

HANSENÍASE: RESUMOS HANSENIASIS ABSTRACTS

BACTERIOLOGIA, IMUNOLOGIA BACTERIOLOGY, IMMUNOLOGY

AHMED, H.A.; TOUN J.; STONER, G.L.; BELEHU, A. Immunoglobulin A (IgA) in nasal washings and saliva of leprosy patients. *Int. J. Lepr.*, 51(1): 22-28, 1983.

IgA levels in nasal washings and saliva were determined in leprosy patients and healthy controls. In addition, serum levels of IgA, IgG, and IgM and total *serum* protein were analyzed. IgA levels in the nasal washings, but not in the salivas, were elevated significantly in the borderline (BL) and lepromatous (LL) groups. In the tuberculoid (TT) and borderline tuberculoid (BT) groups, the IgA levels in both the nasal washings and salivas did not differ from the controls. Total protein was also elevated in the nasal washings in the BL and LL groups. Thus, the IgA expressed as mg/mg protein did not differ significantly from the control group. However, in individual patients the levels of IgA and total protein were not correlated in either the nasal washings or the salivas. The high serum immunoglobulin and protein levels were in accord with the findings of most other workers. — Authors' summary

BACH, MA.; HOFFENBACH, A.; LAGRANGE, P. H.; WALLACH, D.; COTTENOT, F. Mechanisms of T cell unresponsiveness in leprosy. *Ann. Immunol.*, 134D 1): 75-84, 1983.

We analysed the mechanisms of T-cell unresponsiveness to *Mycobacterium leprae* antigens and to unrelated antigens or T-cell mitogens in human leprosy and in an experimental model of amine infection by *M. lepraemurium* (MLM). In human leprosy, monoclonal antibodies OKT3, OKT4 and OKT8 were used to enumerate T cell subpopulations within peripheral

blood. Increased percentages of OKT8 cytotoxic/suppressor cells were observed in untreated, non-reactive lepromatous patients. Conversely, lepromatous patients suffering from erythema nodosum leprosum, an Aithus-like phenomenon, exhibited a transient drop in the percentage of OKT8⁺ cells with a correlative increase in the proliferative response to T cell mitogens. We studied the proliferative response to *M. leprae* of OKT4⁺ and OKT8⁺ cells isolated by a negative selection procedure using antibody-induced cytotoxicity plus complement. None of these subpopulations proliferated when incubated with *M. leprae*. In some patients, control treatment of mononuclear cells with complement alone induced the reappearance of a strong proliferative response to *M. leprae*, suggesting the existence of an active suppressor mechanism through soluble factors of an unknown nature. In MLM-induced murine leprosy, a progressive decrease was observed in the proliferative response to concanavalin A (ConA), and an early decrease in interleukin 2 activity in supernatants from ConA-stimulated spleen cells. Splenic T-cells from MLM-infected mice *transferred* into naive recipients accelerated the local MLM growth in these recipients, suggesting that suppressor T cells may play a pathogenic role in the progression of MLM infection. — Author's summary.

BIRDI, T.J.; MISTRY, N.F.; MAHEDEVAN, P.R.; ANTIÁ, N.H. Alterations in the membrane of macrophages from leprosy patients. *Infect. Immun.*, 41(1):121-127, 1983.

Macrophage cultures pulsed with viable *Mycobacterium leprae* were assessed for erythrocyte rosetting in three groups of individuals, i.e., normal sul sects, and tuberculoid and lepromatous patients. Of these, only the lepromatous group showed a reduction in rosetting ability after infection with *M. leprae*.

The specificity of such a reduction pattern was confirmed by using various mycobacteria to infect the macrophages. A threshold effect was noted in all three groups. Although a reduction was obtained in the amount of resetting of macrophages from lepromatous patients with 10 acid-fast bacilli per culture, tuberculoid and normal macrophages resisted such " effect with as large a dose as 20 x 10 to 30 x 10 and 30 x 10 bacilli per culture, respectively. The *M. leprae*-caused alterations in macrophages from lepromatous patients were reversible by treatment with trypsin and colchicine. Cytochalasin B and Tween 80 were unable to alter the pattern. Treatment of cells with neuraminidase was inconclusive since it enhanced rosetting values of both control and infected cultures. These manipulations were significant in elucidating the target point of the host (macrophage) and parasite (*M. leprae*) interaction and in delineation of the external and internal effects upon the macrophages. Both *M. leprae* and macrophages were participants in Fc reduction, as treatment of the former with rifampicin and of the latter with cycloheximide significantly augmented the rosetting ability. In conclusion, it appears that *M. leprae*, upon entering a lepromatous macrophage, initiates the production of a protein which acts via the microtubules to alter membrane topography. It is possible that the altered membrane prevents effective macrophage-lymphocyte interaction. This could be one of the mechanisms by which cell-mediated immunity is suppressed in lepromatous leprosy. — Authors' summary

CHO, S.N.; YANAGIHARA, D.I.; HUNTER, S.W.; GELBER, R.H.; BRENNAN, P.J. Serological specificity of phenolic glycolipid I from *Mycobacterium leprae* and use in serodiagnosis of leprosy. *Infect. Immun.*, 41(3): 1077-1083. 1983.

The serological activities of the specific phenolic glycolipid I from *Mycobacterium leprae*, its dissected parts, and related glycolipids from other mycobacteria were examined by enzyme-linked immunosorbent assay against hyperimmune anti-*M. leprae* rabbit antiserum and sera from patients with leprosy and other mycobacterial diseases. High anti-phenolic glycolipid I immunoglobulin M antibodies were found in 23 of 24 (96%) of lepromatous leprosy patients on short term chemotherapy and in 8 of 13 tuberculoid leprosy patients (62%). Sera from patients with tuberculosis or atypical mycobacterial infections were devoid of anti-phenolic glycolipid I activity. The structurally related phenolic glycolipids from *Mycobacterium kansasii* and *Mycobacterium bovis* and the aglycone segments of the *M. leprae* product showed no significant activity. Thus, the trisaccharide determinant of phenolic glyco-lipid I is specific in its structure, serological activity, and, to a lesser extent, the antibody class it evokes. — Authors' abstract.

DAVID, H. L.; ASSELINEAU, C. DAFFÉ, M.; LANÉLLE, M. A.; CLEMENT, F.; LÉVY-FREBAULT, V. Taxonomy of mycobacterial strains isolated from the tissues of leprosy patients. *Ann. Microbiol.*, 134B(3): 367-377,

Thirty-six slowly growing mycobacteria isolated from the tissues of leprosy patients were studied using

40 characteristics as well as susceptibility to 27 distinct mycobacteriophages. The composition in mycolic acids of selected strains was also studied. According to the data, the strains formed 5 clusters. Some of the clusters were possibly as yet undescribed species; however, comparison of the data with the known properties of *Mycobacterium leprae* leads to the conclusion that none of the strains were ideateal to the leprosy bacillus. Authors' summary

DUNCAN, M.E.; MELSON, R.; PEARSON, J.M.H.; MENZEL, S.; BARNETSON, R. St. C. A clinical and immunological study of four babies of mothers with lepromatous leprosy two of whom developed leprosy in infancy. *Int. Lepr.*, 51 (1): 7-17, 1983.

One hundred thirteen women and 27 healthy controls were studied throughout pregnancy, at delivery, and followed up with their babies during lactation. Thirty-eight of the mothers with lepromatous leprosy were found to have solid-staining bacilli in skin smears or biopsies, and hence were considered potentially highly infectious to their unborn children by hematogenous spread via the placenta. Two babies of mothers within this group were diagnosed as having leprosy on clinical and histological grounds. A third baby could well have had leprosy, but the case was not proven. The fourth baby did not have leprosy and, although it did have ringworm, was thus deemed to be a reasonable control. The leprosy skin lesions were first observed at a special followup clinic when the children were between the ages of 9 and 17 months. The demonstration of IgA and IgM anti-*M. leprae* antibodies in cord serum was taken as an indication of intrauterine immunologic stimulation, and hence transplacental transmission of *M. leprae*. The two babies with proven leprosy showed an early and significant increase in serum IgA and in particular serum IgM anti-*M. leprae* antibody activity. A third baby, suspected of having leprosy but in whom the diagnosis was not proven, showed a similar but less marked increase in serum IgA and IgM activity. The fourth baby showed no such rise in anti-*M. leprae* activity. A decrease in serum IgG anti-*M. leprae* antibody activity could be demonstrated in one of the babies with leprosy after healing of the leprosy lesions, but not in the second baby. — Authors' summary.

HIRATA, T. Electron microscopic observations of intracytoplasmic inclusions in human and murine leprosy bacilli. *m l. J. Lepr.*, 51 (1): 84-88, 1983.

The intracytoplasmic inclusions of *Mycobacterium leprae* in human lepromata and *M. lepraemurium* in murine lepromata were studied in ultrathin serial sections at the electron microscopic level. The inclusions were mostly homogeneous and spherical, and did not exist uniformly throughout the bacillary cells. They did not appear to be delimited by membranous structures and apparently had no internal structure. There seemed to be fundamentally little difference between *M. leprae* and *M. lepraemurium* in the fine structure of these inclusions. However, the large diffuse inclusions observed in the cells of *M. lepraemurium* may be a special feature of routine bacilli. — Authors' summary

KATO, L. *In vitro* cultivation of *Mycobacterium X* from *Mycobacterium leprae*-infected tissues in acetone-dimethylsulfoxide-tetradecane medium. *Int. J. Lepr.*, 51(1): 77-83, 1983.

Several strains of mycobacteria were cultivable from *Mycobacterium leprae*-infected human and armadillo tissues in a liquid medium containing three dimethyl analogs: dimethylketone, dimethylsulfoxide, and tetradecane [CH₃ · (CH₂)₁₂ · CH₃]. The medium contained PM₂P₄, 7.0 g; Na₂HPO₄, 1.0 g; (NH₄)₂SO₄, 2.0 g; MgSO₄, 0.1 g; iron ammonium citrate, 0.1 g; DMSO, 10 ml; and acetone, 150 ml in distilled water *ad* one liter. Tetradecane 0.1 ml was added aseptically to each tube, containing 10 ml of the sterile medium. The media, inoculated with *M. leprae*, were incubated at 38°C and shaken vigorously twice weekly. Growth developed as a fine emulsion at the upper phase of the two-phase system. This was homogenized by mechanical shaking, permitting growth estimation by turbidity measurements. Microscopic examination showed unmistakably the slow but abundant multiplication of acid-fast rods. The logarithmic growth rate was measurable during two to three months, followed by a plateau. The strains are maintained in subcultures by regular transfer into the mine medium at two- to three-month intervals. The cultures and subcultures do not grow on Lowenstein or in Dubos media, but in the foot pads of mice they produce a multiplication similar to that obtained following injection of host-own *M. leprae*. The cultures are tentatively designated as *Mycobacterium X*. The relationship of *Mycobacterium X* to the pathology of leprosy is not clear. — Author's summary.

MSHANA, R.N.; HARBOE, M.; STONER, G.L.; HUGHES, RAC; KADLUBOWSKI, M.; BELEHU, A. Immune responses to bovine neural antigens in leprosy patients. I. Absence of antibodies to an isolated myelin protein. *Int. J. Lepr.*, 51(1): 33-40, 1983.

Recent electron microscopic demonstration that peripheral nerve demyelination can occur in leprosy patients even in the absence of both morphologically definable *Mycobacterium leprae* or inflammatory cells suggested that recognizable *M. leprae* or locally infiltrating cells need not be present to initiate leprosy neuropathy. The continued presence of *M. leprae* antigens or autoimmune humoral factors may thus be important. We used bovine myelin protein P₂ to detect antibodies to this myelin protein in leprosy patients due to the scarcity of the human equivalent. Furthermore, both proteins show immunological cross-reactivity. Sera from some of the patients were divided into two parts. One part was sent to Guys' Hospital, London, and the remaining portion studied at AHRI, Addis Ababa. For detecting anti-bovine P₂ antibodies, the sera were diluted 1:10, reacted with I-labelled bovine P₂, the complexes precipitated by polyethylene glycol, and the radioactivity counted. Results from both laboratories were very similar. Seven out of 56 leprosy patients had anti-P₂ antibodies which were above two standard deviations from the normal control group: The increased anti-P₂ antibodies bore no correlation with any clinical parameter in terms of disease duration, number of enlarged or tender nerves, or severity of motor or sensory neural function loss. This activity is probably due to high

immunoglobulin concentration in these patients and particularly so in the lepromatous group. Increased immunoglobulin levels could also explain the slight increase in anti-P₂ activity in Ethiopian (mean activity 5.11%) when compared to European controls (mean activity 4.85%). There were no significant differences in the mean values of anti-P₂ antibody activities of any of the groups studied. It is surprising that in leprosy, a disease characterized by prominent nerve damage and the presence of mycobacteria which are strong adjuvants, no antibodies to a peripheral nerve myelin protein, P₂, were seen. Antibodies to other peripheral nerve components, however, should be searched for and their role in the pathogenesis of leprosy neuropathy studied. — Authors' summary

NOORDEEN, S.K.; SANSARRICO, H. Immunization against leprosy: progress and prospects. *Bull. Wld. Hlth. Org.*, 62(1): 1-6, 1984.

The limitations of the current approach to leprosy control through mass treatment of patients are well recognized. The long incubation period of the disease, the insidious onset, the chronic course, and the need for prolonged treatment have made control a formidable task. The recent years have seen tremendous progress in the field of immunology of leprosy, and the availability of large quantities of *Mycobacterium leprae*, grown in the nine-banded armadillo, has given impetus to the search for a vaccine specific for leprosy. Methods for production and purification of *hl. leprae* have now been developed and the resulting preparation has been shown to produce good delayed-type hypersensitivity in mice and guinea pigs. Small-scale studies in human subjects have shown that preparations of *M. leprae* and BCG can induce cell-mediated immunity in Mitsuda-negative patients and contacts. It is now appropriate to consider field trials of vaccine preparations in selected groups before moving on to large-scale trials in different populations — Authors' abstract

NOORDEEN, S.K. & SANSARRICO, H. La vaccination contra la lèpre: progrès et perspectives. *Bull. Wld. Hlth. Org.*, 62(2): 201-207, 1984.

La stratégie actuellement appliquée contre la lèpre, qui passe par un traitement de masse des patients, a des limites que tout le monde reconnaît. La longueur de l'incubation, le caractère insidieux des premiers symptômes, la chronicité de l'évolution et la nécessité d'un traitement prolongé font de la lutte contre la lèpre une tâche difficile. Ces dernières années ont vu l'immunologie de la lèpre marquer des progrès considérables, et la disponibilité de quantités importantes de *Mycobacterium leprae* que l'on peut maintenant multiplier sur la taupe a permis d'entreprendre des recherches sur un vaccin antilépreux spécifique. Des méthodes ont été mises au point pour produire et purifier *M. leprae* et la préparation ainsi obtenue a montré qu'elle suscitait chez la souris et le cobaye une bonne hypersensibilité retardée. Des études restreintes sur des sujets humains ont démontré que des préparations associant *M. leprae* et BCG pouvaient induire une immunité à médiation cellulaire chez des patients et des contacts Mitsuda-négatifs. Il faut maintenant envisager l'épreuve sur le terrain de préparations vaccinées, dans des groupes choisis, avant de passer à des essais à grande échelle dans différentes popula-

PATTYN, S.R. Bacteriology of *Mycobacterium leprae*. *Lepr. Rev.*, (n. esp.): 17-22, Jun. 1983.

A review is presented on the morphologic features, chemical characteristics, growth capacity, drug sensitivity, metabolic activity and antigen structure of *Mycobacterium leprae*. Since the availability of large numbers of *M. leprae* from armadillo tissue, knowledge, particularly on the chemical characteristics has increased. It may be expected that knowledge on the metabolic activities will increase, leading perhaps, one day, to the long-awaited *in vitro* cultivation of the organism. — Authors' summary

RIDLEY, M.J. & RIDLEY, D.S. The immunopathology of erythema nodosum leprosum: the role of extravascular complexes. *Lepr. Rev.*, 54(2): 95-107, 1983.

Summary Skin biopsies of 20 patients with erythema nodosum leprosum were studied histologically, by acid-fast silver and immunological methods for the demonstration of bacterial antigen, and by immunoperoxidase for a variety of immunological factors. The results were compared with those in 10 non-reacting lepromatous patients. At the centre of the ENL lesions there was always disintegration of macrophages and release of bacterial antigen, comprising cell walls and particulate or diffuse components of *Mycobacterium leprae*. These products were found to combine first with IgM, later with IgG, which together with complement components of the classical pathway were present at the same sites. These complexes were found both extracellularly and in neutrophils and macrophages, and were constant features of acute stage lesions. C-reactive protein and B-lipoprotein were present in varying amounts and were associated partly with connective tissue. It is thought that CRP, and the related SAP, may be factors in the disruption or repair of elastic and collagen, which are conspicuous in some ENL lesions. The results support the view that ENL is an immune complex phenomenon, possibly self-perpetuating, occurring at the site of breakdown of small lepromatous granulomas. The immune complexes are extravascular and in this respect ENL

differs from the classical 'serum sickness' described by Arthus. — Authors' summary

SATHISH, M.; BHUTAN L.K.; SHARMA, A.K.; NATH, I. Monocyte-derived soluble suppressor factor(s) in patients with lepromatous leprosy. *Infect. Immun.*, 42(3):890-899, 1983.

Peripheral blood monocytes from polar lepromatous leprosy (LL) patients were unable to support *Mycobacterium leprae*-induced *in vitro* lymphoproliferation of HLA-D-matched T cells from tuberculoid leprosy subjects, whereas those from responder individuals were able to do so. Monocyte-rich adherent cells from untreated LL patients released *de novo* soluble factors which inhibited antigen-induced lymphoproliferation to a greater extent and mitogenic responses to a lesser extent. Suppressive activity varied in different LL patients. However, the degree of suppression was similar in soluble factors obtained *de novo* and after treatment of adherent cells with heat-killed and freshly extracted, cryopreserved *M. leprae*. Treated patients showed less inhibition with *de novo* released soluble factors ($27 \pm 7.7\%$) as compared to parallel soluble factors obtained after antigen treatment ($44 \pm 4.8\%$) or with *de novo* soluble factors from untreated LL patients ($62 \pm 14.2\%$). Similar supernatants from tuberculoid individuals showed no or insignificant effects on antigen-induced lymphoproliferation. The suppressive activity of LL soluble factors was produced for up to 72 h, was heat stable at 56°C for 30 min, was indomethacin resistant, and resided in the $> 25,000$ molecular weight fraction. — Authors' abstract

SIQUEIRA, L.F. de G. *et al.* Comportamento tintorial do *Mycobacterium leprae*. Revisão histórica. *Rev. Saúde Obi.*, 17(4): 297-315, 1983.

A historical review was made of the dyes utilized to identify the *Mycobacterium leprae*. The chemical composition and the tinctorial properties of these substances and the dye assimilation capacity of the bacilli were analyzed. — Authors' summary

PATOLOGIA, FISIOPATOLOGIA, BIOQUÍMICA

PATHOLOGY PHYSIOPATHOLOGY, BIOCHEMISTRY

BALYBIN, E.S. & NAZAROV, K.I. Hydrocortisone production in lepromatous patients with insulin load. *Int. J. Lepr.*, 51(1): 18-21, 1983.

Hydrocortisone production was studied in 36 patients with lepromatous leprosy before and after insulin load as a stress factor using a competitive radioassay. Twenty-three patients showed a so-called paradoxical type of hydrocortisone production suggestive of markedly exhausted hydrocortisone-

producing function of the adrenal cortex. Reserve hydrocortisone production was depressed in most of the patients with active disease; while cured patients showed a partial restoration in reserve hydrocortisone production. Leprosy relapses seem to be among the factors affecting the reserve hydrocortisone-producing function of adrenals. The question of reassessment of the principles of steroid therapy in lepromatous patients with relapses is raised. — Authors' summary

Hansen., *Int.*, 9(1-2): 49-57, 1984

GOMEZ—ESTRADA, H.; MORALES—ORTIZ, R.; GONZALES—MENDOZA, A.; BARBA—RUBIO, J.; CEJA—MENDOZA, S. Deficiencia de peroxidasa en los histiocitos de pacientes con lepra lepromatosa nodular. *Arch. Invest. Méd.*, 14 (2): 127-137, 1983.

The purpose of this study was to investigate the presence of peroxidase (PO) in the histiocytes which are found in the lepromatous lesions of patients with nodular lepromatous leprosy (NLL). We studied dermoepidermal biopsy specimens from lepromatous lesions and blood smears of 10 patients with NLL, eight males and two females 28 to 63 years of age (average 45 ± 6.2), of which nine coursed with the stable form of the disease and one was in lepromatous reaction. Six had received treatment with diaminodiphenylsulphone for more than six months, and the other four, none. As controls we studied the blood smears of 10 healthy controls and 10 rat liver sections. PO was investigated in histiocytes, Kupffer cells and polymorphonuclears by dichlorhydrate oxydation, according to the technique of Kaplow. By means of Fite-Faraco's stain, all ten cases proved to have abundant phagocytized *M. leprae*. PO was not found in histiocytes of lepromatous lesions in nine cases of stable NLL, while it was weakly positive in the patient with NLL in lepromatous reaction. PO was present in Kupffer cells, in polymorphonuclears of patients with NLL and in controls. No difference was found either in the PO or *M. leprae* contents between treated and untreated patients. The PO deficiency in histiocytes of patients with NLL may be related to an incapacity of these cells to destroy *M. leprae*. — Authors' abstract.

HOLLA, V.V.; KENETKAR M.V.; KOLHATKAR, M. K.; KULKARIN, C.N. Leprous. A study of fifty cases. *Int. J. Lepr.*, 51(1): 29-32, 1983.

A study of 50 synovial biopsies of proved lepromatous patients with arthritis was carried out. Out of these 50 cases, 14 cases were suffering from lepra reaction and the histopathological study of the synovium in these 14 cases revealed the presence of only vasculitis and lymphocytic infiltration. In the remaining 36 cases, not associated with lepra reaction, the synovial lining showed hyperplasia and vinous hyper-trophy, and the synovial tissue showed congestion, pannus formation, the presence of macrophage granu-

Lomas and, in some cases, even intact acid-fast bacilli. Since there was no other cause for arthritis, it is perhaps likely that the primary synovial involvement in these 36 cases may be the cause of the arthritis. In the ten cases of lepromatous leprosy without arthritis studied as controls, no histopathological abnormality in the synovium could be detected. — Authors' summary

MUKHERJEE, A.; GIRDHAR B.K.; MALVIYA, G. N.; RAMU, G.; DESIKAN. K.V. Involvement of subcutaneous veins in lepromatous leprosy. *Int. J. Lepr.*, 51(1): 1-6, 1983.

Venous involvement in 31 patients with lepromatous leprosy has been studied in biopsies from clinically involved and clinically normal subcutaneous veins from the forearm. Twenty-nine of these showed histological evidence of leprous phlebitis. The earliest lesion was intimal cell hyperplasia with the presence of acid-fast bacilli in small groups in the Intimai cells. This gradually progressed to total occlusion of the vein by lepromatous exudate. The results indicate much greater involvement of veins and possibly other components of the vascular system in patients with lepromatous leprosy than is generally accepted. The importance of such involvement in the pathogenesis of leprosy is also discussed. — Authors' summary

SAOJI, A.M. & KELKAR, S.S. Erythrocyte glucose-6-phosphate dehydrogenase isoenzyme phenotypes in leprosy. *Int. J. Lepr.*, 51(1): 41-44, 1983.

Hemolysates from 50 cases of leprosy and five controls were studied for glucose-6-phosphate dehydrogenase (G-6-PD) isoenzyme phenotypes by polyacrylamide disc gel electrophoresis using a miniaturized system. The cases were classified as lepromatous (24), borderline lepromatous (5), borderline tuberculoid (5), and tuberculoid (16) according to the Ridley-Jopling scale. All had been on treatment with dapsone for between two and 12 years. None of the cases showed deficiency of erythrocyte G-6-PD. All the cases and the controls showed the G-6-PD phenotype to be of the BT variety. Therefore this genetic marker does not appear to be related to susceptibility to leprosy or to the clinical variety of the disease in our situation. — Authors' summary

HANSENÍASE EXPERIMENTAL, LEPPRA ANIMAL

EXPERIMENTAL HANSENÍASIS, ANIMAL LEPROSY

BACH, M.A. & HOFFENBACH, A. A monoclonal antibody against *Mycobacterium lepraemurium* which recognizes a cross reacting mycobacterial antigen. *Ann. Immunol.*, 134C(3) : 302-309, 1983. Spleen cells from BALB/c mice infected two weeks earlier with *Mycobacterium lepraemurium* were

fused with myeloma cells, and, using an indirect immunofluorescence assay, a hybridoma was selected which secreted an anti-*M. lepraemurium* IgM antibody. In the same assay, this monoclonal antibody also recognized 17 other species of *Mycobacteria* (including *M. leprae*) and two strains of *Nocardia*. — Authors' summary

Hansen., *Int.*, 9(1-2):49-57, 1984

ISHAQUE, M. Respiratory activities of *in vitro* grown *Mycobacterium lepraemurium*. *Int. J. Lepr.*, 51 (1): 64-71, 1983.

Mycobacterium lepraemurium was cultivated on Ogawa egg-yolk medium and its respiratory activities using several substrates were investigated. Glycerol and succinate were oxidized at a slow rate by the cell-free extracts prepared from *in vitro* grown Hawaiian and Keishicho strains of *M. lepraemurium*. None of the other intermediates of the glycolysis cycle was oxidized by the whole cell suspensions or cell-free extracts. Likewise, many sulfur compounds such as cystine, mercaptosuccinate, monothio glycerol, thioacetate, etc., were inactive. However, sulfhydryl compounds such as L-cysteine, D-cysteine, DL-cysteine, dithioerythritol, dithiothritol, and DL penicillamine were actively oxidized. Yeast extract was also readily oxidized by cell suspensions of *in vitro* grown *M. lepraemurium*. Tween 80 was very poorly oxidized by whole cell suspensions but the cell-free preparations catalyzed an active oxidation of Tween 80. While bovine serum albumin was oxidized at a slow rate by cell-free extracts, egg albumin was inactive. The thiolbinding agents, p-hydroxymercuribenzoate and N-ethylmaleimide were effective inhibitors of succinate and NADH oxidation, thus indicating the involvement of sulfhydryl compounds in the metabolism of *M. lepraemurium*. — Authors's summary

MATSUO, Y. Use of cycloheximide for cultivating *Mycobacterium lepraemurium* in cell culture. *Int. J. Lepr.*, 51(1): 72-76, 1983.

A serial increase in the number of *Mycobacterium lepraemurium* with successful subcultures has been obtained in cell culture with cycloheximide treatment. The infected cells seldom floated off the culture vessel. They could be maintained and would support the bacillary multiplication in good condition for ten weeks or more without changing the medium frequently. An overall generation time of the intracellular bacilli up to the tertiary culture for the total period of 35 weeks was 22.1 days. — Author's summary

MOR N. Intracellular location of *Mycobacterium leprae* in macrophages of normal and immune-deficient mice and effect of rifampin. *Infect. Immun.*, 42(2): 802 - 811, 1983.

Soon after more than 10^6 *Mycobacterium leprae*, freshly harvested from armadillo liver or harvested and ^{60}Co irradiated, were inoculated into the hind footpads of either normal or thymectomized and irradiated (T900R) mice, the organisms were found to reside within phagosomes of polymorphonuclear and mononuclear cells. On the other hand, 7 and 8 months after 10^6 freshly harvested *M. leprae* were inoculated into the footpads of normal or T900R mice and the organisms had multiplied to their maximum in the normal mice, many organisms, largely intact by electron-microscopic criteria, were found to reside free in the cytoplasm of the footpad macrophages, whereas damaged organisms were contained within phagosomes. After 11 months, many intact organisms were found to lie free in the cytoplasm of the macrophages of T900R mice, whereas, only damaged intraphagosomal *M. leprae* cells were observed in the macrophages of normal mice. Finally, a remarkably large proportion

of damaged extraphagosomal *M. leprae* was found in T900R mice administered rifampin for 2 days in a bactericidal dosage. It appears that *M. leprae* multiplies free in the cytoplasm of the footpad macrophages of infected mice, whereas *M. leprae* cells resident within the phagosomes of the macrophages are dead. As the result of treatment with rifampin, the organisms appeared to have been killed in their extraphagosomal location, only afterwards being incorporated into phagosomes. However, the intracellular site in which *M. leprae* is killed in the course of an effective immune response remains unclear. — Authors' abstract

PETERS, J.H.; GORDON, G.R.; MURRAY JR., J.F. Disposition of prothionamide in rats and armadillos. *Int. J. Lepr.*, 51 (1): 54-63, 1983.

A new method for the sensitive and selective measurement of prothionamide (PTH) and its S-oxide metabolite (PTHSO) in biological fluids was described. The limit of sensitivity was approximately 0.01 μg of drug/ml of plasma. Endogenous materials, 2-propylisonicotinamide, ethionamide, dapsone, or monoacetyl dapsone did not interfere or contribute. Rats receiving PTH, intravenously or orally, showed a sexual dimorphism in the ability to oxidize PTH to PTHSO, with males exhibiting greater capacities for this conversion. Both sexes cleared the administered PTH more rapidly from the plasma than the metabolite, PTHSO. Following oral or intravenous administration of equimolar doses of PTHSO, both sexes exhibited an ability to reduce the administered PTHSO to PTH, with the female showing greater capacities for this conversion. Clearances after oral PTHSO administration were again more rapid for PTH than for PTHSO in both sexes. However, the total of PTH and PTHSO in the plasma during 8 hr following PTHSO administration was consistently less than following PTH dosing. Therefore, although PTHSO is retained longer than PTH after either PTH or PTHSO administration, giving PTHSO yielded less total active drug in the circulation. Comparison of plasma patterns of PTH and PTHSO in unfasted rats receiving one oral or eight daily oral doses of PTH did not indicate that PTH induces its own metabolism. Limited studies in armadillos receiving PTH and PTHSO intravenously led to the same general conclusions as those we derived from the rat studies regarding the disposition of PTH and PTHSO. — Authors' summary

SHEPARD, C.C.; VANLANDINGHAM, R.M.; WALKER, L.L. Recent studies of antileprosy drugs. *Lepr. Rev.*, (n. esp.): 23-30, Jun. 1983.

As a part of the programme of the Therapy of Leprosy (THELEP) Scientific Working Group, a number of compounds with potential activity against *Mycobacterium leprae* were prepared in other laboratories. We report here the results of studies of their activity against *M. leprae* with the use of the kinetic method in mice. A modified protocol is described that facilitates comparison of drugs in the same experiment. Two analogues of cycloserine, glycyldihydroxamic acid and beta-analylyl dioxamic acid were inactive in a dosage of 0.1% in the diet. Isoetam, (D-2-2'-(ethylendrimino) di-l-butanol)di-isoniazid methane sulphionate was also inactive at this dosage. Three

compounds related to dapsone, 4-nitro-N¹-phenylsulphonamide, 4-amino-N¹-phenylsulphonamide, and 4,4-diaminobenzene sulphonic acid phenyl ester, had little or no activity at dosages of 0.01% in the diet in experiments with strains shown to have normal susceptibility to dapsone. Two thiosemicarbazones, p 4-thiosemicarbazone and pyridinal²-thiosemicarbazone, were inactive in dosages of 0.01%; the latter was inactive at 0.01% in an experiment where thiacetazone was shown to have bactericidal-type activity at a dosage of 0.1% and marginal activity at 0.01%. Brodimoprim, a dihydrofolate reductase inhibitor, which is related to trimethoprim but has a longer half-life, was inactive in a dosage of 0.1%; it had no synergistic effect with 0.01% dapsone against a dapsone-susceptible strain. It was also inactive against

a dapsone-resistant strain, alone or in combination with dapsone. The cyanimino analogs of ethionamide and prothionamide were inactive in a dosage of 0.1% against an ethionamide-susceptible strain. Experiments with a series of compounds related to chaulmoogric acid were unsuccessful because the compounds were too toxic. Experiments with a series of compounds Mated to clofazimine were unsuccessful because their pharmacokinetics were unfavourable for study at dosages where clofazimine itself was active. The limitations imposed by the mouse-foot-pad system are discussed and related to those in other experimental systems. — Authors' summary.

CLÍNICA, DIAGNOSTICO

CLINICAL ASPECTS, DIAGNOSIS

SCHOCHINA, M.; WOLF, J.; BLANK, A.; GONEN, B.; SHESKIN, J. El reflejo de Hoffman en el nervio tibial en la hanseniasis. *Actas Dermo-Sif.*, **74** (7-8): 225-229, 1983.

Among 17 patients whose Hoffman reflex was examined, a normal response was found in 3, a pathological response in 12, and a doubtful response in 2. The tendon test, studied in the same 17 patients, yielded results that were similar, pathological responses in 12, normal in 2, and doubtful in 2. However, not all of the patients were found to yield the same kind of response to both tests. The Hoffman reflex permits examination of the status of the proximal tract of the tibial nerve, between the popliteal fossa and the spinal cord, whereas the tendon test permits examination of the status of the distal tract between the Achilles tendon and the spinal cord. Both methods are easily applied, and are more sensitive and less

traumatic than earlier means of evaluating nerve function. Moreover, these methods permit more exact localization of damage to the tibial nerve. Authors' summary.

RAVETTINNI, BA.; CAPECE, A.C.; ACHENBACH, R.E. Lepra lepromatosa en la infancia. *Rev. Argent. Dermatol.*, **64**(2): 133-142, 1983.

Three cases of lepromatous leprosy in the second infancy are discussed. On the light of the current literature the following aspects are analyzed: transmission mechanism, age, sex, clinical manifestations, bacteriology, histopathology and immunology. They presented different characteristics, one of them with reactive erythema nodosum. No prepuberal exacerbation was observed. The rare frequency of this form of leprosy during this period of life is pointed out. — Authors' summary

TERAPEUTICA

THERAPY

PEARSON, J.M.H. Dapsone-resistant leprosy. *Lepr. Rev.*, (n. esp.): 85-95, Jun. 1983.

It is likely that in 1983 over 10% of patients with lepromatous leprosy have developed dapsone resistance; the primary resistance rate of new cases is probably about 25%. Patients with active dapsone-resistant leprosy who are still receiving only dapsone mono therapy may well form a larger source of infection than all other infectious cases. Supervisable and cost-effective drug regimens designed to prevent the emergence of dapsone resistance and to control the infectivity of dapsone-resistant cases deserve urgent consideration. — Authors' summary

PETERS, J.H.; GORDON, G.R.; MURRAY JR., J.F.; SIMMON, V.F. Mutagenic activity of antileprosy drugs and their derivatives. *Int. J. Lepr.*, **51**(1): 45-53, 1983.

We tested the mutagenic activity of antileprosy drugs (clofazimine, ethionamide, prothionamide, prothionamide-S-oxide, rifampin, and dapsone and many of its derivatives) using the Ames *Saimonella/microsome* assay system. None of these, including N-acetylated and N-hydroxylated derivatives of dapsone, were found to be positive with or without metabolic activation in this test. However, the sulfoxide and sulfide analogs of dapsone were found to be mutagenic

with metabolic activation. These two analogs could not be detected in pharmaceutical preparations of dapsone (<0.01%) nor could they be found (in either unconjugated or conjugated form) in urine from volunteers taking a single oral dose of 50 mg of dapsone or from patients receiving daily oral doses of 100 mg of dapsone. Also, urine concentrates from

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volunteers taking 50 mg of dapsone did not exhibit mutagenic activity in the Ames screen. These results indicate that patients receiving antileprosy therapy with clofazimine, dapsone, ethionamide, prothionamide, and/or (if thereby possible) carcinogenic) drugs.

Authors' summary.

CIRURGIA, FISIOTERAPIA, REABILITAÇÃO FÍSICA

SURGERY, PHYSIOTHERAPY, PHYSICAL REHABILITATION

BRANDSMA, J.W. & LIJFTOGT, T. Timing of tendon-transfer surgery. *Lepr. Rev.*, 54(2): 109-114, 1983.

Summary Thirty-five leprosy patients who had tendon-transfer surgery recovered nerve function postoperatively. The tendon transfers were performed to correct paralytic deformities resulting from ulnar, median and common peroneal nerve damage. Nerve function recovery was found in 2-8% of the hands that had claw-Huger correction for ulnar palsy; in 5-1% of the hands, that had opponens replacement for median palsy and in 6-9% of the operated drop-feet. Analysis of the records showed that none of the patients had been operated on within 6 months after the onset of nerve damage. Postoperative deformity following nerve function recovery was rare in the hand, but occurred in 5 out of 18 of the feet that showed postoperative recovery. — Authors' summary

GANAPATI, R.; GASTON, D.; REGO, D.J.; BODKHE, L.D.; KULKARNI, D.R. Epoxy resin mouldings as aids for leprosy patients with deformities. *J. Rehab. Asia*. 24 (1): 19-25, 1983.

The focus of attention at the global level on the handicapped segments of the population during the International Year of Disabled Persons prompted the authors to devise simple and cheap aids for subjects with hand deformities. An epoxy resin called ARALDITE A.V. 1001 IN (with hardener HV 1001 IN) was tried successfully for providing hand grips by moulding on to handles of various articles used by people having improper grips owing to severe deformities of the hands fingers. This illustrated presentation points out the possibilities of wide practical application of these aids to leprosy patients with a variety of hand deformities in view of the cheapness of the material and the ease with which mouldings can be prepared. — Authors' abstract.

EPIDEMIOLOGIA, PREVENÇÃO

EPIDEMIOLOGY, CONTROL

SANSARRICQ, H. Recent changes in leprosy control. *Lepr. Rev.*, (n. esp.): 7-16, Jun. 1983.

The implementation of the secondary prevention strategy for leprosy control based on dapsone monotherapy had to face many difficulties. The main global results obtained during the period of the dapsone monotherapy approach may be summarized as follows: (a) **Worldwide**. More than 5 million leprosy cases out of an estimated total of about 10 million existing cases are now under treatment. It can be estimated that from 1 to 1.1 million leprosy patients have been released from control during the last decade; (b) Under favourable circumstances reductions of prevalence of 80% were achieved in a few countries or areas. The shortcomings of dapsone monotherapy have been increasingly realized over the last 15 years. A new

approach to secondary prevention of leprosy through multidrug therapy of all cases has been recently recommended by WHO. The contribution of the THELEP Scientific Working Group to the development of the newly recommended regimens has been essential, clearly demonstrating transfer of the results of research to control efforts. For the first time the results of worldwide research efforts, stimulated and coordinated at the global level, have been translated into important changes in the strategy for leprosy control. However, in the long term, primary prevention methods, the important being an effective vaccine, are an essential need in an effective strategy for leprosy control. In addition, immunological tools which would allow the identification of individuals at high risk of developing lepromatous leprosy will be of great help. In any case, it is unlikely that conclusions on the

efficacy of a vaccine will be available within the next decade, or that new potent drugs can be developed. Therefore, for the years to come, and despite the shortcomings and limitations of the secondary prevention approach, the implementation of effective chemotherapeutic regimens based on combinations of bacte-

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ricidal drugs is a must if we do not want the leprosy problem to become unmanageable and the gains made so far to be lost. Consequently, in the WHO leprosy programme for the next quinquennium top priority been given to the implementation of multidrug therapy. — Authors' conclusion.