

LITERATURA CORRENTE

CURRENT LITERATURE

CLÍNICA

ABBOT, N.C.; BECK, J.S.; FEVAL, E; WEISS, E; MOBAYEN, M.H.; GHAZI-SAIDI, K.; DOWLATI, Y.; VELAYATI, A.A.; STANFORD, J.L. Immunotherapy with *Mycobacterium vaccae* and peripheral blood flow in long-treated leprosy patients, a randomised, placebo-controlled trial. *Eur. J. Vasc. Endovasc. Surg.*, v.24, n.3, p.202-8, Sep., 2002.

OBJECTIVE: to evaluate immunotherapy as a means of improving peripheral blood flow in chronic leprosy patients. **DESIGN:** this was a double-blind, randomised, placebo-controlled, clinical trial. **MATERIALS:** heat-killed *Mycobacterium vaccae* 1mg plus 0.02 microg Tuberculin protein per 0.1 ml dose in borate buffer, with saline as placebo. Those studied were 92 long-treated residents of a leprosy centre in Iran, 10 of their healthy children and 10 staff members. Evaluation employed the Perimed PF2, Laser-Doppler Flowmeter, a platinum skin thermistor, and a thermal sensibility tester. **METHODS:** single intradermal injections of test or placebo were given to 103 patients 18 months before the blinded evaluation. Fingerpulp blood flux was measured in controlled conditions and vasomotor reflexes and skin sensation to touch, pain and heat were evaluated in 45 and 47 patients in the placebo and *M. vaccae* groups, respectively, and in 20 healthy control persons. **RESULTS.** Laser-Doppler flux, skin temperature, vasomotor reflexes and sensation were impaired in leprosy patients. Immunotherapy improved ($p < 0.05$) Laser-Doppler flux, skin temperature and temperature sensation. **CONCLUSIONS:** immunotherapy, given 18 months earlier, significantly improved blood flow and temperature sensation, in fully-treated, chronic, leprosy patients. The same principles might be employed in other conditions of reduced peripheral blood flow

MAAS, M.; SLIM, E.J.; HEOKSMA, A.F.; Van der Kleij, A.J.; AKKERMAN, E.M.; den HEETEN, G.J.; FABER, W.R. MR imaging of neuropathic feet in leprosy patients with suspected osteomyelitis. *Int. J. Leprosy*, v.70, n.2, p.97-103, Jun., 2002.

This study was undertaken to analyze MRI findings in leprosy patients with neuropathic feet, which are suspected of having osteomyelitis. As far as we know, there is no literature concerning osteomyelitis and MRI in neuropathic leprosy feet at present. Therefore, we have included MRI examination of 18 events of suspected osteomyelitis in 12 leprosy patients. All patients with long-standing neuropathic foot problems were clinically suspected of having osteomyelitis. All patients underwent the MRI protocol

with the inclusion of Two Point Dixon Chemical Shift Imaging as a fat-suppression sequence. For the MRI evaluation, we used signs that are described in literature for detecting osteomyelitis in diabetic feet. The primary MRI signs were positive in 17 of 18 patients. The secondary MRI signs were positive in 100% of the patients. Our results show that MRI with the use of Two Point Dixon Chemical Shift Imaging is a promising diagnostic modality to detect osteomyelitis in the presence of neurosteoarthropathic changes in patients with leprosy. Whenever available, MRI could play an important role in detecting osteomyelitis in leprosy patients with long-standing neuropathic feet

MALIK, R.; HUGHES, M.S.; JAMES, G.; MARTIN, P; WIGNEY, D.I.; CANFIELD, P.J.; CHEN, S.C.; MITCHELL, D.H.; LOVE, D.N. Feline leprosy: two different clinical syndromes. *J. Feline Med. Surg.*, v.4, n.1, p.43-59, Mar., 2002.

Feline leprosy refers to a condition in which cats develop granulomas of the subcutis and skin in association with intracellular acid-fast bacilli that do not grow on routine laboratory media. In this study, the definition was extended to include races not cultured, but in which the polymerase chain reaction (PCR) identified amplicons characteristic of mycobacteria. Tissue specimens from 13 such cases from eastern Australia were obtained between 1988 and 2000. This cohort of cats could be divided into two groups on the basis of the patients' age, histology of lesions, clinical course and the sequence of 16S rRNA PCR amplicons. One group consisted of four young cats (less than 4 years) which initially developed localised nodular disease affecting the limbs. Lesions progressed rapidly and sometimes ulcerated. Sparse to moderate numbers of acid-fast bacilli were identified using cytology and/or histology, typically in areas of caseous necrosis and surrounded by pyogranulomatous inflammation. Organisms did not stain with haematoxylin and ranged from 2 to 6 microm (usually 2 to 4 microm). *Mycobacterium lepraemurium* was diagnosed in two cases based on the sequence of a 446 bp fragment encompassing the V2 and V3 hypervariable regions of the 16S rRNA gene. A different sequence was obtained from one additional case, while no PCR product could be obtained from the remaining case. The clinical course was considered aggressive, with a tendency towards local spread, recurrence following surgery and development of widespread lesions over several weeks. The cats resided in suburban or rural environments. A second group consisted of nine old cats (greater than 9 years) with generalised skin involvement, multibacillary histology and a slowly progressive

clinical course. Seven cats initially had localised disease which subsequently became widespread, while two cats allegedly had generalised disease from the outset. Disease progression was protracted (compared to the first group of cats), typically taking months to years, and skin nodules did not ulcerate. Microscopically, lesions consisted of sheets of epithelioid cells containing large to enormous numbers of acid-fast bacilli 2 to 8 microm (mostly 4 to 6 microm) which stained also with haematoxylin. A single unique sequence spanning a 557 bp fragment of the 16S rRNA gene was identified in six of seven cases in which it was attempted. Formalin-fixed paraffin-embedded material was utilised by one laboratory, while fresh tissue was used in another. The same unique sequence was identified despite the use of different primers and PCR methodologies in the two laboratories. A very slow, pure growth of a mycobacteria species was observed on Lowenstein-Jensen medium (supplemented with iron) and semi-solid agar in one of three cases in which culture was attempted at a reference laboratory. Affected cats were domiciled in rural or semi-rural environments. These infections could generally be cured using two or three of rifampicin (10-15 mg/kg once a day), clofazimine (25 to 50 mg once a day or 50 mg every other day) and clarithromycin (62.5 mg per cat every 12 h). These findings suggest that feline leprosy comprises two different clinical syndromes, one tending to occur in young cats and caused typically by *M. lepraemurium* and another in old cats caused by a single novel mycobacterial species.

MUTHUKUMAR, T.; JAYAKUMAR, M.; FERNANDO, E.M.; MUTHUSETHUPATHI, M.A. Acute renal failure due to rifampicin: a study of 25 patients. *Am. J. Kidney Dis.*, v.40, n.4, p.690-6, Oct, 2002.

BACKGROUND: Acute renal failure (ARF) caused by rifampicin typically occurs on intermittent administration. There are isolated case reports and only one series reported in the literature. Systematic data, especially from countries endemic for tuberculosis and leprosy, are sparse. **METHODS:** We studied demographic, clinical, biochemical, and histopathologic features and prognosis of 25 consecutive patients with rifampicin-associated ARF admitted from July 1990 to June 2000. **RESULTS:** Rifampicin-associated ARF constituted 2.5% of all cases of ARF seen during the study period. The most common pattern of drug intake resulting in ARF (40%) was ingestion of a single dose preceded by a drug-free period (range, 10 days to 6 years) after a course of daily rifampicin (range, 8 days to 18 months). Onset was with gastrointestinal and flu-like symptoms 4 hours (median) after drug intake. All patients were oliguric. Anemia and thrombocytopenia each occurred in 60% of patients. Acute hepatitis was present in 32%. Among 12 patients who underwent kidney biopsy, 7 patients (58%) had acute interstitial nephritis (AIN). Crescentic glomerulonephritis was seen in 1 patient, and mesangial proliferation, in 3 patients. No single feature at

presentation predicted the severity of renal failure. There were no deaths, and all patients recovered renal function. **CONCLUSION:** Patients with rifampicin-associated ARF were oliguric and presented with gastrointestinal and flu-like symptoms, typically after reintroduction of the drug after a drug-free period. Anemia and thrombocytopenia were common. AIN was the most common biopsy finding. No factor predicted severity, but the renal prognosis was good.

DIAGNÓSTICO

ALDASORO, JUAN M. El citodiagnóstico en dermatología: alcances y limitaciones / Cytodiagnosis in dermatology: its reaches and limitations. *Arch. argent. Dermatol.*, v.52, n.2, p.49-55, mar-abr. 2002.

El citodiagnóstico, ampliamente difundido, virtualmente carece de aplicación práctica en dermatología. En parte, por las características inherentes al método y además por la particular histoarquitectura de la piel y membranas mucosas sanas y enfermas. Sin embargo, su técnica sencilla puede constituirse en un auxiliar valioso en fterias dermatosis, en particular vesicopollares y tumorales. Se revisa éste método diagnóstico y sus limitaciones y se rescatan aquellos casos en los que puede ofrecer utilidad.

EPIDEMIOLOGIA E CONTROLE

AROLE, S.; PREMKUMAR, R.; AROLE, R.; MAURY, M.; SAUNDERSON, P. Social stigma: a comparative qualitative study of integrated and vertical care approaches to leprosy. *Leprosy Rev.*, v.73, n.2, p.186-96, Jun., 2002.

Integration of leprosy into the general health system is very much emphasized by health care planners. One prime reason stated for this is to reduce stigma attached to this disease. This study was conducted in the state of Maharashtra, India, to compare the level of social stigma towards leprosy in communities with a vertical and an integrated programme. The data were collected in three areas of five villages each. The first two areas were in an integrated programme to test for internal consistency and the third in a vertical programme. All the leprosy patients with visible deformities in these villages were enrolled in the study, and an in-depth stigma measurement scale was administered. In addition, focus group discussions were conducted among the family members of leprosy patients and participative rural appraisal was done in the communities. The data were analysed using qualitative methods. A total of 24 leprosy patients with visible deformities participated in the in-depth stigma measurement exercise from 15 villages. Fifteen focus group discussions were conducted with families of leprosy patients and an equal number of participatory rural appraisals with communities were done. The results show that social stigma was virtually non-existent among the communities with the

integrated approach and minimally experienced by leprosy patients in this model. However, a high level of self-stigmatization among leprosy patients was observed in the vertical approach and equally a high level of social stigma was found in their communities, which led to reduced interaction between the leprosy patients and their communities. The integrated approach to community-based primary health care is effective in reducing leprosy stigma in society.

BAKKER, M.I.; HATTA, M.; KWENANG, A.; KLATSER, P.R.; OSKAM, L. Epidemiology of leprosy on five isolated islands in the Flores Sea, Indonesia. *Trop. Med. Int. Health*; v.7, n.9, p.780-7, Sep., 2002.

We conducted a population-based survey on five small islands in South Sulawesi Province (Indonesia) to collect baseline data previous to a chemoprophylactic intervention study aiming at interrupting the transmission of *Mycobacterium leprae*. Here we describe the present leprosy epidemiology on these geographically isolated islands. Of the 4774 inhabitants living in the study area 4140 were screened for leprosy (coverage: 87%). We identified 96 leprosy patients (85 new and 11 old patients), representing a new case detection rate (CDR) of 205/10 000 and a prevalence rate of 195/10 000. CDRs were similar for males and females. Male patients were more often classified as multibacillary (MB) than women. Of the new patients, 33 (39%) were classified as MB, 16 (19%) as paucibacillary (PB) 2-5 lesions and 36 (42%) as PB single lesion. In this area of high leprosy endemicity leprosy patients were extensively clustered, i.e. not equally distributed among the islands and within the islands among the houses.

DE WIN, M.M.; THEUVENET, W.J.; ROCHE, P.W.; DE BIE, R.A.; VAN MAMEREN, H. The paper grip test for screening on intrinsic muscle paralysis in the foot of leprosy patients. *Int. J. Leprosy*, v.70, n.1, p.16-24, Mar., 2002.

Plantar intrinsic foot muscles provide structure to the foot during walking and thus regulate mechanical foot sole stresses. When paralyzed, for instance in leprosy patients with neuropathy of the distal part of the tibial nerve, there is a high prevalence of plantar ulceration and deformities, especially when muscle weakness goes together with loss of foot sole sensibility. These patients should get immediate care involving education, special footwear and reconstructive surgery before further foot impairment and deformity becomes manifest. Thus far, in leprosy patients little attention is paid to screening of plantar intrinsic muscles activity. This can be done with a new simple and non-invasive method, the Paper Grip Test (PGT). There are two variants for detecting intrinsic muscle weakness of the foot, PGT1 for the great toe and PGT2 for the combined lesser toes. In this study, 517 leprosy patients and 170 healthy volunteers were investigated with the PGT. Sensibility of the foot sole was tested by means of a 10 gram monofilament. Specificity to the PGT1 is found to be about 95.3% which is considered good for physical

diagnostic tests. PGT2 is less specific than PGT1. Individual muscle power and understanding of the patient seems to influence the outcome of the test to a certain extent. Sensitivity can only be calculated when the diagnosis is confirmed by electromyography. Especially patients with anesthetic feet, females, older patients and patients with PN-, BB- or LL-types of leprosy appeared to have a higher prevalence of intrinsic foot muscle weakness. All results were analyzed by means of the bivariate Pearson correlation-analysis and proved to be statistically significant ($p = < 0.05$). It is concluded that the PGT1, more than the PGT2, is a useful screening test on the function of plantar intrinsic foot muscles in leprosy patients in hospitals and during fieldwork in developing countries.

GENÉTICA

PLANCOULAINE, S.; ALCAIS, A; ABEL, L.; CASANOVA, J.L. [Human mycobacterial infections: impact of host genetic factors]. *Infections mycobactériennes humaines: impact des facteurs génétiques de l'hôte. Rev. Med. Liege*, v.57, n.3, p.165-70, Mar., 2002.

Humans are exposed worldwide to a variety of environmental mycobacteria (EM) and most children are inoculated with live Bacille Calmette-Guérin (BCG) vaccine. Although rarely pathogenic, poorly virulent mycobacteria, including BCG and most EM, may cause a variety of clinical diseases. *M. tuberculosis* and *M. leprae* are more virulent, causing tuberculosis, and leprosy, respectively. Remarkably, only a minority of individuals develop clinical disease, even if infected with virulent mycobacteria. There is now accumulating evidence that the large interindividual variability of clinical outcome results in part from variability in the human genes that control host defense. We review here in current knowledge about genetic predisposition to common (leprosy and tuberculosis) and rare (BCG and EM infections) mycobacterial infections.

WIBAWA, T.; SOEBONO, H.; MATSUO, M. Association of a missense mutation of the laminin alpha2 gene with tuberculoid type of leprosy in Indonesian patients. *Trop. Med. Int Health*, v.7, n.7, p.631-6, Jul., 2002.

Leprosy, an infection caused by *Mycobacterium leprae*, has a specific tropism for the myelinating Schwann cells of peripheral nerves. Recently, the G domain of laminin alpha2 has been shown to be a mediator for *M. leprae* to bind to alpha-dystroglycan in Schwann cells. In order to analyse the association of leprosy with the mediator, three genetic polymorphisms encoding the G domain of the laminin alpha2 chain were analysed by direct sequencing in 53 leprosy patients and 58 healthy contact individuals from Indonesia. There was no significant difference in the incidence of the polymorphisms between patients and non-patients. Remarkably, it was found that a missense mutation

(T7809C) substituting valine with alanine (V2587A) was found to be more frequent in the tuberculoid type than in the lepromatous type leprosy. It is supposed that this missense mutation is one of the determinant factors in the early onset of peripheral nerve damage in Indonesian tuberculoid leprosy patients.

HISTÓRIA

IRGENS, L.M. [The discovery of the leprosy bacillus]. *Oppdagelsen av leprabasillen. Tidsskr. Nor. Laegeforen*, v.122, n.7, p.708-9, Mar. 10, 2002.

Gerhard Henrik Armauer Hansen (1841-1912) worked on leprosy throughout his career. Following his discovery of the leprosy bacillus in 1873, he proposed legislation that, when enacted in 1877 and 1885, established preventive measures aimed at isolating infectious patients. Around 1920, leprosy was more or less eradicated in Norway after a period of decline starting in 1850. Over this period, more than 8,000 cases were registered. Armauer Hansen's unique research achievement was based on a scientific and medical infrastructure in place long before he started his work. This context had several implications, though the discovery of the leprosy bacillus holds a particular fascination, with bearings on the interaction between medicine and the community even today.

MARMOR, M.F. The ophthalmic trials of G. H. A. Hansen. *Surv. Ophthalmol*, v.47, n.3, p.275-87, May-Jun., 2002.

G. H. A. Hansen (1841-1912) is widely known as the discoverer of the infectious cause of leprosy. It is less well known that his career was threatened by an episode involving experimentation on the eye. As a staff physician at the leprosy hospitals of Bergen, Norway, early in his career, Hansen learned about ocular involvement in leprosy and co-authored *Leprous Diseases and the Eye*. In 1873 he observed bacilli in leprosy nodules, but proof of an infectious origin was difficult to obtain because the agent could not be cultured and no one had demonstrated direct transmission. Hansen tried several unsuccessful experiments, and in 1879 he passed a cataract knife that had incised an active leprosy nodule into a woman's conjunctiva. No nodule developed, but the woman complained of pain and said she was never asked for permission. Hansen was brought to trial where eminent physicians testified on his behalf- but Hansen himself readily admitted that no permission had been sought for fear the woman would say no. He was convicted, and relieved of his post as staff physician, but he was allowed to retain an appointment as Chief Medical Officer of Health for Leprosy, in which capacity he worked for the rest of his life.

IMUNOLOGIA

BRAHMBHATT, S.; HUSSAIN, R.; ZAFAR, S.; DAWOOD, G.; OTTENHOFF, T.H.; DRIJFHOUT, I.W.; BOTHAMLEY, G.; SMITH, S.; LOPEZ, F.V.; DOCKRELL, H M Human T cell responses to peptides of the *Mycobacterium leprae* 45-kD serine-rich antigen. *Gin. Exp. Immunol.*, v.128, n.1, p140-8, Apr., 2002.

In order to identify T cell epitopes within the *Mycobacterium leprae* 45-kD serine-rich antigen, we analysed responses to overlapping 17-mer peptides encompassing the whole antigen in non-exposed UK controls, Pakistani leprosy patients and tuberculosis patients in both the United Kingdom and Pakistan. This antigen has been described as M. leprae-specific, although it has a hypothetical homologue in M. tuberculosis. Human peripheral blood mononuclear cells were stimulated with peptide for 5 days and IFN-gamma measured in supernatants by ELISA. Some peptides were recognized more frequently by T cells from tuberculoid leprosy patients than those from UK controls, suggesting that such T cell epitopes might have diagnostic potential, other peptides induced greater responses among UK control subjects. Short-term cell lines confirmed that these assays detected specific T cell recognition of these peptides. However, many tuberculosis patients also recognized these potentially specific peptides suggesting that there could be a true homologue present in M. tuberculosis.

COOPER, AM; ADAMS, L.B.; DALTON, D.K; APPELBERG, R.; EHLERS, S. IFN-gamma and NO in mycobacterial disease: new jobs for old hands. *Trends Microbiol.*, v.10, n.5, p.221-6, May, 2002.

Granulomatous disease following exposure to *Mycobacterium tuberculosis*, *Mycobacterium leprae* or *Mycobacterium avium* is correlated with strong inflammatory and protective responses. The mouse model of mycobacterial infection provides an excellent tool with which to examine the inter-relationship between protective cell-mediated immunity and tissue-damaging hypersensitivity. It is well established that T cells and interferon (IFN)-gamma are necessary components of anti-bacterial protection. We propose that IFN-gamma also modulates the local cellular response by downregulating lymphocyte activation and by driving T cells into apoptosis, and that the events that limit excessive inflammation are largely mediated by IFN-gamma-induced nitric oxide (NO). In several murine models of mycobacterial infection, the absence of IFN-gamma and/or NO results in dysregulated granuloma formation and increased lymphocytic responses, which, in the case of M. avium infection, even leads to reduced bacterial growth.

FIALLO, P.; CLAPASSON, A.; FAVRE, A.; PESCE, C. Overexpression of vascular endothelial growth factor and its endothelial cell receptor KDR in type 1 leprosy reaction. *Am. J. Trop. Med. Hyg.*, v.66, n.2, p.180-5, Feb., 2002.

The sites of expression of vascular endothelial growth factor (VEGF) and of KDR, its endothelial cell receptor, were investigated in leprosy reaction Type 1, or reversal reaction (RR), by immunohistochemistry and in situ hybridization. In comparison with nonreactional leprosy, overexpression of both VEGF and KDR was seen in granuloma cells, especially epithelioid and foreign body-type giant cells, the epithelium and the vascular endothelium of RR specimens. In granuloma cells, hybridization for VEGF was stronger than immunostaining, a finding that may reflect the rapid turnover of VEGF in an immunologically dynamic situation such as RR. In the epidermis, double immunohistochemistry revealed VEGF overexpression in CD1a-positive dendritic cells. The VEGF may not only be relevant for hyperpermeability and mononuclear cell differentiation (the key morphologic features in the acute, clinically evident phase of RR), but it could also be implicated in RR onset, when dendritic cells are activated in response to antigen stimulation.

KOÇAK, M.; BALCI, M.; PENCE, B.; KUNDAKÇI, N. Associations between human leukocyte antigens and leprosy in the Turkish population. *Gin. Exp. Dermatol.*, v.27, n.3, p.235-9, May, 2002.

Leprosy is a chronic infection caused by an intracellular microorganism. Genetic predisposition to both disease susceptibility and to host immunological response has been postulated for many years. The aim of this study was to determine whether there is HLA-linked susceptibility to leprosy and its different types. HLA-class I (A, B, C) and II (DR, DQ) antigen frequencies in 80 patients with leprosy (35 borderline lepromatous, 25 lepromatous, 15 borderline tuberculoid, five tuberculoid) were compared with those in 120 healthy individuals. HLA-class I antigens A9, A10, A32, B5, B21, Bw4, Bw6, Cwt, Cw2 and HLA-class II antigens DR9, DR10, DRw52, DQ1, DQ3 were found to be significantly more frequent in patients with leprosy, whereas HLA-class I antigens A3, B44, B49 and HLA-class II antigen DQ5 were so in controls. However, there was no significant difference in HLA-class I and II antigen frequencies between subtypes of leprosy. HLA-A null antigen was found to have weak expression in patients with leprosy. In conclusion, factors other than HLA-class I and class II antigens may have a more critical role in the pathophysiology of leprosy infection in man.

LOCKWOOD, D.N.; COLSTON, M.J.; KHANOLKAR-YOUNG, S.R. The detection of *Mycobacterium leprae* protein and carbohydrate antigens in skin and nerve from leprosy patients with type 1 (reversal) reactions. *Am. J. Trop. Med. Hyg.* v.66, n.4, p.409-15, Apr., 2002.

Type 1 (reversal) reactions are the most common immunological complications of leprosy. These episodes of

delayed hypersensitivity produce severe local immunopathology and ultimately nerve damage. To date, the *Mycobacterium leprae* antigens associated with type 1 reactions have not been identified. Using monoclonal antibodies to defined protein and carbohydrate *M. leprae* epitopes (65, 35 and 28 kd and lipoarabinomannan [LAM]) in a two-step immunoperoxidase staining technique, *M. leprae* antigens were demonstrated in skin and nerve biopsies from patients in reversal reaction. Antigen presence and staining patterns were similar in skin and nerve lesions, implying that the pathological processes are similar in the two sites. Antigens were present both in macrophages and Schwann cells but also as a diffuse extracellular infiltrate associated with the inflammatory infiltrate. The 28-kd antigen was present most strongly and may be a potential candidate antigen for initiating type 1 reactions. LAM also stained strongly and persisted after treatment. The possible roles of LAM and 65 kd in the cellular events of type 1 reactions are discussed.

MANANDHAR, R.; SHRESTHA, N.; BUTLIN, C.R.; ROCHE, P.W. High levels of inflammatory cytokines are associated with poor clinical response to steroid treatment and recurrent episodes of type 1 reactions in leprosy. *Gin. Exp. Immunol.*, v.128, n.2, p.333-8, May, 2002.

Levels of leprosy antigen-induced interferon-gamma (IFN-gamma), tumour necrosis factor alpha (TNF-alpha) and interleukin-10 (IL-10) were measured in 96 leprosy patients with type 1 reactions (Ti R) before, during and after a standard 12-week course of steroids. Peripheral blood mononuclear cells (PBMC) from leprosy patients with untreated Ti R produced significantly more TNF-alpha than leprosy patients without Ti R. Median levels of IFN-gamma and TNF-alpha in Ti R patients fell during treatment with steroids; however, TNF-alpha levels increased as the steroid dose was reduced. Median IL-10 levels increased throughout the steroid treatment period and were associated strongly with TNF-alpha levels. Patients with high cytokine levels had a poorer recovery of sensory or voluntary muscle nerve function, a higher risk of reactivation of symptoms during steroid treatment, and a higher risk of another episode of Ti R within 2 months of completing the steroid regimen. Rapid and effective reversal of the inflammatory process in Ti R is critical to prevent permanent nerve damage from Ti R and monitoring cytokine levels during treatment may be useful.

RAMBUKANA, A.; ZANALII, G.; TAPINOS, N.; SALZER, J L Contact-dependent demyelination by *Mycobacterium leprae* in the absence of immune cells. Comment In: *Science*, v.297, n.5586, p.1475-6, Aug. 30, 2002; Discussion In: *Science*, v.296, n.5569, p.927-31, May 3, 2002.

Demyelination results in severe disability in many neurodegenerative diseases and nervous system infections, and it is typically mediated by inflammatory responses. *Mycobacterium*

Ieprae, the causative organism of leprosy, induced rapid demyelination by a contact-dependent mechanism in the absence of immune cells in an in vitro nerve tissue culture model and in Rag1-knockout (Rag1^{-/-}) mice, which lack mature B and T lymphocytes. Myelinated Schwann cells were resistant to *M. Ieprae* invasion but undergo demyelination upon bacterial attachment, whereas nonmyelinated Schwann cells harbor intracellular *M. Ieprae* in large numbers. During *M. Ieprae*-induced demyelination, Schwann cells proliferate significantly both in vitro and in vivo and generate a more nonmyelinated phenotype, thereby securing the intracellular niche for *M. Ieprae*.

SIDDIQUI, M.R.; MOREIRA, A.L.; NEGESSE, Y.; TAYE, G.A.; HANEKOM, WA.; HASLETT, P.A.; BRITTON, S.; KAPLAN, G. Local nerve damage in leprosy does not lead to an impaired cellular immune response or decreased wound healing in the skin. *Infect. Dis.*, v.186, n.2, p.260-5, Jul 15, 2002.

This study investigated whether peripheral nerve damage in patients with leprosy impairs local cellular immune responses, thereby reducing wound healing and leading to chronic skin ulceration. Anesthetic and contralateral sensitive skin sites in 42 patients with leprosy were compared for delayed-type hypersensitivity responses to purified protein derivative (PPD) of tuberculin. Leukocyte recruitment, epidermal activation, keratinocyte proliferation, and rates of wound healing after skin biopsy were compared. No significant differences in PPD-induced induration, epidermal activation and thickening or numbers of total T cells, CD8⁺ T cells, CD1a⁺ Langerhans cells, and proliferating Ki67⁺ keratinocytes were observed between anesthetic and sensitive skin sites. Similarly, rates of wound healing over 5 days after skin biopsy did not differ significantly. Thus, local leprosy-associated anesthesia does not appear to contribute to local immune compromise or impaired wound healing. Rather, chronic cutaneous ulceration in leprosy most likely results from repeated trauma associated with loss of sensation.

WU, Q.; YIN, Y.; ZHANG, L.; CHEN, X.; YU, Y.; LI, Z.; YU, H.; LU, C.; FENG, S.; LI, X.; HUO, W.; YE, G. A study on a possibility of predicting early relapse in leprosy using a ND-O-BSA based ELISA. *Int. J. Leprosy*, v.70, n.1, p.1-8, Mar., 2002.

Serological methods have been used for detecting infection with *Mycobacterium Ieprae*. We have applied a serological test to explore the possibility it could detect a bacterial relapse among patients who have been cured with chemotherapy. More specifically we used an indirect enzyme-linked immunosorbent assay (ELISA) using the natural disaccharide (ND) of the phenolic glycolipid antigen of *M. Ieprae* linked to bovine serum albumin as antigen. Antibody levels were measured in sera from normal controls, active leprosy cases, cured leprosy patients, and relapsing leprosy patients. We correlated antibody levels with the type of leprosy, the bacterial index, and with relapse among cured

leprosy patients. In our hands, the ND-ELISA, when applied to screening for infection with *M. Ieprae*, had excellent sensitivity, specificity, positive and negative predictive values, and both a low false positive rate and a low false negative rate. Antibody levels gradually increased among active patients from the tuberculoid to the lepromatous end of the leprosy spectrum. There was a year-by-year fall in antibody levels in patients responding to chemotherapy. Antibody levels and the bacterial index were correlated using the Spearman's rank correlation method. Serial antibody levels were measured in 666 leprosy patients after being cured with dapson monotherapy. Over a three year follow up, 95 multibacillary patients became antibody positive and 12 of them had bacterial relapses of their disease. In contrast, among 335 cases that remained antibody negative, only one relapse was seen. Among 44 paucibacillary cured patients who became antibody positive, there was one relapse. There were 192 such patients who remained antibody negative and one relapsed. The risk of relapse is 6.7 times higher among cured multibacillary patients compared to cured paucibacillary patients. Overall, the cumulative relapse rate among antibody positive cases was 13.7%, compared to 0.4% among antibody negative patients. We conclude that the ND-ELISA is a useful tool both for screening for early infection with *M. Ieprae* and for predicting a relapse in cured patients, particularly in cured multibacillary patients.

MICROBIOLOGIA

SHEI IY, V.P.; ANTIA, N.H. Light and ultrastructural study of sciatic nerve lesions induced using intraneural injection of viable *Mycobacterium Ieprae* in normal and immunosuppressed Swiss white mice. *Int. J. Leprosy*, v.70, n.1, p.25-33, Mar., 2002.

Freshly harvested *M. Ieprae* were microinjected into the sciatic nerves of nonimmunosuppressed (non-TR) and immunosuppressed (TR) mice using the technique described by Wisniewski and Bloom. The lesions thus induced, on bypassing the blood-nerve barrier, were biopsied at regular intervals beginning 24 hr and followed up to one year. The fate of *M. Ieprae* and the ensuing inflammation and nerve damage were studied using light and electron microscopy. The lesions in both non-TR and TR mice at 24 hr showed an influx of polymorphonuclear leukocytes and an increase in mast cells. The influx and peaking of lymphocytes were delayed by two weeks and 6 weeks, respectively, in TR mice, but the density of lymphocytes at the peak intervals was comparable in both. The plasma cells denoting the humoral response were seen in both, but there was a delay of 3 weeks in non-TR mice. The lesions in non TR mice showed differentiation of macrophages into epithelioid cells and the formation of giant cells depicting borderline tuberculoid leprosy (BT), Whereas in TR mice, the macrophages showed foamy cytoplasmic changes depicting borderline lepromatous leprosy (BL). Other significant observations common to both non TR and TR mice were: a) The

lesions remained highly localized and showed signs of regression at the 6th and the 12th month intervals. b) The characteristic segmental demyelination and some attempt at remyelination were seen at the site. c) The influx of lymphocytes concurred well with demyelination. d) Bacteria were only seen in the macrophages and never in the Schwann cells or endothelial cells. e) Bacteria persisted in the macrophages, but appeared progressively degenerate at the 6th and 12th post-inoculation months, suggesting loss of viability. The study shows that there was a very effective containment of the infection and that the Schwann cells were resistant to *M. leprae* infection in the neural milieu. Nerve damage and Schwann cell bacillation do not go hand-in-hand.

SINGH, N.; ARORA, V.K.; JAIN, A.; BHATTACHARYA, S.N.; BHATIA, A. Cytology of testicular changes in leprosy. *Acta Cytol.*, v.46, n.4, p.659-63, Jul-Aug., 2002.

OBJECTIVE: To study the changes in testicular aspirates and semen of patients with leprosy. STUDY DESIGN: A prospective study of 56 patients in the reproductive-age group, with no record of treatment for leprosy. Both Ridley-Jopling and WHO classification systems were used. Skin and/or nerve biopsies were performed for documentation of the diagnosis. Semen analysis and fine needle aspirates of the testes were performed. Smears from the testicular aspirates were stained with May-Grünwald-Giemsa and Ziehl-Neelsen stain. RESULTS: Five patients were unable to produce an ejaculate. Abnormal semen analysis and/or testicular aspirates were seen in 24 (42.8%) patients. Eleven had oligospermia and eight azoospermia. Abnormalities in testicular aspirates ranged from hypospermatogenesis (4) through maturation arrest (1) and atrophy (11). Two patients had hydrocoele, and two had associated microfilariae. Three patients with multibacillary leprosy had type 2 reaction. Mycobacterium lepre was demonstrable in testicular aspirates from all patients with multibacillary and in three with paucibacillary leprosy. CONCLUSION: Abnormal semen analysis and/or testicular aspirates occur in a very high percentage of patients with leprosy. While this is expected for multibacillary disease, the high incidence in the paucibacillary form was surprising. With the rapid elimination of leprosy, fertility-related disability might emerge as a major problem in these people.

OFTALMOLOGIA

DANIEL, E.; KOSHY, S. Intraocular lens implantation in leprosy. *Int. J. Leprosy*, v.70, n.1, p:9-15, Mar., 2002.

The preoperative, operative and postoperative ocular complications in 48 eyes of 39 leprosy patients who underwent standard extracapsular cataract extraction and posterior chamber intraocular lens implantation, by the same surgeon, were studied retrospectively. Seventeen were male and 22 were female.

Thirteen (33%) were paucibacillary (PB) while 26 (67%) were multibacillary (MB) patients. Three patients were smear-positive at the time of surgery. Grade 2 deformity that included claw hands, absorbed fingers, saddle noses and foot drop were present in 64% of the patients. None of the patients had any previous intraocular inflammation although one patient had previously had a Type 1 reaction and 5 patients had previously had Type 2 reactions. Preoperative complications like corneal opacities (3 eyes) and lagophthalmos (5 eyes) were not associated with lower vision postoperatively. No significant operative complications like vitreous loss, endothelial damage or iris tear were encountered, except in one eye where there was a posterior capsular tear. Seventeen eyes (35%) developed uveitis of 3+ or more in the immediate postoperative period, but abated with routine topical steroid eye drops. Six months after surgery 7 out of 47 eyes (15%) had developed posterior capsular opacities. There were no significant differences ($p > 0.05$) in the visual acuity outcomes or in ocular complications when MB patients were compared with PB patients. Smear-positive patients were not significantly different from smear-negative patients when postoperative complications were compared. Visual outcomes in the 23 eyes followed up at two years after surgery were 6/18 or higher, except in one eye which had sustained a severe injury one year after surgery. IOLs were found to be safe and beneficial in this series of patients, but a much larger prospective study with matched normal controls is needed to prove the safety and efficacy of IOLs in leprosy patients.

KALK, A.; KONIG, J. NGO and state: co-operation between a leprosy relief association and other institutions in South America. *Leprosy Rev.*, v.73, n.2, p.160-6, Jun., 2002.

In a structured questionnaire format, the German Leprosy Relief Association (GLRA) interviewed its representatives in two Federal states of Brazil and four other Latin American countries about the distribution, between itself, the state and other institutions of a) responsibility for funding and b) implementation of activities, in relation to leprosy control. Wherever the political commitment was given, GLRNs role could be reduced to the highly effective support of the government structure in well-defined areas, most particularly in staff training, health education and eventually in programme supervision. This public-private partnership under the umbrella of the host government sustains a small, but important specialized leprosy component whilst routine services are well integrated into the general health system.

KASTURIARATCHI, N.D.; SETTINAYAKE, S.; GREWAL, P. Processes and challenges: how the Sri Lankan health system managed the integration of leprosy services. *Leprosy Rev.*, v.73, n.2, p.177-85, Jun., 2002.

At the end of 1999, the Ministry of Health in Sri Lanka took the bold decision to integrate its Leprosy Services within the

country's general health system. The integration was completed in February 2001 and is already starting to bear fruit, but implementing the necessary changes has been a challenging task. Many new procedures had to be established, logistics improved, attitudes changed and health workers trained. A broad bridge between curative and preventative health services needed to be built. Integration efforts were supported by an advertising campaign to inform people that leprosy, like any other illness, can be treated at all health facilities. Contrary to the expectation that quality of service would drop following integration, more cases are now detected and an extensive network of government doctors is able to diagnose, treat and manage leprosy patients more efficiently. Prevalence has increased by 36% and the new case load by 41%. A few areas still need more attention, such as integrating MDT supplies within existing systems and improving the flow of information, but nonetheless the ownership of leprosy is shifting rapidly to local health services.

NAMADI, A.; VISSCHEDIJK, J.; SAMSON, K. The leprosy elimination campaign in Jigawa, Nigeria: an opportunity for integration. *Leprosy Rev.*, v.73, n.2, p.138-46, Jun., 2002.

Integration of leprosy control into the general health services is regarded as an important condition for increasing the accessibility and sustainability of leprosy services. However, it is often difficult to embark on such an integration process. In Jigawa State in Northern Nigeria, the leprosy elimination campaign was used as the initiator and catalyst for the integration process. In this article, this challenging process is described and analysed. Available information is used to identify the constraints that emerged and to assess the consequences of integration for important aspects of leprosy control, such as case detection and case-holding and the accessibility and quality of the provided services. Some lessons from this experience are drawn that can be helpful for integration in other States or countries.

PORTER, J.D.; OGDEN, J.A.; RAO, P.V.; RAO, V.P.; RAJESH, D.; BUSKADE, RA.; SOUTAR, D. Lessons in integration—operations research in an Indian leprosy NGO. *Leprosy Rev.*, v.73, n.2, p.147-59, Jun., 2002.

Since the Alma Ata Declaration in 1978, health systems supporting the treatment and control of infectious diseases like leprosy and tuberculosis have been encouraged to 'integrate' into the primary health care structure within countries. Now, more than 20 years later, countries are still grappling with the concept of integration and looking for ways to achieve it. This study reports findings from a leprosy/Tuberculosis/AIDS awareness pilot project conducted by LEPRO India, a leprosy non-governmental organization (NGO), between 1996 and 2000 in Koraput district, Orissa. The project addressed the issue of integration on two levels. On the one hand LEPRO used the context of the project to explore ways in which to integrate TB services into their existing

leprosy control structure. On the other hand, lessons from the pilot study were intended to help the organization find ways of linking with the government health care structure. Following a 'qualitative approach', this operations research project assessed the perceptions of communities and providers about leprosy and tuberculosis services. Providers across the spectrum of this plural healthcare system were asked to provide comment on developing stronger networks with each other, with NGOs and with government, while patients and communities were asked to describe the resources available to them and the constraints they face in accessing health care in general, and for leprosy and TB in particular. LEPRO staff from top management to the outreach workers were also approached for their views. Patients and communities noted that physical access to treatment was a major constraint, while the existence of local providers and family support structures facilitated health and health care. Providers expressed a willingness to collaborate (with LEPRO and the government), but lacked training, adequate staff support and the appropriate equipment/technical resources. Also lacking were adequate information campaigns to inform the public about these diseases and their treatment. This information has provided LEPRO with an understanding of how they might best fill gaps in the existing system and therefore assist in the process of integrating services in their own organization and through the primary health care structure. To achieve this aim, LEPRO will increasingly become involved in developing relationships and partnerships with government in the delivery of training and services and in infrastructure development.

RAO, V.P.; BHUSKADE, R.A.; RAJU, M.S.; RAO, P.V.; DESIKAN, K.V. Initial experiences of implementation of functional integration (FI) in LEPRO India projects in Orissa. *Leprosy Rev.*, v.73, n.2, p.167-76, Jun., 2002.

In 2000, the Government of the State of Orissa (population 37 million) in India decided to introduce functional integration for the control of leprosy, in place of the long-established vertical programme, using the general health services and the primary health care system. This paper describes the initial (9 months) experience of implementing this strategy in two projects run by LEPRO India. One of these, in the district of Koraput, was established in 1991 and covers a population of 1.5 million people. The other, in Kalahandi district, started in 1997 and covers a population of 600,000. Both projects operate under difficult conditions with regard to terrain, the use of numerous tribal languages, illiteracy, water shortage, poor roads and communications. The preparatory phase included intensive health education of the public on leprosy, using a wide range of educational media and techniques. At the same time, LEPRO India supported the Government in the training and orientation of trainers, medical officers, primary health care staff and female health workers at village level. In all, over 2000 were trained. This paper describes all aspects of the implementation of functional

integration in these two areas. In the 9-month period, 4207 suspect cases were referred to medical officers by health workers, but only 256 (6%) were confirmed as having leprosy. There were 169 confirmed self-reporting cases. Despite the clearly understood intention to involve primary health staff in case detection, 67% of all cases were in fact detected by LEPRO India, possibly due to overlapping attendance at clinics by vertical and general staff. There is obviously a need for further training of the general staff since only 6% of cases referred by them were confirmed as having leprosy. Steps must also be taken to ensure that the emphasis on case detection, confirmation and treatment shifts from the vertical to the general health staff. The supply of anti-leprosy drugs and steroids to primary health centers needs improvement. Appropriate teaching and learning material is urgently needed for both field staff and medical officers.

SAUNDERSON, P.R.; ROSS, W.F. Training for integration. *leprosy Rev.*, v.73, n.2, p.130-7, Jun., 2002.

Training is often suggested as the solution to the inadequacies of the health care system, and there is little doubt that without it, service quality would suffer and new techniques and technologies would be difficult to introduce; clearly it is an important component in any drive to achieve quality of care. However, in this era of cost-effectiveness and cost cutting, which is part of the reason for integration, it is surprising that training is often not well planned and is rarely evaluated in a rational manner. This paper relies on recent discussions within ILEP about training and the use of training materials for leprosy in the present environment—one in which most programmes are being integrated into the general health services. The development of a National Training Plan for Leprosy is proposed, with clear objectives, in order to best utilize the resources available.

TERAPÉUTICA

ABDEL LATIF, A.M.; ESSA, EA. Study of HLA-DR expression on skin lesions of leprosy before and during multiple drug therapy. *Int.J. Leprosy*, v70, n.2, p.104-10, Jun., 2002.

Leprosy is a dynamic disease in which cell mediated immunity (CMI) plays an important role in host defense and control of the clinical spectrum. This study was carried out to detect immune activation in the granuloma of leprosy during multiple drug therapy (MDT) by studying the expression of human leukocytic antigen-DR (HLA-DR) in the granuloma before and during therapy. Skin punch biopsies were taken before and at least once 2-4 weeks after starting MDT in 20 newly diagnosed patients. Two biopsies, 2-4 weeks apart, were also taken from 10 new patients who did not yet receive any treatment, for comparison. Furthermore, biopsies were taken before and during corticosteroid therapy in five patients who developed reversal reaction during MDT. The biopsy specimens were studied for the expression of HI A-DR using the immunofluorescent staining

which was found to be visibly increased in 17 out of 20 new cases (85%) within 2-4 weeks after starting MDT, while no change in the expression was noticed in those who did not receive any treatment ($p < 0.001$). This might reflect the increased production of interferon gamma (IFN gamma) specially from granuloma lymphocytes after being stimulated with the excessive release of mycobacterial antigen from killed bacilli during therapy. The five patients who developed reversal reaction during MDT had strong HLA-DR expression in the first biopsies which declined subsequently 2-6 weeks after starting prednisolone therapy. Our results suggest that CMI was activated in skin lesions of leprosy during MDT. Such activation was not only restricted to those who developed reversal reaction across the therapeutic course, which indicates that the difference between patients who developed such reaction and those who did not, was likely to be quantitative rather than qualitative, with a more exaggerated CMI response in the former. Furthermore, it seems that the beneficial effect of MDT is accompanied by important changes in the immune cell profile which have a great role in overcoming such infection.

BOURÉE, P; JOSEPH, P.F.; FILS-AIMÉ, F.; MORELL-GIL, R.E.; JOSEPH, P.F. Leprosy in Haiti. *Sante*, v.12, n.2, p.281-2, Apr-Jun, 2002.

Leprosy has yet a great impact on public health in Haiti. A study was carried out in Haiti from 1977 to 1999. On 2,160 registered cases, mostly are paucibacillaries: 412 cases are under 15 year old patients and 1,306 more than 15 year old. Multibacillaries cases are 85 in under 15 year old patients and 357 in more than 15 year old. By the improvement of sanitary conditions, detecting cases and multidrug therapy, leprosy had decreased during these last years, with an incidence from 0.1 to 0.2%. However, with the increasing poverty and political disorders, the control of leprosy remains difficult in Haiti.

DÍAZ-VALLE, D.; MIGUÉLEZ SANCHEZ, R.; TOLEDANO FERNANDEZ, N.; ALMONEDA, C.; MORICHE CARRETERO, M. [Immunomediata scleritis in a patient with lepromatous leprosy'. Escleritis inmunomediada en paciente con lepra lepromatosa. *Arch. Soc. Esp. Oftalmol.*, v77, n.3, p.558, Mar, 2002.

CASE REPORT: A 55 year-old Spanish woman with a personal history of lepromatous leprosy treated for 10 years with anti-lepromatous triple therapy was referred to us presenting nodular scleritis in her left eye with no other clinical manifestations. Ophthalmological evaluation disclosed several inflammatory features in both eyes. Complementary tests performed were negative and the clinical picture was diagnosed as an immuno-mediated manifestation of leprosy. A favorable outcome was achieved with steroidal treatment. DISCUSSION: Scleritis and some immunomediata conditions may appear during the evolution of lepromatous patients whose disease may have been declared clinically cured.