:* 787, 1984.

268. Ridel,P-R., Jamet,P., Robin, Y. and Bach, M-A. Interleukin-1 released by blood monocyte-derived macrophages from patients with leprosy. *Infect Immun 52:* 303, 1986.

269. Beutler, B., Cerami, A. Cachectin and tumour necrosis factor as two sides of the same biological coin. *Nature 320:* 584, 1986

270. Peters, P.M., Octaldes, J.R., Shalaby M.R., Sevedersky, L.P., Nedwin, G.E., Bringman, T.S., Hass, P.E., Aggarwal, B.B., Herberman, R.B., Goeddel, D.Y. and Palladino, M.A. Natural killer sensitive targets stimulate production of TNF- α but not TNF- γ (lymphotoxin) by highly purified human peripheral blood large granular lymphocytes. *J Immunol 137:* 2592, 1986.

271. Culturi,M.C., Murphy, M., Costa-Giomi,M.P., Weinmann, R., Perussia, B. and Trinchieri, G. Independent regulation of tumour necrosis factor and lymphotoxin production by human peripheral blood lympocytes. *J Exp Med 165:* 1581, 1987.

272. Scuderi,P., Lam, K.S., Ryan, K.J., Petersen, E., Sterling,K.E.,Finley, P.R., Ray, C.G., Slymen, D.J. and Salmon, S.E. Raised serum levels of tumour necrosis factor in parasitic infections. *Lancet ii:* 1364, 1986.

273. Silva, C.L. and Foss, N.T. Tumour necrosis factor in leprosy patients. *J Infect Dis 159:* 787, 1989.

274. Barnes, P.F., Chatterjee, D., Brennan, P.J., Rea, T.H. and Modlin, R.L. Tumour necrosis factor production in patients with leprosy. *Infect Immun 60:* 1441, 1992.

275. Pisa,P., Gennene,M., Soder, O., Ottenhoff, T., Hansson, M. and Kiessling, R. Serum tumour necrosis factor levels and disease dissemination in leprosy and leishmaniasis. *J Infect Dis 161:* 988, 1990.

276 Foley,N., Lambert,C., McNicol,M., Hohnson, N. and Rook, G.A.W. An inhibitor of the toxicity of tumour necrosis factor on the serum of patients with sarcoidosis, tuberculosis and Crohn's disease. *Clin Exp Immunol 80:* 395, 1990.

277. Arnoldi, J., Gerdes, J. and Flad, H.D. Immunohistologic assessment of cytokine production of infiltrating cells in various forms of leprosy. *Am J Pathol 137:* 749, 1990.

278. Sullivan, L., Sano, S., Pirmez, C., Salgame, P., Mueller, C., Hofman, F., Uyemura, K., Rea, T.H., Bloom, B.R. and Modlin, R.L. Expression of adhesion molecules in leprosy lesions. *Infect Immun 59:* 4154, 1991.

279. Bermudez, L.E.M. and Young, L.S. Tumour necrosis factor, alone or in combination with IL-2, but not IFN-gamma, is associated with macrophage killing of *Mycobacterium avium* complex. *J Immunol 140:* 3006, 1988.

280. Adams, L.B., Franzblan, S.G., Vavrin, Z., Hibbs, J.B. and Krahenbuhl, J.L. L-Arginine-dependent macrophage effector functions inhibit metabolic activity of *Mycobacterium leprae*. *J Immunol 147:* 1642, 1991.

281. Beutler, B.and Cerami, A. Cachectin: More than a tumour necrosis factor. *N Engl J Med 316:* 379, 1987.

282. Selmaj, K.W. and Raine, C.S. Tumour necrosis factor mediates myelin and oligodendrocyte damage *in vitro*. *Ann Neurol 23:* 339, 1988.

283. Thomson, B.M., Mundy, G.R. and Chambers, T.J. Tumour necrosis factors alpha and beta induce osteoblastic cells to stimulate osteoclastic bone resorption. *J Immunol 138:* 775, 1987.

284. Bjune, G. *In vitro* lymphocyte stimulation in leprosy; simultaneous stimulation with *Mycobacterium leprae* antigens and phyto-hemagglutinin. *Clin Exp Immunol 36:* 479, 1979.

285. Mehra, V., Mason, L.H., Fields, J.P. and Bloom, B.R. Lepromin-induced suppressor cells in patients with leprosy. *J Immunol 123:* 1813, 1979.

286. Mehra, V., Convit, J., Rubinstein, A. and Bloom, B.R. Activated suppressor T cells in leprosy. *J Immunol,129:* 1946, 1982.

287. Mehra, V., Mason, L.H., Rothman, W., Reinherz, E., Schlossman, S.F. and Bloom, B.R. Delineation of a human T-cell subset responsible for lepromin-induced suppression in leprosy patients. *J Immunol 125:* 1183, 1980.

288. Stoner, G.L., Mshana, R.N., Touw, J. and Belehu, A. Studies on the defect in CMI in lepromatous leprosy using HLA-D-identical siblings. Absence of circulating suppressor cells and evidence that the defect is in the T-lymphocyte rather than the monocyte population. *Scand J Immunol 15:* 33, 1982.

289. Stoner, G.L., Atlaw, T., Touw, J. and Belehu, A. Antigen-specific suppressor cells in subclinical leprosy infection. *Lancet ii:* 1372, 1981.

290. Nath, I., Narayanan, R.B., Mehra, N.K., Sharma, A.K.and Gupta, M.D. Concanavalin A-induced suppressor activity in human leprosy. *J Clin Lab Immunol 2:* 319, 1979.

291. Nath, I. and Singh, R. The suppressive effect of *M. leprae* on the *in vitro* proliferative responses of lymphocytes from patients with leprosy. *Clin Exp Immunol 41:* 406, 1980.

292. Moretta, L., Webb, S.R., Grossi, C.E. Lydyard, P.M. and Cooper, M.D. Functional analysis of two human T-cell subpopulations: Help and suppression of B-cell responses by T cells bearing receptors for IgM and IgG. *J Exp Med 146:* 184, 1977.

293. Singh, S. and Nath, I. Reduction of a subset of T cells bearing Fc receptors for IgG in lepromatous leprosy. *Int Arch Allergy Appl Immunol 62:* 81, 1980.

294. Scheper, R.J., Parker, D., Noble B. and Turk, J.L. The relation of immune depression and B-cell stimulation during the development of delayed type hypersensitivity to soluble antigens. *Immunology, 32:* 365, 1977.

295. Nath, I. Immunology of human leprosy—Current status. *Lep Rev (Special Issue):* 31S, 1983.

296. Mosman, T.R. and Coffman, R.L. TH1 and TH2 cells: Differnt patterns of lymphokine secretion lead to different functional properties. *Ann Rev Immunol 7:* 145, 1989.

297. Mosman, TR and Moore K.W. The role of IL-10 in cross regulation of TH1 and TH2 responses. *Immunol Today 12:* A49, 1991.

298. Boom, W.H., Leibster, L., Abbas, A.K. and Titus, R.G. Patterns of cytokine secretion in murine leishmaniasis: Correlation with disease progression or resolution. *Infect Immun 58:* 3863, 1990.

299. Scott, P. IFN-modulates the early development of Th1 and Th2 responses in a murine model of cutaneous leishmaniasis. *J Immunol 147:* 3149, 1991.

300. Sher, A., Fiorentino, D., Cospar, P., Pearce, E. and Mosmann, T. Production of IL-10 by CD4 T lymphocytes in helminth infection. *J Immunol 147:* 2713, 1991.

301. Salgame, P., Abrams, J.S. Clayberger, C., Goldstein, H., Convit, J., Modlin, R.L. and Bloom, B.R. Differing lymphokine profiles of functional subsets of human CD4 and CD8 T cell clones. *Science 254:* 279, 1991.

302. Gonza'lez-Amaro, R., Salazar-Gonza'lez, J.F., Baranda, L., Abud-Mendoza, C., Moncarda, R., Gracia, R. and Icoocer-Varela, J. Evidence of cell-mediated immune contra-suppression in lepromatous leprosy: Modulation of a putative T contra-suppressor cell-subset. *Clin Exp Immunol 71:* 399, 1988.

303. Green, D.R., Earley, D.D., Kimura, A., Murphy, D.B., Yamauchi, K. and Gershon, R.K. Immunoregulatory circuits which modulate responsiveness to suppressor cell signals: Characterization of an effector cell in the contra suppressor circuit. *Eur J Immunol 11:* 973, 1981.

304. Haregewoin, A., Godal, T., Mustafa, A.S., Belehu, A. and Yemaneberhan, T. T cell conditioned media reverse T-cell unresponsiveness in lepromatous leprosy. *Nature 303:* 342, 1983.

305. Nogueira, N., Kaplan, G., Levy, E., Sarno, E.N., Kushner, P., Granelli-Piperno, A., Vieira, L., Gould, V.C., Levis, W., Steinman, R., Yip, Y.K. and Cohn, Z.A. Defective γ interferon production in leprosy. Reversal with antigen and interleukin 2. *J Exp Med 158:* 2165, 1983.

306. Modlin, R.L., Hofman, F.M., Horwitz, D.A., Husmann, L.A., Gillis, S., Taylor, C.R. and Rea, T.H. *In situ* identification of cells in human leprosy granulomas with monoclonal antibodies to interleukin 2 and its receptor. *J Immunol 132:* 3085, 1984.

307. Nathan, C.F., Kaplan, G., Levis, W.R., Nusrat, A., Witmer, M.D., Sherwin, S.A., Job, C.K., Path, F.R.C., Horowitz, C.R., Steinman, R.M. and Cohn, Z.A. Local and systemic effects of intradermal recombinant interferon in patients with lepromatous leprosy. *N Eng J Med 315:* 6, 1986.

308. Nath, I., Sathish, M., Jayraman, T., Bhutani, L.K. and Sharma, A.K. Evidence for the presence of *M. leprae* reactive T lymphocytes in patients with lepromatous leprosy. *Clin Exp Immunol 58:* 522, 1984.

309. Kaplan, G., Weinstein, D., Steinman, R.M., Levis, W.R., Elvers, U., Patarroyo, M.E. and Cohn, Z.A. An analysis of *in vitro* T cell responsiveness in lepromatous leprosy. *J Exp Med 162:* 917, 1985.

310. Nath, I., Jayraman, J., Sathish, M., Bhutani, L.K. and Sharma, A.K. Inhibition of interleukin-2 production by adherent cell factors from lepromatous leprosy patients. *Clin Exp Immunol 58:* 531, 1984.

311. Kaplan, G. and Cohn, Z.A. The immunobiology of leprosy. *Exp Pathol 28:* 45, 1986.

312. Mohagheghpour, N., Gelber, R.H., Larrick, J.W., Sasaki, D.T., Brennan, P.J. and Engleman, E.G. Defective cell-mediated immunity in leprosy: Failure of T cells from lepromatous leprosy patients to respond to *Mycobacterium leprae* is associated with defective expression of interleukin 2 receptors and is not reconstituted by interleukin 2. *J Immunol 135:* 1443, 1985.

313. Mohagheghpour, N., Gelber, R.R. and Engleman, E.G. T cell defect in lepromatous leprosy is reversible *in vitro* in the absence of exogenous growth factors. *J Immunol 138:* 570, 1987.

314. Wong, L., Salgame, P., Torigian, V,K., Fu, T.H.,Rea, T.H. and Modlin, R.L.CD2 Expression and function in lepromatous leprosy. *Infect Immun 57:* 2815, 1989.

315. Nelson, D.S., Penrose, J.M., Waters, M.F.R., Pearson, J.M.H. and Nelson, M. Depressive effect of serum from patients with leprosy on mixed lymphocyte reactions. Influence of anti-leprosy treatment. *Clin Exp Immunol 22:* 385, 1975.

316. Potts, R.C., Sheriff, M.M., Robertson, A.J., Gibbs, J.H., Brown, R.A. and Beck, J.S. Serum inhibitory factor in lepromatous leprosy, its effect on the pre-S phase cell cycle kinetics of mitogen stimulated normal human lymphocytes. *Immunology 14:* 269, 1981.

317. Kerr, M.A., Hussein, Y.N., Potts, R.C., Beck, J.S. and Sheriff, M.M. Characterisation of a factor in leprosy serum that inhibits the growth of mitogen stimulated normal human lymphocytes. *Immunology 61:* 117, 1987.

318. Naik, S., Bhusan, K., Surinder, K., and Sehgal, S. Cold reactive lymphocytotoxic antibodies in patients with tuberculoid and lepromatous leprosy. *Int J Lepr 55:* 273, 1987.

319. D'Souza, D., Das, B.C. and Thomas, I.M. Effects of lepromatous leprosy (LL) serum factor(s) on normal blood lymphocytes. *Int J Lepr 58:* 666, 1990.

320. Modlin, R.L., Kato, H., Mehra, V., Nelson, E.E., Xue-Dong,F., Rea, T.H., Pahengae, P.K. and Bloom, B.R. Genetically restricted suppressor T-cell clones derived from lepromatous leprosy lesions. *Nature 322:* 459, 1986.

321. Kaplan, G., Gandhi, R.R., Weinstein, D.E., Levis, W.R., Patarroyo, M.E., Brennan, P.J. and Cohn, Z.A. *Mycobacterium leprae* antigen induced suppression of T cell proliferation *in vitro. J Immunol 138:* 3028, 1987.

322. Molloy, A., Gaudernack, G., Levis, W.R., Cohn, Z.A. and Kaplan, G. Suppression of T-cell proliferation by *Mycobacterium leprae* and its products: The role of lipopolysaccharide. *Proc Natl Acad Sci USA 87:* 973, 1990.

323. Holzer, T.J., Nelson, K.E., Schauf, V., Crispen, R.G. and Andersen, B.R. *Mycobacterium leprae* fails to stimulate phagocytic cell superoxide anion generation. *Infect Immun 51:* 514, 1986.

324. Vachula, M., Holzer, T.J. and Anderson, B.R. Suppression of monocyte oxidative responses by phenolic glycolipid I of *Mycobacterium leprae. J Immunol 142:* 1696, 1989.

325. Parkash, O. and Sengupta, U. Survival of *Mycobacterium leprae* in mononuclear phagocytes: A possible role of complement system. *Acta Leprol 7:* 375, 1991.

326. Neuberger, P.E., Pagano, J.S., Greenberger, J.S., Karpas, A. and Cohen, H.J. Dissociation of opsonised particle phagocytosis and respiratory burst activity in an Epstein-bar virus-infected myeloid cell line. *J Cell Biol 85:* 549, 1980.

327. Wright, S.D. and Silverstein, S.C. Receptors for C3b and C3bi promote phagocytosis but not the release of toxic oxygen from human phagocytes. *J Exp Med 158:* 2016, 1983.

328. Yamamoto, K. and Johnston Jr. R.B. Dissociation of phagocytosis from stimulation of the oxidative metabolic burst in macrophages. *J Exp Med 159:* 405, 1984.

329. Mosser, D.M. and Edelson, P.J. The mouse macrophage receptor for C3bi (CR3) is a major mechanism in the phagocytosis of leishmania promastigotes. *J Immunol 135:* 2785, 1985.

330. Mosser, D.M. and Edelson, P.J. The third component of complement (C3) is responsible for the intracellular survival of *Leishmania major. Nature 327:* 329, 1987.

331. Neill, M.A. and Klebanoff, S. The effect of phenolic glycolipid-I from *Mycobacterium leprae* on the antimicrobial activity of human macrophages. *J Exp Med 167:* 30, 1988.

332. Kaplan, G., Ghandi, R., Weinstein, D.E., Levis, W.R., Patarroyo,M.E., Brennan, P.J. and Cohn, Z.A. *Mycobacterium leprae* antigen induced suppression of T cell proliferation *in vitro. J. Immunol. 138:* 3034, 1987.

333. Moreno, C. Mehlert, A. and Lamb, J. The inhibitory effects of mycobacterial lipoarabinomannan and polysaccharides upon polyclonal and monoclonal human T cell proliferation. *Clin Exp Immunol 74:* 206, 1988.

334. Sibley,L.D., Hunter, S.W., Brennan, P.J. and Krahenbuhl, J.L. Mycobacterial lipoarabinomannan inhibits gamma interferon-mediated activation of macrophages. *Infect Immun 56:* 1232, 1988.

335. Sibley. L.D., Adams, L.B. and Krahenbuhl, J.L. Inhibition of interferon-gamma-mediated activation in mouse macrophages treated with lipoarabinomannan.*Clin Exp Immunol 80:* 141, 1990.

336. Fine,P.E.M., Gruer, P.J.K., Maine, N., Ponnighaus, J.M., Rees, R.J.W. and Stanford, J.L. Failure of *Mycobacterium leprae* soluble antigens to suppress delayed-type hypersensitivity reaction to tuberculin. *Clin Exp Immunol 77:* 226, 1989.

337. Parkash, O. and Sengupta, U. Possible roles of anti-*Mycobacterium leprae* antibodies in suppression of cell-mediated immune response against *M.leprae. Immunol Today 13:* 513, 1992.

338. Tyagi, P., Patil, S.A., Girdhar, B.K., Katoch, K. and Sengupta, U. The suppressive effect of circulating immune complexes from leprosy patients on the lymphocyte proliferation induced by *M.leprae* antigens in healthy responders. *Int J Lepr 60:* 562, 1992.

339. Thole, J.E.R., Hindersson, P., de Bruyn, J., Cremers, F., Van der Zee, J., de Cock, H., Tommassen, J. Van Eden, W. and Van Embden, J.D.A. Antigenic relatedness of a strongly immunogenic 65-kDa mycobacterial protein antigen with a similarly sized ubiquitous bacterial common antigen. *Microb Pathogen 4:* 71, 1988.

340. Colston, M.J.and Lamb, F.I. Molecular biology of the mycobacteria. *Lepr Rev 60:* 93, 1989.

341. Naafs, B., Kolk, A.H.J., Chin A Lien, R.A.M., Faber, W.R., VanDijk, G., Kuijper, S., Stolz, E. and Van Joost, T. Anti-*Mycobacterium leprae* monoclonal antibodies cross-react with human skin: An alternative Explanation for the immune responses in leprosy. *J Invest Dermatol 94:* 685, 1990.

342. Cunningham, M.W., Hall, N.K., Krisher, K.K. and Spanier, A.M. A study of anti-group A streptococcal monoclonal antibodies cross-reactive with myosin. *J Immunol 136:* 293, 1986.

343. Holoshitz, J., Drucker, I., Yaretzky, A., Van Eden, W., Klajman, A., Lapidol, Z., Frenkel, A. and Cohen, I.R. T-lymphocytes of rheumatoid arthritis patients show augmented reactivity to a fraction of mycobacteria cross-reactive with cartilage. *Lancet ii:* 305, 1986.

344. Stefansson, K., Dieperink,M.E., Richman, D.P., Gomez, C.M. and Marton, L.S. Sharing of antigenic determinants between the nicotinic acetylcholine receptor and proteins in *Escherichia coli. Proteus vulgaris*, and *Klebsiella pneumoniae. N Eng J Med 312:* 221, 1985.

345. Wood, J.N., Hudson, L., Jessell, T.M. and Yamamoto, M. A monoclonal antibody defining antigenic determinants on subpopulations of mammalian neurones and *Trypanosoma cruzi* parasites. *Nature 296:* 34, 1992.

346. Ottenhoff, T.H.M. and De Vries, R.R.P. HLA class II immune response and suppression genes in leprosy. *Int J Lepr 55:* 521, 1987.

347. DeVries, R.R.P., Mehra, N.K., Vaidya, M.C., Gupte, M.D., Meera Khan, P. and Van Rood, J.J. HLA-linked control of susceptibility to tuberculoid leprosy and association with DR types. *Tissue Antigens 16:* 294, 1980.

348. Miyanaga, K., Juji, T., Maeda, H., Nakajima, S. and Kobayashi, S. Tuberculoid leprosy and HLA in Japanese. *Tissue Antigens 18:* 331, 1981.

349. Izumi, S., Sugiyama, K., Matsumoto, Y. and Ohkawa, S. Analysis of the immunogenetic background of Japanese leprosy patients by the HLA system. *Vox Sang 42:* 243, 1982.

350. Van Eden, W., De Vries, R.R.P., D' Amaro, J., Schreuder, I., Leiker, D.L., and Van Rood, J.J. HLA-DR associated genetic control of the type of leprosy in a population from Surinam. *Human Immunol 4:* 393, 1982.

351. Todd, J.R., West, B.C. and McDonald, J.C. Human leukocyte antigen and leprosy: Study in Northern Louisiana and review. *Rev Infect Dis 12:* 63, 1990.

352. Rani, R., Zaheer, S., and Mukherjee, R. Do human leukocyte antigens have a role to play in differential manifestation of multibacillary leprosy: A study on multibacillary leprosy patients from north India. *Tissue Antigens 40:* 124.1992.

This write-up (in 3 parts) was contributed by Dr. U. Sengupta, Central Jalma Institute for Leprosy, Agra.

ABSTRACTS

Some Research Projects Completed Recently

A study of toxocariasis.

The study was carried out to prepare and purify excretory-secretory (ES) antigens from second stage larvae of *Toxocara canis*, assess the antigenicity of crude ES antigens and fractions, and for comparative evaluation of enzyme linked immunosorbent assay (ELISA) and indirect haemagglutination assay (IHA) for serodiagnosis and seroepidemiology of toxocariasis.

Second stage larvae of *T. canis* were cultured *in vitro* in RPMI-1640 media at larval concentration of 1× 10^4 ml for collection of ES antigens. The SDS-PAGE of crude ES antigenic extract of larvae revealed eight protein fractions with molecular weights ranging from 42 to 117 kDa. However, SDS-PAGE of the sephadex G-25 fractionated crude antigen revealed seven protein fractions with molecular weights ranging from 15 to 169 kDa; 42 kDa fraction proved to be very specific for the detection of toxocara antibody and for skin testing.

Seroprevalence and seroepidemiological studies for toxocariasis were carreid out on 169 individuals clinically suspected to have toxocariasis and 150 healthy blood donors (control). The overall seropositivity in clinically suspected individuals was found to be 29.5 and 18.4 per cent with ELISA and IHA respectively, where as in controls only 2.6 per cent were positive (ELISA). The IgG levels were significantly higher than IgM in clinically suspected subjects while both were significantly higher compared to controls.

In an attempt to study the effect of visceral larva migrans, histopathology of different organs of rabbits, infected with different doses of infective *T. canis* eggs, was done. High eosinophilic infiltration, accumulation of macrophages, inflammation and oedema of the intestine was seen. Lungs showed peribronchiolar accumulation of eosinophils with eosinophilic exudates in the bronchioles and alveoli together with diffused interalveolar eosinophilic infiltration. Liver showed hepatic tissue destruction with haemorrhage and leukocyte infiltration followed by oedema and production of fibroblasts.

Seroepidemiological studies in 100 stray dogs using ELISA with larval ES as well as adult somatic antigens, showed 64 per cent seropositivity with larval ES antigens, and 50 per cent positivity with adult somatic antigen. Thus, the ES antigen appeared to be more specific than the somatic antigen.

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Frequency and nature of preneoplastic hepatocellular lesions in human and animal liver.

The study was carried out to determine the frequency of hepatocytic alterations of preneoplastic nature in livers of population groups with different incidences of hepatocellular carcinoma and Wister strain albino rats and rhesus monkeys exposed to different hepatocarcinogenic agents. Morphological and cytochemical profiles of preneoplastic cells were also studied.

Rats were treated with dimethylnitrosamine (single dose of 0.4 mg/100 g body wt. intraperitoneally 24 h after partial hepatectomy) or acetylaminofluorene (3 doses of 3 mg/100 g body wt. i.p. at 24 h intervals followed by partial hepatectomy 24 h after the last dose). A total of 5 rats and 4 monkeys were treated with aflatoxin B_1.

Qualitatively and quantitatively the sequence of preneoplastic and neoplastic events were similar in rats irrespective of the carcinogen used. Structurally altered hepatocytes occurred usually as small foci which later evolved into larger areas as nodules of altered liver cells. In monkeys treated with aflatoxin B_1 changes were mild and the lesions few. Histochemical localization of enzymes of carbohydrate metabolism *viz* glycogen synthetase, glycogen phosphorylase or glucose-6 phosphate dehydrogenase revealed no significant change in these enzymes. No significant changes were also noticed with the other enzymes. The acidophilic cells showed a variable pattern of staining for various enzymes.

It appears that chemical carcinogenesis induces multifocal hepatic glycogenosis which may be related to development of multicentric tumours. It is probable that metabolic disturbances leading to hepatocellular glycogenosis might be related to the neoplastic transformation of the hepatocytes.

Liver sections prepared from livers obtained from medico-legal autopsies of 114 cases (55 from Madras and 59 from New Delhi) were studied for the presence of altered hepatocytes. Altered cell foci were observed in 19 (34.5%) cases from Madras compared to 14 (23.7%) in New Delhi. The commonest cell type was the clear (glycogen rich) cell and some of these foci had acidophil cells admixed. The number of foci with acidophil cells were more in livers obtained from Madras compared to New Delhi.

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Effects and nature of corticosteroid treatment on various serological and bronchoalveolar lavage abnormalities in patients with sarcoidosis.

A total of 29 patients with sarcoidosis (mean age 39.5 yr) were studied to assess immunological abnormalities in serum and bronchoalveolar lavage (BAL) fluid. Attempts were also made to study the relationship, if any, between these abnormalities and clinical, physiological and radiological parameters in patients and the effect of corticosteroid treatment on various immunological abnormalities. None of the patients had any evidence of mycobacterial, fungal or parasitic infection or history of exposure to organic or inorganic material known to cause granulomatous lung disease. Controls (20 healthy individuals, matched for age) had normal chest radiographs and ancillary investigations including CT chest and bronchoscopy.

Pretreatment, the patients with sarcoidosis had increased total cell count, proportion of lymphocytes and helper/inducer cells (CD4+) and CD4+/CD8+ ratio in the BAL fluid. But the proportion of B cells in the BAL fluid was not significantly different from that of normal subjects. Absolute lymphocyte count, proportion of lymphocytes and helper/inducer cells (CD4+) were decreased significantly in the peripheral blood in patients of sarcoidosis. Levels of IgG, IgA and IgM as also whole complement (CH50) and C_3 and C_4 were increased in both peripheral blood and BAL fluid in patients. The circulating immune complexes (CICs) were increased in the peripheral blood in patients. Patients had low carbon monoxide diffusing capacity (DLco.) Their forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) were normal.

Patients were treated with prednisolone, 30 mg/day (for 6 weeks), and tapered at the rate of 2.5 mg/week until maintenance dose of 0.25 mg/kg/day was reached. Maintenance dose was given for 4-6 months. Twenty patients were followed up for clinical, physiological and radiological improvement.

Treatment brought about significant fall in the levels of IgG, IgA, IgM, C_3, C_4 and CH50 in both BAL fluid and peripheral blood. Absolute lymphocyte counts, the percentage of lymphocytes as also CD3+, CD4+, CD8+ and B cells in BAL fluid showed significant fall. But absolute lymphocyte counts and percentage of CD3+ and CD4+ cells in the peripheral blood increased significantly. However, in the peripheral blood, the proportion of lymphocytes did not change significantly after treatment whereas the percentage of B cells decreased significantly.

Of the 20 patients who were followed up, 14 responded to treatment. Total cell counts and the percentage of lymphocytes in both BAL fluid and peripheral blood and alveolar macrophages in BAL fluid did not differ significantly in responders and non responders. The proportion of CD3+ cells and levels of CH50 were higher and IgG and C_4 lower in BAL fluid in responders. Levels of IgG, IgA and CH50 were significantly lower while IgM, C_4 and CICs were higher in peripheral blood in responders.

Treatment resulted in significant increase in FVC and DLco. The FEV_1/FVC ratio remained unchanged.

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ICMR NEWS

The following meetings of various Expert Groups/Task Forces of the Council were held at New Delhi.

Expert Group on Pan Masala	February 22, 1994
Task Force on District level Project for Control of Cervical Cancer	March 2-3, 1994
Task Force on Child Psychiatric Epidemiology	March 16-17, 1994

Participation of ICMR Scientists in Scientific Events:

Dr. S.P. Pani, Dy. Director, Vector Control Research Centre, (VCRC), Pondicherry, participated in the meeting of the Steering Committee on Applied Field Research in Tropical Diseases (of the WHO Special Programme for Research and Training in Tropical Diseases) at Geneva (February 7-11, 1994).

Dr. D.A. Gadkari, Dy. Director, National AIDS Research Institute (NARI), Pune, visited Johns Hopkins University, Baltimore, in co...ection with the

preparation of a draft proposal for the next phase of PAVE (Preparation for AIDS Vaccine Evaluation) Project. (February 14-23, 1994)

Dr. S.P. Tripathy, Director-General, ICMR, participated in the meeting of the Apex Committee of the Indo-US Vaccine Action Programme at New Delhi (February 21, 1994).

Dr. G.V. Satyavati, Senior Dy. Director-General, ICMR, New Delhi, gave a Guest Lecture on "Rasayana Concept of Ayurveda—How Relevant is it Today?" and also chaired the session on 'WhitherAyurveda' at the 'Update Ayurveda Conference' at Bombay (February 24-25, 1994). She also chaired the session on Medicinal Plant Products at the 2nd International Symposium on Innovations in Pharmaceutical Sciences, and Technology at Ahmedabad (February 26-27, 1994).

Dr. K.N. Panicker, Dy. Director, VCRC, Pondicherry, participated in the International Conference on Community based Vector Control at San Pedro Sula (March 6-9, 1994).

Dr. V. Kumaraswami, Asstt. Director, Tuberculosis Research Centre, Madras, participated in the Meeting of the Filariasis Field Trial's Task Force of the Special Programme for Research and Training in Tropical Diseases at Geneva (March 14-16, 1994).

National Science Day Celebrations:

The Indian Council of Medical Research Headquarters celebrated the National Science Day at its campus on February 28, 1994. The celebrations included various items like—display/demonstration of specimens of medicinal plants/household herbal products used in day-to-day practice; and display/demonstrations of various common food items of daily use. In addition, general science quiz and computerized general health quiz were organised for school children. A general health quiz competition was held for the non-scientific employees of the ICMR Headquarters.

Students from four Delhi Schools participated in various quiz programmes conducted and winners in all the competitions were given suitable prizes.

Technology Transfer Programme:

The ICMR organized, in collaboration with the Directorate General of Health Services, New Delhi, a workshop for the transfer of technology for the control of Rheumatic Fever and Rheumatic Heart Diseases at the Primary Health Care Level at New Delhi (March 7-9, 1994).

Appointments:

Dr. C.R. Ramachandran, Director Grade Scientist, has been appointed as Senior Deputy Director-General, Division of Non-Communicable Diseases, ICMR Headquarters.

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The Council announces with regret the sudden demise of Dr. Anil R. Sheth, formerly Director of its Institute for Research in Reproduction, Bombay, on March 13, 1994 (Please see obituary).

ICMR AIDED SYMPOSIA/SEMINARS/WORKSHOPS/COURSES/CONFERENCES

Symposium/Seminar/Workshop/ Course/Conference	Date & Place	Contact Address
International Conference on Safe Motherhood in South Asia : Challenges Ahead.	March 3-5, 1994; (at Chandigarh)	Dr. R.S. Goyal, Conference Director, SID International Conference on Safe Motherhood, SCO-809-810, Chandigarh.
Indo-German Training Course and Workshop on Application of Flow-Cytometry in Cellular and Molecular Biology.	March 14-16, 1994; (at Delhi)	Dr. V.P. Bhardwaj, Course Coordinator, Institute of Nuclear Medicine and Allied Sciences, Delhi.
National Symposium on Cellular and Molecular Biophysics.	March 15-17, 1994; (at Chandigarh)	Dr. M.P. Bansal, Organising Secretary, Biophysics Symposium, Department of Biophysics, Punjab University, Chandigarh.

COUNCIL'S TRAINING PROGRAMMES FOR 1994-95

Virology

At the National Institute of Virology, Pune:

... Diploma in Medical Virology (June 1994-May1995).

Reproductive Biology

At the Institute for Research in Reproduction, Bombay:

... Workshop on Gynaecologic Cytology and Immunocytochemistry (September 26-October 1, 1994).

Endocrinology

At the National Institute of Nutrition, Hyderabad:

... Annual Training Course on Endocrinological Techniques and their Applications (August 1-September 16, 1994).

Nutrition

At the National Institute of Nutrition, Hyderabad:

... M.Sc in Applied Nutrition (June 1,1994-February 28, 1995).

... Annual Training Course in Nutrition (December 1, 1994-February 28, 1995).

Occupational Health

At the National Institute of Occupational Health, Ahmedabad:

... Orientation Course on Occupational Health for Industrial Medical Officers (September 19-24, 1994).

... Training Course on Air Pollution Monitoring and Risk Assessment (October 19-25, 1994).

... Training Course in Pesticide Residue Analysis (December 5-9, 1994).

Medical Entomology

At the Vector Control Research Centre, Pondicherry:

... M.Sc in Medical Entomology (from August 1994: for 2 years).

... Short-term Course on Malaria, Filariasis and Urban Vector Control for in-service candidates (June 1994).

Laboratory Animal Technology

At the Laboratory Animal Information Service Centre, National Institute of Nutrition, Hyderabad:

... Training Course for Laboratory Animal Technicians (June 15-July 31, 1994).

... Training Course for Laboratory Animal Supervisors (September 12- December10, 1994).

Clinical Pharmacology

At the Seth G.S. Medical College, Bombay:

... Training Course in Clinical Pharmacology (March 1-25, 1994).

Haematology

At the Institute of Immunohaematology, Bombay:

... Training Course in Blood Group Serology and Blood Bank Methodology for Technicians (August 9-September 8, 1994).

... Training Course in Blood Group Serology and Blood Bank Methodology for Medical Officers (August 9-October 7, 1994).

SOME AVAILABLE ICMR PUBLICATIONS

	Price Rs.
Nutritive Value of Indian Foods (1985), by C. Gopalan, B.V. Ramasastri and S.C. Balasubramaniam. Revised and Updated (1989), by B.S. Narasinga Rao, K.C. Pant and Y.G. Deosthale	18.00
Growth & Physical Development of Indian Infants and Children (1972), Reprinted 1989	10.00
Studies on Weaning & Supplementary Foods (1974). Reprinted 1984	6.00
Studies on Pre-School Children (1974). Reprinted 1984	6.00
A Manual of Nutrition . Second Edition (1974). Reprinted 1990	4.50

Low Cost Nutritious Supplements , Second Edition (1975), Reprinted 1990	3.00
Menus for Low Cost Balanced Diets and School Lunch Programmes Suitable for North India, Third Edition (1977), Reprinted 1984	4.50
Menus for Low Cost Balanced Diets and School Lunch Programmes Suitable for South India, Third Edition (1977), Reprinted 1991	4.50
Some Common Indian Recipes and their Nutritiv Value, Fourth Edition (1977), Reprinted 1991, by Swaran Pasricha and L.M. Rebello	10.00
Nutrition for Mother and Child, Third Edition (1978), Reprinted 1991, by P.S. Venkatachalam and L.M. Rebello	9.00
Japanese Encephalitis in India ,Revised Edition (1980)	5.00
Some Therapeutic Diets , Fourth Edition (1981), Reprinted 1983, Revised 1988, by Swaran Pasricha	4.50
Nutrient Requirements and Recommended Dietary Allowances for Indians (1990)	13.00
Lathyrism: A Preventable Paralysis, Revised Edition (1983)	3.50
A Manual of Laboratory Techniques (1983), Edited by N. Raghuramulu, K. Madhavan Nair and S. Kalyanasundaram	30.00
Fruits (1983), by Indira Gopalan and M. Mohan Ram	7.00
Count What You Eat (1989), by Swaran Pasricha	9.00
Dietary Tips for Elderly (1992), by Swaran Pasricha and B.V.S Thimmayamma	3.50
*Depressive Disease (1986), by A. Venkoba Rao	58.00
**The Anophelines of India Revised Edition (1984), by T. Ramachandra Rao	150.00
**Medicinal Plants of India, Vol.2 (1987)	136.00

* 10 per cent discount allowed to individuals. ** 25 per cent discount allowed to individuals.

These publications are available on prepayment of cost by cheque or postal order (bank and postal charges will be extra) drawn in favour of the Director-General, Indian Council of Medical Research, New Delhi. Money orders are not acceptable. All correspondence in this regard should be addressed to the Chief, Division of Publication and Information, Indian Council of Medical Research, Post Box No.4508, Ansari Nagar, New Delhi-110029.

Unpriced Publications

(for limited distribution)

Proceedings of the Indo-UK Workshop on Leishmaniasis (1983)
Collaborative Study on Blindness, 1971-74 (1987)
National Task Force Study on Problems of the Aged Seeking Psychiatric Help, 1981-84 (1987)
Endomyocardial Fibrosis in India (1983)
Epidemiological Survey of Endemic Goitre and Endemic Cretinism (1989)
Illegal Abortion in Rural Areas (1989)
Perinatal Determinants of Child Survival (1989)
Contraceptive Research Today & Tomorrow (1989)
Collaborative Study on Phenomenology and Natural History of Acute Psychosis (1989)
Melatonin (1991) by Dr. S. Parvathi Devi
Field Supplementation Trial in Pregnant Women with 160mg, 120mg and 180mg of iron with 500µg of Folic Acid (1992)

Dr. Anil. R. Sheth, PhD, FASc, FNA
(August 5, 1933—March 13, 1994)

A TRIBUTE

Dr. Anil R. Sheth, former Director, Institute for Research in Reproduction (IRR) of ICMR at Bombay, passed away on March 13, 1994, leaving behind a vacuum which will not be easy to fill.

Dr. Sheth dedicated his entire life to research in the area of reproductive biology and to the service of the IRR. Along with the late Dr. Shanta S. Rao, he was instrumental in bringing the Institute to its present status of national and international repute. Through his dedicated efforts spanning over nearly four decades, Dr. Sheth contributed significantly to the development of reproductive biology as a discipline in India, particularly through his contributions in areas like male and female fertility regulation, studies on protein hormones, characterization, assay and mechanism of hormone action, sperm physiology *etc*. He was one of the pioneers in the field of research in Inhibin.

Dr. Sheth was Fellow of a number of major and reputed professional scientific Societies/ Associations in India including the National Science Academy. He was a prolific science communicator and published over 400 research papers in both National and International Journals. He also guided many young students for their postgraduate degrees (25) and doctorate theses (14).

Dr. Sheth was the recipient of many honours/awards for his outstanding contributions to medical science including the Oration Award of the Endocrine Society of India (1985), Oration Award of the Geriatric Society of India (1986), Dr. Subhas Mukherjee Memorial Lecture Award of the Cryogenics Council (1988), the prestigious Basanti Devi Amir Chand Award of ICMR (1987), among others. He was elected Fellow of various Science Academies *eg* Indian Academy of Sciences (1988); Indian National Science Academy (1993); Maharashtra Academy of Sciences (1989) and Gujarat Science Academy (1991).

With the sudden departure of Dr. Anil Sheth, the IRR has lost a friend, philosopher and Guide as also a genuine well-wisher. His great desire to develop Inhibin as an antifertility agent and as a diagnostic tool for prostatic cancer remains unfulfilled. His colleagues at the Institute will endeavour to complete this unfinished task.

Dr. Sheth has left behind many sweet lingering thoughts and memories of his jovial nature for all to cherish.

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