Volume 70, Number 2
Printed in the U.S.A.
(ISSN 0148-916X)

CURRENT LITERATURE

This department carries selected abstracts of articles published in current medical journals dealing with leprosy and other mycobacterial diseases.

General and Historical

Arcas, C. M. The diseases yudam and baras (leprosy) in treatises of Islamic Law (Maliki Doctrine). Dynamis **21** (2001) 55–71. (in Spanish)

Two diseases that appear in the legal treatises, yudam and baras, are semantically ambiguous and present difficulties when it comes to establishing their meaning. However, comparison of lexicographical and medical sources with modern bilingual and monolingual Arabic dictionaries bring us closer to the real meanings of the terms within the spacial and temporal contexts of the Maliki legal treatises. In these treatises, they appear as vitia redhibitoria in certain types of contract and also as diseases subject to regulations for the prevention of infection.—Author's Abstract

Garcia, J. R. L. Between madness and leprosy: historical interfaces of instituted practices and policies. Hansen. Int. **26** (2001) 14–22.

Madness and leprosy, two very different pathological pictures, present in their history several similarities and complementation in respect to practices and public health policies. This paper studies this relationship. A reviewing of the literature showed that indeed existed interfaces between both, in regard to historical, social and cultural aspects. Among the main similarities were social isolation, segregation, stigma, and in many moments negligence within the policies of Mental Health and Sanitary Dermatology. Starting with dissemination of the ancient European leprosariums in the middle ages, which later belonged to the insane by historical inheritance, leprosy and madness are relegated to asylums. Nowadays, we see that those two realities maintain traces of these historical processes, specially in the Brazilian context, where we still can find an prevalence of leprosy and the "Movement Antimanicomial" for more than one decade has tried to grant basic citizenship rights to mentally impaired people. The physical disabilities and pain in leprosy, and the mental struggle are not the only distress faced by its sufferers. They continue at the margin of society, still not comprehended by a social context that segregates the different.—Author's Abstract

Jagannathan, S. A. History and development of the Hind Kusht Nivaran Sangh and its contribution to leprosy work in India. Indian J. Lepr. **73** (2001) 247–261.

This article discusses the history and development of the Indian Leprosy Association (ILA)/"Hind Kusht Nivaran Sangh", and its contribution to leprosy management in India that includes treatment through leprosy clinics and research work. The history of the Indian Journal of Leprosy, and the current activities of ILA are also discussed.—Trop. Dis. Bull.

Porter, J. D. H. and Kessel, A. S. Needing to know? Ethical dilemmas in leprosy treatment and control. Lepr. Rev. **72** (2001) 246–249.

The impact of a patient education program, which involves the diagnosis of new leprosy cases, on community health is evaluated. The ethical issues involved in leprosy treatment and control and the principles of bioethics are discussed. An approach to reduce the stigma of leprosy is suggested.—Trop. Dis. Bull.

Worboys, M. The colonial world as mission and mandate: leprosy and empire, 1900–1940. Osiris **15** (2000) 207–218.

The history of medicine in twentieth-century empires has been dominated by studies of "imperial tropical medicine" (ITM) and its consequences. Historians have been fascinated by the work of medical scientists and doctors in the age of high imperialism, and there are many studies of medicine as a "tool of empire." This paper reviews work that explores colonial medicine as a broader enterprise than ITM in three spheres: missionary activity, modernization, and protection of the health and welfare of indigenous peoples. To illustrate the themes of mission and mandate, it discusses the development of policies to control leprosy in the tropical African and Asian colonies of Britain in the first half of this century, especially the work of the British Empire Leprosy Relief Association (BELRA). Although BELRA's efforts did little to change imperial medical and health agendas, they had an important impact locally and ideologically, and show how closely interwoven the themes of Christian caring, medical humanism, colonial development, and welfare policy had become by the outbreak of the Second World War.—Author's Abstract

Chemotherapy

Barry, C. E., 3rd. Preclinical candidates and targets for tuberculosis therapy. Curr. Opin. Investig. Drugs **2** (2001) 198–201.

Like many neglected diseases of the developing world, tuberculosis (TB) has a thin portfolio of new compounds currently in the discovery pipeline with near-term clinical potential. Co-development of broad-spectrum antibacterials for TB indications is superficially attractive but unlikely to result in significant advances in therapy. Genomic information has been useful in the redesign of second-line antituberculars such as ethambutol and such molecules will likely soon enter preclinical development. New targets and lead compounds with activity against the mycobacterial cell wall and non-replicating bacilli are the subject of current discovery programs.—Author's Abstract

Dhople, A. M. *In vivo* activity of epiroprim, a dihydrofolate reductase inhibitor, singly and in combination with dapsone, against *Mycobacterium leprae.* Int. J. Antimicrob. Agents **19** (2002) 71–74.

The antimicrobial effects of a new dihydrofolate reductase inhibitor, epiroprim, either singly or in combination with dapsone against *Mycobacterium leprae,* were evaluated *in vivo* using a mouse footpad model. When fed to mice at concentration of 0.05% in diet, epiroprim completely inhibited the growth of both dapsone-sensitive and dapsone-resistant strains of *M. leprae* in the footpads of mice and the effects were bactericidal. To achieve similar effects, the concentration of dapsone in the diet had to be 0.0005% and 0.01%, respectively. When used in combination, the concentrations of the drugs in the diet could be lowered by 50–80% and still achieve bactericidal effects. The data support the earlier results on *in vitro* studies and suggest the use of epiroprim in the multidrug regimen in the treatment of leprosy.—Author's Abstract

Ignotti, E., Andrade, V. L. G., Sabroza, P. C. and Araújo, A. J. G. Study of adhesion to treatment of the leprosy in municipal district of Deque de Caxias - Rio de Janeiro: Abandoning or abandoned? Hansen. Int. **26** (2001) 23–30.

The objective of this research was to analyze the most important determinants of leprosy treatment default in the municipality of Duque de Caxias, Rio de Janeiro, Brazil, which is an area of high endemicity for leprosy and presents one of the highest rates of treatment default in the state. From the 855 cases reported between 1995 and 1997, administrative cohorts were built with a total of 483 patients, 160 multibacillary and 323 paucibacillary cases. Seventy-three cases were registered at the local level as treatment default. It was observed that multibacillary cases have twice the chance

of defaulting treatment when compared to paucibacillary cases (OR = 2.07 (1.21 – 3.55)). This is of special interest when considering that multibacillary cases present up to five times more physical disability than paucibacillary cases. GIS analysis showed that both detection and treatment default are distributed throughout the entire municipality. The results indicate that the rates of treatment default are overestimated when considering the current treatment protocol proposed for multibacillary cases. In addition, when analyzing the compliance indices, these cases are of no epidemilogic importance for the maintenance of leprosy transmission since only 3.5% of the patients received insufficient doses. To increase the success in the control of leprosy it is recommended that the strategies adopted focus on early detection, which will influence on the reduction of treatment default.—Authors' Abstract

Prakash, J., Kumar, N. S., Saxena, R K. and Verma, U. Acute renal failure complicating rifampicin therapy. J. Assoc. Physicians India **49** (2001) 877–880.

BACKGROUND : Since 1971, 55 case-reports of rifampin-induced acute renal failure (ARF) have been published. Covic et al described 60 consecutive cases of rifampin-induced ARF during a period of eight years (1987–1995) from Iasi Dialysis Centre, Romania. The systemic data on this condition are not available, in view of the anecdotal nature of the observation from our country. OBJECTIVE: The aims of study were to analyze clinical features, course and outcome of ARF complicating rifampin therapy at our center. METHODS: We retrospectively studied prevalence, clinical presentations and renal histology and outcome of 11 cases (eight males, three females, aged 42–72 years) who were referred to Nephrology Unit of University Hospital, Varanasi for acute renal failure following retreatment with rifampin between period of 1994–1999. RESULTS: The gastrointestinal symptoms (abdominal pain, nausea and vomiting) and 'flu like' (fever, weakness and body ache) syndrome were the most frequent presenting features. The clinical signs of intravascular hemolysis were observed in four cases. The commonest laboratory findings included: Anemia (7), leukocytosis (5), thrombocytopenia (3) and toxic hepatitis in (2) patients. Toxic hepatitis, hemolysis and ARF was seen in one patient in combination. The typical clinical features of allergic interstitial nephritis and acute tubular necrosis were seen in six and two patients respectively. Renal biopsy in three cases revealed crescentic GN (1) and ATN in (2) patients. Acute renal failure complicating rifampin accounted for 1.8% (11/607) of all ARF cases hospitalized in our center during the study period. Renal function returned to normal in nine cases and one patient died on account of hepatic failure (toxic hepatitis). The patients with crescentic GN remained anuric and became dialysis dependent. Thus, clinical course of rifampin induced ARF was favorable; with only one mortality, compared to a 18% mortality rate among all ARF patients. CONCLUSION: Acute renal failure complicating rifampin therapy is not an uncommon condition, and typically occurs after reintroduction of rifampin. The renal prognosis is usually favorable. Intermittent or interrupted therapy appears to be a significant risk factor for the development of acute renal failure.—Authors' Abstract

Clinical Sciences

Bharath, S., Shamasundar, C., Raghuram, R. and Subbakrishna, D. K. Correlates of psychiatric morbidity in patients with leprosy. Indian J. Lepr. **73** (2001) 217–228.

The relationship between psychiatric morbidity in 30 leprosy patients under treatment as assessed by the General Health Questionnaire (GHQ-12) and certain variables of their illness and psychosocial factors is examined in this paper. Physical disability and duration of illness were the illness variables considered; knowledge and adjustment were the psychosocial variables included. Bell's Adjustment Inventory

(BAI) measured the latter, psychiatric morbidity was positively correlated with physical disability ($p < 0.05$), knowledge about the disease ($p < 0.01$) and social, emotional and health maladjustment ($p < 0.01$), but not with duration of illness ($p > 0.05$). The importance of appropriate knowledge, social stigma and physical disability in leprosy is discussed in addressing the psychiatric morbidity of leprosy patients.—Authors' Abstract

Crampin, A. C. and Damisoni, H. HIV/AIDS testing and counselling. Lepr. Rev. **72** (2001) 345–351.

This paper highlights the need for human immunodeficiency virus (HIV) testing and its potential benefits to the individual. The issues that should be covered in pre- and post-test counselling sessions are summarized. Training and support for counsellors are discussed. Ethical issues in HIV testing and counselling are briefly evaluated. Other topics are counselling children, counselling without testing and HIV testing in leprosy patients.—Trop. Dis. Bull.

Diaz-Valle, D., Miguelez, Sanchez, R., Toledano Fernandez, M. Lamoneda C. and Moriche Carretero, M. Immunomediate scleritis in a patient with lepromatous leprosy. Arch. Soc. Esp. Oftalmol. **77** (2002) 155–158. (in Spanish)

CASE REPORT: A 55 year-old Spanish woman with a personal history of lepromatous leprosy treated for 10 years with antilepromatous 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 immunomediated conditions may appear during the evolution of lepromatous patients whose disease may have been declared clinically cured.—Authors' Abstract

Ferrari, T. C. A., Araújo, M. G. and Ribeiro, M. M. F. Hepatic involvement in lepromatous leprosy. Lepr. Rev. **73** (2002) 72–75.

Hepatic involvement in a lepromatous leprosy (LL) patient is reported. The serum concentrations of aminotransferases were much higher than previously described in the leprosy literature. Other causes for hepatic damage were ruled out. Such hepatic involvement and elevation of aminotransferases have never been described in leprosy.—Authors' Abstract

Gebre-Yesus, A. and Saunderson, P. Comparative value of active and passive surveillance over time in treated leprosy patients, in the prevention of further disability. Lepr. Rev. **72** (2001) 221–223.

After release from treatment during the period 1990–1992, 223 patients in the ALERT MDT Field Evaluation Study (AMFES) in central Ethiopia were seen every six months under a scheme of active surveillance while another 184 formed a cohort that was not folowed actively. Sixty-eight (37%) of 184 in the passive surveillance group could not be traced due to change of address or death. Sixty-three (54%) of 116 and 108 (48%) of 223 patients under passive and active surveillance, respectively, were multibacillary. It is suggested that more effort should be put into educating and supporting patients before they are released from treatment. It is concluded that active surveillance only slightly reduces further disability and that the Eye-Hand-Foot score is a useful method for assessing any intervention whose main purpose is to prevent impairment.—Trop. Dis. Bull.

Kulkarni, R. B., Patil, R. T. and Praveena, S. Actinomycotic mycetoma due to Norcardia brasiliensis in a case of leprosy. Indian J. Lepr. **73** (2001) 263–265.

Various bacterial and fungal infections associated with non-healing ulcers in cases of leprosy have been reported (G. Ebenzer, *et al.*, 2000, Rama Ramani, *et al.*, 1990).

There are no reports of mycetoma associated with leprosy patients in the literature. We report here a case of actinomycotic mycetoma due to Nocardia brasiliensis associated with the non-healing plantar ulcer of a leprosy patient.—Authors' Abstract

Kumano, K. Leprosy reactions. Nihon Hansenbyo Gakkai Zasshi **71** (2002) 3–29. (in Japanese)

In leprosy, the causative bacteria, *Mycobacterium leprae,* will not threaten the lives of the hosts directly because they proliferate only slowly in the Schwann cells of the peripheral nerves. It is the "reactions" which give the patients irreversible morbidity through the inflammatory damages to the peripheral nerves. Physicians should be aware of the possibility of the state of the "reaction" when they examine leprosy patients. They also should be aware of the possibility of leprosy and the state of the "reaction" when they examine patients with cutaneous lesions and/or peripheral nerve disturbances, because it may be the first presenting symptom of the disease. In this review, recent advances on the issue about the reactions are discussed including pathogenesis, immunology, clinical features, pathology, treatment and prevention.—Author's Abstract

Lockwood, D. N. Kellersberger Memorial Lecture 1998: Nerve damage in leprosy: a problem for patients, doctors and scientists. Ethiop. Med. J. **37** (1999) 133–140.

There are interesting challenges in leprosy right now. The last fifteen years have seen the world-wide implementation of multidrug therapy with tangible benefits for patients and doctors. Paradoxically this success has revealed how much we still need to understand about leprosy nerve damage. For patients it is imperative that nerve damage is detected at an early stage when damage is still reversible. They need effective education to prevent the development of disability and to minimise the social and economic effects of nerve damage. For doctors and paramedical workers nerve damage needs effective treatment. We need to use current treatments effectively and also develop new treatments. This lecture looks critically at the pathology, detection and treatment of nerve damage, reviewing our present knowledge and looking to future developments.—Author's Abstract

Narayan, N. P., Ramu, G., Ilangumaran, S., Desikan, K. V. and Juthukaruppan, V. R. Poor correlation of systemic immunological parameters with clinical features in macular leprosy. Indian J. Lepr. **73** (2001) 239–246.

On the basis of clinical features and bacteriological status, macular skin lesions of nine cases of leprosy were classified as falling within a spectrum between the tuberculoid at one end and the lepromatous at the other. While histologic correlation was seen in 60% of cases, humoral and cellular systemic immunologic features were found to be uncharacteristic. It is suggested that macular lesions form an early stage in the development of leprosy where the systemic immunological response is yet to set in fully.—Authors' Abstract

Peters, E. J., Ansa, V. O., Imananagha, K. K. and Antia, E. A. Time of presentation for treatment and profile of deformities among leprosy patients in South Eastern Nigeria. West Afr. J. Med. **20** (2001) 237–241.

A 10-year review of leprosy patients seen at Leprosy Hospital Ekpene Obom in South Eastern Nigeria (1988–1997) was carried out to evaluate the effect of early identification and treatment of leprosy patients in the limitation of deformities among them. A total of 2,597 patients comprising 1,714 (66%) males and 883 (34.0%) females formed subjects for the study. Of these 288 (11.1%) were aged 15 and below while 2,309 (88.9%) were above 15 years. Their case records were thoroughly reviewed noting the duration of disease before presentation, type and location of deformity as well as the type of leprosy. Though there was a steady decline in the total number of leprosy patients seen over the study period as well as a decrease in the

mean duration of illness before presentation, approximately 19% of patients still had deformities at presentation, a figure much lower than those reported by other workers. Analysis of the pattern of deformities shows that most patients (71.2%) presented with affectation of the upper and lower limbs with consequent functional disability. We conclude that early treatment is an effective means of reducing the prevalence of deformity and thus disability from leprosy. More effective implementation of health education and treatment programs initiated by the W.H.O should further reduce the scourge of leprosy in our community.—Authors' Abstract

Ponninghaus, J. M., Jaeger, G. and Baum, H. P. Anetoderma Schwenninger-Buzzi in a dark-skinned patient. Hautarzt **52** (2001) 950–951. (in German)

A 10-year-old boy in Uganda developed primary anetoderma (Schwenninger-Buzzi). It is important not to confuse anetoderma with BL leprosy in spite of some superficial resemblance of the two diseases. Primary anetoderma is probably extremely rare in patients with dark skin although this may partly be due to a lack of dermatologists in Africa who could diagnose the disease.—Authors' Abstract

Saoji, V. and Salodkar, A. Lucio leprosy with lucio phenomenon. Indian J. Lepr. **73** (2001) 267–272.

Leprosy is one of the commonly seen disease in any dermatology outpatient department in our country. India accounts for a major portion of the leprosy patients in the world. All types of the disease, such as tuberculoid, borderline, lepromatous, neuritic and indeterminate leprosy, are seen. However, "Lucio leprosy" which is considered a special type of lepromatous leprosy characterised by diffuse involvement has not been reported from India. We are presenting here two cases of "Lucio leprosy" with "Lucio phenomenon", the Lucio phenomenon being a special type of lepra reaction seen in Lucio leprosy.—Authors' Abstract

Shetty, V. P., Wakade, A. and Antia, N. H. A high incidence of viable *Mycobacterium leprae* in post-MDT recurrent lesions in tuberculoid leprosy patients. Lepr. Rev. **72** (2001) 337–344.

A study was carried out to determine whether viable bacteria are present in recurrent lesions of tuberculoid and borderline tuberculoid (BT) leprosy cases. A total of 25 skin lesional biopsies obtained from 25 cases of BT leprosy with recurrent lesions 1–13 years after the release from multiple drug therapy were studied histopathologically and tested for the presence of viable *Mycobacterium leprae* [India]. Results showed that 12/25 (48%) of the biopsies showed presence of viable *M. leprae*. The incidence of viable *M. leprae* in the lesions that showed histopathological evidence of reversal reactions (7/12 or 58%) was higher than the ones with no evidence of reversal reactions (5/13 or 38.5%).—Trop. Dis. Bull.

Toribio, R. C., Alvarez, R. R. A., Mendes, G. F. and de Souza, A. L. B. Ocular complications and visual deficiency observed in patients with Hansen's disease—a study in the Federal District. An. Bras. Dermatol. **76** (2001) 543–550.

BACKGROUND: According to data from the World Health Organization (WHO), leprosy figures among the principal causes of blindness, and is influenced by various factors, such as: clinical form, disease duration and treatment. Recent studies have reported that the prevalence of visual incapacity bas been reduced since the introduction of polychemotherapy to treat leprosy. OBJECTIVES: To describe the ocular complications and classify the level of visual incapacity of the patients registered in the Federal District Leprosy Control Program. METHODS: An ophthalmological evaluation in a sample of 153 patients, using the protocol proposed by the WHO, in 1987. RESULTS: The most common ocular complaint observed was ardor, occurring in 30.1% of the patients; 5.2% presented visual deficiency and 1.3% serious visual deficiency, there were no cases of total blindness; the most frequent ocular alterations

were cataracts, reported in 15.0% with multibacillary forms and 3.1% with paucibacillary forms; lagophthalmia in 3.9%; reduction in corneal sensitivity in 23.5% and iridocyclitis in 7.8% of the patients; regarding the degree of visual incapacity, 74.8% of the sample presented Level 0; while Level 1 and 2 occurred in 23.6% and 1.6%, respectively. CONCLUSIONS: The age, disease duration of less than five years in 60.7% of the patients and treatment with polychemotherapy, appear to have influenced the level of visual incapacity.—Authors' Abstract

Immuno-Pathology

Abulafia, J. and Vignale, R. A. Leprosy: accessory immune system as effector of infectious, metabolic, and immunologic reactions. Int. J. Dermatol. **40** (2001) 673–687.

This paper discusses the functional bipolarity of macrophages and lymphocytes in leprosy, and the bipolarity of dendritic cell systems related to leprosy immunity, as well as the role of other nonimmunological dendritic cells in leprosy. Results of histopathological, immunohistochemical and electron microscopic examinations of 20 patients with leprosy (tuberculoid (n=8), lepromatous (n=8), histoid (n=2) and erythema nodosum leprosum (n=2)) are reported.—Trop. Dis. Bull.

Adams, L. B., Scollard, D. M., Ray, N. A., Cooper, A. M., Frank, A. A., Orme, I. M. and Krahenbuhl, J. L. The study of *Mycobacterium leprae* infection in interferon-gamma gene-disrupted mice as a model to explore the immunopathologic spectrum of leprosy. J. Infect. Dis. **185** (2002) S1–8.

Mycobacterium leprae infection was evaluated in interferon-gamma knockout (GKO) mice. At 4 months, growth of the bacilli in the footpads of GKO mice plateaued a log(10) higher than that in control mice. Control mice exhibited mild lymphocytic and histiocytic infiltrates, whereas GKO mice developed large, unorganized infiltrates of epithelioid macrophages and scattered CD4 and CD8 T cells. Flow cytometric analysis of popliteal lymph node cells demonstrated similar profiles of T cells; however, GKO cells exhibited an elevated proliferative response to *M. leprae* antigen. Expression of inducible nitric oxide synthase mRNA was decreased in GKO mice, whereas macrophage inflammatory protein-1alpha and interleukin-4 and -10 mRNA expression were augmented. Control and GKO activated macrophages inhibited bacterial metabolism and produced nitrite. Thus, although deficient in an important Th1 cytokine, GKO mice possess compensatory mechanisms to control *M. leprae* growth and feature elements resembling mid-borderline leprosy in humans.—Authors' Abstract

Arvieux, J. Renaudineau, Y., Mane, I., Perraut, R., Krillis, S. A. and Youinou, P. Distinguishing features of anti-beta2 glycoprotein I antibodies between patients with leprosy and the antiphospholipid syndrome. Thromb. Haemost. **87** (2002) 599–605.

Anticardiolipin (ACA), anti-beta2 glycoprotein I (beta2GPI), and antiprothrombin antibodies of IgG and IgM classes were quantitated by enzyme-linked immunosorbent assays in 176 untreated leprosy patients across the histopathological spectrum. Positivity rates ranged from 21% (IgG ACA) to 30% (IgM anti-prothrombin) versus 4% in healthy controls ($p < 10^{-2}$) to 10^{-3}). Levels of IgM anti-beta2GPI and IgG ACA were significantly higher in lepromatous leprosy and multibacillary patient subgroups. IgG3 was the most common subclass reactive to both beta2GPI and prothrombin in selected high-titer leprosy sera, unlike antibodies from patients with the antiphospholipid syndrome (APS) largely restricted to IgG2. In leprosy patients, but not in the APS control group, there was no statistical correlation between ACA and anti-beta2GPI an-

tibody levels. Likewise, a large fraction of anti-beta2GPI positive sera (36/45 and 28/44 for IgG and IgM, respectively) were unreactive in the standard ACA assay. Most assayed anti-beta2GPI antibodies from leprosy patients showed (i) ability to recognize both human and bovine beta2GPI immobilized on non-irradiated polystyrene plates, (ii) concentration-dependent inhibition of binding by cardiolipin, and (iii) relatively high avidity binding to fluid-phase beta2GPI, thereby differing from those found in APS. Finally, the location of the major epitopic region on the beta2GPI molecule targeted by autoantibodies was different in leprosy and APS, as assessed by direct binding to domain I- and V-deleted mutants and competition with the mouse monoclonal antibody 8C3, directed at domain I. Thus, leprosy-related antiphospholipid antibodies comprise persistent IgG and IgM anti-beta2GPI that differ from APS-related ones with respect to IgG subclass, avidity and epitope specificity, possibly reflecting distinct pathophysiological significance.—Authors' Abstract

Casanova, J. L. and Abel, L. Genetic dissection of immunity to mycobacteria: the human model. Annu. Rev. Immunol. **20** (2002) 581–620.

Humans are exposed to a variety of environmental mycobacteria (EM), and most children are inoculated with live Bacille Calmette-Guerin (BCG) vaccine. In addition, most of the world's population is occasionally exposed to human-borne mycobacterial species, which are less abundant but more virulent. Although rarely pathogenic, mildly virulent mycobacteria, including BCG and most EM, may cause a variety of clinical diseases. *Mycobacterium tuberculosis*, *M. leprae*, and EM *M. ulcerans* are more virulent, causing tuberculosis, leprosy, and Buruli ulcer, respectively. Remarkably, only a minority of individuals develop clinical disease, even if infected with virulent mycobacteria. The interindividual variability of clinical outcome is thought to result in part from variability in the human genes that control host defense. In this well-defined microbiological and clinical context, the principles of mouse immunology and the methods of human genetics can be combined to facilitate the genetic dissection of immunity to mycobacteria. The natural infections are unique to the human model, not being found in any of the animal models of experimental infection. We review current genetic knowledge concerning the simple and complex inheritance of predisposition to mycobacterial diseases in humans. Rare patients with Mendelian disorders have been found to be vulnerable to BCG, a few EM, and *M. tuberculosis*. Most cases of presumed Mendelian susceptibility to these and other mycobacterial species remain unexplained. In the general population leprosy and tuberculosis have been shown to be associated with certain human genetic polymorphisms and linked to certain chromosomal regions. The causal vulnerability genes themselves have yet to be identified and their pathogenic alleles immunologically validated. The studies carried out to date have been fruitful, initiating the genetic dissection of protective immunity against a variety of mycobacterial species in natural conditions of infection. The human model has potential uses beyond the study of mycobacterial infections and may well become a model of choice for the investigation of immunity to infectious agents.—Authors' Abstract

Cooper, A. M., Adams, L. B., Dalton, D. K., Appelberg, R. and Ehlers, S. IFN-gamma and NO in mycobacterial disease: new jobs for old hands. Trends Microbiol. **10** (2002) 221–226.

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.—Authors' Abstract

Fleury, R. N., Ura, S., Martelli, A. C. C., Delanina, W. F. B. and Opromolla, D. V. *A.* Late manifestation of erythema nodosum leprosum with necrotic and exudative arteritis, cicatricial arteritis, reticular livedo, reactional nodules and plaques with foci of necrosis. Hansen. Int. **26** (2001) 37–42.

The authors describe a patient with lepromatous leprosy who has been presenting reactional episodes for 7 years after withdraw from treatment, with plaques and nodules in lower limbs associated with reticular livedo, ulceration and pain. Several biopsies have been done and the most constant change observed has been the exudative and necrotic arteritis in the deep dermis and subcutis. Scarce foci of residual lepromatous infiltrate has been present and bacilli (granular) have been found only on the wall of involved arteries. Obstructive and cicatricial arteritis, cicatricial phlebitis and dermal changes suggestive of vasculitis livedoid have been observed in some biopsies. The authors believe that these episodes may depend on persistency of antigens on the wall of vessels, probably due to the intense parasitism of vessels during the most active phases of lepromatous leprosy. The livedoid skin pattern could be related to exudative and necrotic acute arteritis and the cicatricial arteritis with vascular obstruction would remain as a sequel.—Authors' Abstract

Jayapal, V., Selvibai, G., Mahalakshmi, K., Pushkala, Regunath, K. and Subramanin, S. Comparative study of anti-PGL-1, anti-35 kDa and anti-lipoarabinomannan assays for serodiagnosis of leprosy. Indian J. Lepr. **73** (2001) 229–237.

Three antibody assays (anti-PGL-1, anti-35 kDa and anti-LAM) were used to determine the levels of antibodies in the sera of untreated leprosy patients. All the three assays showed higher levels of antibodies in BL/LL patients as compared to I and TT/BT patients, as well as healthy controls. BL/LL patients showed positivity of 100%, 84.2% and 78.9% by anti-PGL-1, anti-35 kDa and anti-LAM assays respectively. All the three assays were negative for leprosy in healthy controls. Anti-PGL-1 assay was positive in 20% of TT/BT patients and 17.9% of I patients. Anti-35 kDa assay was negative in all the TT/BT patients and positive in 7.14% of I patients. Anti-LAM assay was positive in 13.3% of TT/BT patients and in 10.7% of I patients. Hence, while these assays are valuable in diagnosing BL/LL patients, their usefulness in diagnosing I, BT or TT leprosy is limited.—Authors' Abstract

Kurade, N., Dhamanaskar, P. K., Jadhav, V. H. and Jadhav, M. V. Protein profile in leprosy. Indian J. Med. Sci. **55** (2001) 319–325.

Serum proteins and plasma fibrinogen were estimated in 103 patients in various groups of leprosy and 52 patients of reactional leprosy. Total proteins, serum globulin and fibrinogen showed significant rise while serum albumin showed fall over the immunological spectrum from TT to LL. Type II reactional leprosy similarly revealed significant rise in globulin and fibrinogen. The comparison of these parameters between most of the comparable groups of leprosy was statistically significant. ENL patients after complete subsidence of reaction and after steroid treatment showed significant decrease in these protein fractions, thus conferring some prognostic implication on these tests.—Authors' Abstract

Manandhar, R., Shrestha, N., Butlin, C. R. and Roche, P. W. High levels of inflammatory cytokines are associated with poor clinical response to steroid treatment and recurrent episodes to type 1 reactions in leprosy. Clin. Exp. Immunol. **128** (2002) 333–338.

Levels of leprosy antigen-induced interferon-gamma (IFN-gamma), tumor necrosis factor alpha (TNF-alpha) and interleukin-10 (IL-10) were measured in 96 leprosy patients with type 1 reactions (T1R) before, during and after a standard 12-week course of steroids. Peripheral blood mononuclear cells (PBMC) from leprosy patients with untreated T1R produced significantly more TNF-alpha than leprosy patients without T1R. Median levels of IFN-gamma and TNF-alpha in T1R 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 T1R within 2 months of completing the steroid regimen. Rapid and effective reversal of the inflammatory process in T1R is critical to prevent permanent nerve damage from T1R and monitoring cytokine levels during treatment may be useful.—Authors' Abstract

Maslov, A. K., Luzhnova, S. A. and Kalyanina, O. V. Effect of peroxidase in complex with basic antileprosy drugs on liver, blood, and functional activity of phagocytes in mice with experimental leprosy. Bull. Exp. Biol. Med. **132** (20012) 1084–1086.

Therapeutic effect of lyophilized horseradish peroxidase in complex with the basic antileprosy drugs diaminodiphenylsulfone and rifampin was studied in experimental leprosy. Oral therapy with drug complexes was more effective than monotherapy. Treatment with drug combinations activated myeloperoxidase in blood neutrophil, produced an antiinflammatory effect, stimulated cell immunity, and had no toxic effect on mouse liver.—Authors' Abstract

Nsanze, H., Ameen, A. S., Fares, E., Vargees, L. and Mustafa, N. Serodiagnosis of tuberculosis and leprosy by enzyme immunoassay. Clin. Microbiol. Infect. **3** (1997) 236–239.

OBJECTIVE: To evaluate the use of serodiagnosis for tuberculosis and leprosy using mycobacterial antigen 38-kDa, with kits from Omega laboratories, to detect IgG by enzyme immunoassay (EIA). METHODS: The study population consisted of 58 patients with evidence of tuberculous infection (culture of *Mycobacterium tuberculosis* complex or microscopic evidence), of whom 23 had pulmonary and 35 had extrapulmonary disease. There were six subjects who had recently been treated for tuberculosis, 11 patients on treatment for leprosy and 137 patients suspected of having tuberculosis on clinical or radiologic grounds (without laboratory evidence). A control group comprised 35 healthy individuals or patients suffering from diseases other than tuberculosis. RESULTS: The tests showed that there was a significant difference in antibody levels between the patients with active pulmonary disease, extrapulmonary tuberculosis and leprosy in comparison with the control group ($p < 0.001$). The sensitivities of the two tests together for proven pulmonary tuberculosis were 100% and 95.7% at 1.0–1.5 and >1.6 EIA cut-off points respectively, while the specificities were 88.5% and 100% at the same cut-off points. The sensitivities for extrapulmonary tuberculosis were 71.4% and only 51.4% at 1.0–1.5 and >1.6 EIA cut-off points. The test was positive in 30 (21.9%) of the 137 suspected patients, while 43 (31.4%) had an equivocal result and the remaining 64 (47.7%) suspects were definitely negative. There was again a significant difference in positivity rates between suspects and the control group. CONCLUSIONS: Omega IgG test is useful in the serodiagnosis of active pulmonary tuberculosis and leprosy, but less sensitive in extrapulmonary disease, particularly in children. Equivocal results may only add to the evidence of tuberculosis in early or minimal disease.—Authors' Abstract

Oliveira, M. M., Charlab, R. and Pessolani, M. C. V. *Mycobacterium bovis* but not *Mycobacterium leprae* induces TNF-α secretion in human monocytic

THP-1 cells. Mem. Inst. Oswaldo Cruz **96** (2001) 973–978.

In this study, we compared the level of TNF-α secretion induced in monocytic THP-1 cells after phagocytosis of *Mycobacterium leprae,* the causative agent of leprosy, and *M. bovis* BCG, an attenuated strain used as a vaccine against leprosy and tuberculosis. The presence of *M. leprae* and BCG was observed in more than 80% of the cells after 24 h of exposure. However, BCG but not *M. leprae,* was able to induce TNF-α secretion in these cells. Moreover, THP-1 cells treated simultaneously with BCG and *M. leprae* secreted lower levels of TNF-α compared to cells incubated with BCG alone. *M. leprae* was able, however, to induce TNF-α secretion both in blood-derived monocytes as well as in THP-1 cells pretreated with phorbol myristate acetate. The inclusion of streptomycin in our cultures, together with the fact that the use of both gamma-irradiated *M. leprae* and heat-killed BCG gave similar results, indicate that the differences observed were not due to differences in viability but in intrinsic properties between *M. leprae* and BCG. These data suggest that the capacity of *M. leprae* to induce TNF-α is dependent on the stage of cell maturation and emphasize the potential of this model to explore differences in the effects triggered by vaccine strain versus pathogenic species of mycobacteria on the host cell physiology and metabolism.—Trop. Dis. Bull.

Ryan, T. J., Jones, R. L., Mortimer, P. S. and Singh, G. Lymphatics in leprosy: relationship to elastic fibres and observations following intra-lesional injections of colloidal carbon. Lepr. Rev. **73** (2002) 52–63.

An investigation of skin lymphatics in leprosy has been undertaken. Examination of 62 skin biopsies from 31 patients with various classifications of leprosy has revealed dilated initial lymphatics within granulomas of lepromatous leprosy, but no significant abnormalities in non-lepromatous disease or in non-granulomatous skin. Colloidal carbon injected intra-lesionally failed to appear within granulomas, but could be seen in lymphatics in non-granulomatous dermis. Elastic fibres were also absent within granulomas. AFB were clearly identified within endothelial cells of initial lymphatics. We suggest lymphatic malfunction may be compartmental, existing only within the granulomas and not in the surrounding normal appearing dermis.—Authors' Abstract

Parkash, O. Progress towards development of immunoassays for detection of *Mycobacterium leprae* infection, employing 35kDa antigen: an update. Lepr. Rev. **73** (2002) 9–19.

The 35kDa antigen of *Mycobacterium leprae* is a membrane component that contains both B- and T-cell stimulating epitopes. Monoclonal antibodies, primarily specific to *M. leprae,* have been developed against this antigen. Moreover, this antigen has been genetically engineered. Using recombinant 35kDa antigen and/or a monoclonal antibody against an epitope on 35kDa, a variety of antibody/antigen detecting tests have been described for detection of *M. leprae* infection. 35kDa protein also stimulates peripheral blood mononuclear cells (PBMCs) from the majority of paucibacillary (PB) patients. Approaches using combined antibody and T cell are discussed.—Author's Abstract

Rambukkana, A., Zanazzi, G., Tapinos, N. and Salzer, J. L. Contact-dependent demyelination by *Mycobacterium leprae* in the absence of immune cells. Science **296** (2002) 927–931.

Demyelination results in severe disability in many neurodegenerative diseases and nervous system infections, and it is typically mediated by inflammatory responses. *Mycobacterium leprae,* 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. leprae* invasion but undergo demyelination upon bacterial attach-

ment, whereas nonmyelinated Schwann cells harbor intracellular *M. lepra* in large numbers. During *M. leprae*-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. leprae*.—Authors' Abstract

Microbiology

Brennan, P. J. and Vissa, V. D. Genomic evidence for the retention of the essential mycobacterial cell wall in the otherwise defective *Mycobacterium leprae*. Lepr. Rev. **72** (2001) 415–428.

The obligate intracellularism of *Mycobacterium leprae* may be attributable to the effects of mutations in major metabolic areas due to a genome capable of encoding only about 1600 proteins. Yet cell wall biosynthesis capability remains relatively intact and comparisons with the genome of *Mycobacterium tuberculosis* provide insights into the genetic basis of a minimal mycobacterial cell wall.—Authors' Abstract

Chae, G. T., Kim, M. J., Kang, T. J., Lee, S. B., Shin, H. K., Kim, J. P., Ko, Y. H., Kim, S. M. and Kim, N. H. DNA-PCR and RT-PCR for the 18-kDa gene of *Mycobacterium leprae* to assess the efficacy of multi-drug therapy for leprosy. J. Med. Microbiol. **51** (2002) 417–422.

DNA-PCR and reverse transcription (RT)-PCR for the 18-kDa protein of *Mycobacterium leprae* were used to examine the efficacy of multi-drug therapy (MDT) in leprosy. MDT was administered for 0–24 months. Fourteen (63.6%) of 22 patients showed positive PCR results after treatment for 12 months and the positive results decreased to 30% after 24 months of MDT. These results did not correlate with the bacterial index (BI) or the IgM antibody titre for the phenolic glycolipid (PGL)-1. One-dimensional densitometric analysis of agarose gels from PCR from the longitudinal study showed a gradual reduction of the 360-bp band after 12–24 months of MDT. RT-PCR for mRNA of the 18-kDa protein successfully tracked bacterial RNA changes in the biopsies and confirmed a decrease in the RNA of *M. leprae* in patients after MDT for 12 months. Thus, DNA- and RT-PCR for the 18-kDa protein of *M. leprae* are effective in assessing the efficacy of MDT for leprosy.—Authors' Abstract

Chae, G.-T., Lee, S.-B., Kang, T.-J., Shin, H.-K., Kim, J.-P., Ko, Y.-H., Kim, S.-H. and Kim, N.-H. Typing of clinical isolates of *Mycobacterium leprae* and their distribution in Korea. Lepr. Rev. **73** (2002) 41–46.

Although there is no genetic diversity in isolates of *Mycobacterium leprae*, the variance of tandem repeats in the *rpoT* gene was recently demonstrated. We have typed clinical isolates of *M. leprae* in Korea using difference of the tandem repeats in the *rpoT* gene. Among 69 patients, 65 Korean isolates (94.2%) demonstrated four copies of the 6 bp tandem repeat (GACATC) in the *rpoT* gene, and incidences of three copies were found in only two Koreans and two foreigners (2.9%, respectively).—Authors' Abstract

Chakrabarty, A. N., Dastidar, S. G., Sen, A., Banerjee, P. and Roy, R. Leprosy bacillus—possibly the first chemoautotrophic human pathogen cultivated *in vitro* and characterized. Indian J. Exp. Biol. **39** (2001) 962–983.

Leprosy bacillus (LB) and leprosy derived *in vitro* culture forms, the chemoautotrophic nocardioform (CAN) bacteria, showed an extremely close homology and identity with each other as regards a chemoautotrophic nutritional pattern, a nocardioform morphology, a weak acid-fastness coupled with Gram and Gomori's stain pos-

itivity, an exclusive mycolate and lipid profile, a phenolic glycolipid (PGL-I) and a highly sequestrated DNA characteristic, namely, a unique small size, a low G+C % mole, an exceptionally high gamma and UV radiation resistance, and a high thermal resistance. LB/CAN bacteria (CANb) gave positive signals for 36 kDa protein PCR, as well as, for 65 kDa epitope, and hybridisation with two or more probes and also by RFLP-analysis. Both LB/ and CAN bacteria exhibited bacillary multiplication in the mouse footpads (MFP), nerve infiltration and evidences for local pathogenicity associated with pronounced systemic invasion. A highly reproducible mutilation model could be established which enabled a successful application of the postulates of Koch. The proof of their total identity was their anergic reactions in LL cases counterpoised against Mitsuda type strong nodular responses, mirroring the reactions of leprosy bacilli in TT cases, in accordance with the dictum of XIth International Leprosy Congress (1978). Thus, the chemoautotrophic nutritional requirements of LB, entirely unsuspected for a medically important pathogenic bacterium, having dimorphic (both bacillary and mycelial) characters with spores, mycelia and granules and unique pathogenicity of multilation manifested through the virulence factor, the enzyme collagenase, made LB or *M. leprae* the highly enigmatic bacterium for so long.—Authors' Abstract

Eiglmeier, K., Parkhill, J., Honore, N., Garnier, T., Tekaia, F., Telenti, A., Klatser, P., James, K. D., Thomson, N. R., Wheeler, P. R., Churcher, C., Harris, D., Mungall, K., Barrell, B. G. and Cole, S. T. The decaying genome of *Mycobacterium leprae*. Lepr. Rev. **72** (2001) 387–398.

Everything that we need to know about *Mycobacterium leprae,* a close relative of the tubercle bacillus, is encrypted in its genome. Inspection of the 3.27 Mb genome sequence of an armadillo-derived Indian isolate of the leprosy bacillus identified 1,605 genes encoding proteins and 50 genes for stable RNA species. Comparison with the genome sequence of *Mycobacterium tuberculosis* revealed an extreme case of reductive evolution, since less than half of the genome contains functional genes while inactivated or pseudogenes are highly abundant. The level of gene duplication was approximately 34% and, on classification of the proteins into families, the largest functional groups were found to be involved in the metabolism and modification of fatty acids and polyketides, transport of metabolites, cell envelope synthesis and gene regulation. Reductive evolution, gene decay and genome downsizing have eliminated entire metabolic pathways, together with their regulatory circuits and accessory functions, particularly those involved in catabolism. This may explain the unusually long generation time and account for our inability to culture the leprosy bacillus.—Authors' Abstract

Lodes, M. J., Dillon, D. C., Mohamath, R., Day, C. H., Benson, D. R., Reynolds, L. D., McNeill, P., Sampaio, D. P., Skeiky, Y. A. W., Badaro, R., Persing, D. H., Reed, S. G. and Houghton, R. L. Serological expression cloning and immunological evaluation of MTB48, a novel *Mycobacterium tuberculosis* antigen. J. Clin. Microbiol. **39** (2001) 2485–2493.

Improved diagnostics are needed for the detection of *M. tuberculosis,* especially for patients with smear-negative disease. To address this problem, we have screened *M. tuberculosis* (H37Rv and Erdman strains) genomic expression libraries with pooled sera from patients with extrapulmonary disease and with sera from patients with elevated reactivity with *M. tuberculosis* lysate. Both serum pools were reactive with clones expressing a recombinant protein referred to here as MTB48. The genomic sequence of the resulting clones was identical to that of the *M. tuberculosis* H37Rv isolate and showed 99% identity to the *M. bovis* and *M. bovis* BCG isolate sequences. The genomic location of this sequence is 826 bp upstream of a region containing the *esat-6* gene that is deleted in the *M. bovis* BCG isolate. The *mtb48* 1380-bp open reading frame encodes a predicted 47.6-kDa polypeptide with no known function. Southern

and Western blot analyses indicate that this sequence is present in a single copy and is conserved in the *M. tuberculosis* and *M. bovis* isolates tested but not in other mycobacterial species tested, including *M. leprae* and *M. avium*. In addition the native protein was detected in the cytoplasm, as was a processed form that was also shed into the medium during culture. Serological analysis of recombinant MTB48 and the *M. tuberculosis* 38-kDa antigen with a panel of patient and control sera indicates that the inclusion of recombinant MTB48 in a prototype serodiagnostic test increases assay sensitivity for *M. tuberculosis* infection when it is combined with other known immunodominant antigens, such as the 38-kDa antigen. The GenBank accession number for *mtb48* is AY029285.—Trop. Dis. Bull.

Manjunatha, U. H., Dalal, M., Chatterji, M., Radha, D. R., Visweswariah, S. S. and Nagaraja, V. Functional characterization of mycobacterial DNA gyrase: an efficient decatenase. Nucleic Acids Res. **30** (2002) 2144–2153.

A rapid single step immunoaffinity purification procedure is described for *Mycobacteri smegmatis* DNA gyrase. The mycobacterial enzyme is a 340-kDa heterotetrameric protein comprising two subunits each of GyrA and GyrB, exhibiting subtle differences and similarities to the well-characterized *Escherichia coli* gyrase. In contrast to *E. coli* gyrase, the *M. smegmatis* enzyme exhibits strong decatenase activity at physiological Mg(2+) concentrations. Further, the enzymes exhibited marked differences in ATPase activity, DNA binding characteristics and susceptibility to fluoroquinolones. The holoenzyme showed very low intrinsic ATPase activity and was stimulated 20-fold in the presence of DNA. The DNA-stimulated ATPase kinetics revealed apparent K (0.5) and k (cat) of 0.68 mM and 0.39 s(-1), respectively. The dissociation constant for DNA was found to be 9.2 nM, which is 20 times weaker than that of *E. coli* DNA gyrase. The differences between the enzymes were further substantiated as they exhibited varied sensitivity to moxifloxacin and ciprofloxacin. In spite of these differences, mycobacterial DNA gyrase is a functionally and mechanistically conserved enzyme and the variations in activity seem to reflect functional optimisation for its physiological role during mycobacterial genome replication.—Authors' Abstract

Zumla, A. and Grange, J. Infection and disease caused by environmental mycobacteria. Curr. Opin. Pulm. Med. **8** (2002) 166–172.

Many species of mycobacteria that normally live as environmental saprophytes, the environmental mycobacteria (EM), are opportunist causes of disease in humans and animals. Many, but not all, cases are associated with some form of immune deficiency. An increasing number of species and clinical presentations are being described, and advances are being made in the understanding of the underlying predisposing factors. In recent years, four aspects of EM disease have become particularly relevant to human health: (1) the high prevalence of EM disease in patients with AIDS; (2) the emergence of Buruli ulcer, an ulcerative skin disease caused by *Mycobacterium ulcerans*, as the third most prevalent mycobacterial disease; (3) the effect of infection by EM on the immune responses to BCG vaccination and on the course and outcome of tuberculosis and leprosy; (4) the controversy over the involvement of mycobacteria, notably *M. avium* subspecies paratuberculosis, in human inflammatory bowel disease. These aspects change the status of EM from mere curiosities to important direct, indirect, and putative causes of serious and increasingly common human disease.—Authors' Abstract

Experimental Infections

Yogi, Y., Endoh, M., Banba, T., Kobayashi, M., Katoh, H., Suzuki, K. and Nomaguchi, H. Susceptibility to *Mycobacterium leprae* of congenic hypertensive nude rat (SHR/NCrj-rnu) and production of cytokine from the resident peritoneal macrophages. Nihon Hansenbyo Gakkai Zassshi **71** (2002) 39–45. (in Japanese)

We have established a congenic hypertensive nude rat strain, SHR/NCrj-rnu, carrying nude (rnu) and hypertension genes which was produced using females of the SHR/NCrj rat and males of the F344/NJcl nude rat by cross-intercross system for 12 generations. We demonstrated the susceptibility to *M. leprae* infection of SHR/NCrj-rnu rats as compared with F344/NJcl-rnu rats. SHR/NCrj-rnu rats were highly susceptible to *M. leprae*, and the SHR/NCrj-rnu rats of both sexes showed massive swelling of legs due to multiplication of *M. leprae*. However, F344/NJcl-rnu rats of both sexes revealed very poor susceptibility to *M. leprae*. There was a wide difference in the susceptibility to *M. leprae* between the SHR/NCrj-rnu and the F344/NJcl-rnu rats. We also examined the cytokine production. The resident peritoneal macrophages of SHR/NCrj-rnu rats produced IL-1 alpha, IL-6, IL-10 and TNF alpha, whereas those of F344/NJcl-rnu rats produced only TNF alpha.—Authors' Abstract

Epidemiology and Prevention

Crampin, A. C., Mwinuka, V., Malema, S. S., Glynn, J. R. and Fine, P. E. M. Field-based ramdom sampling without a sampling frame: control selection for a case-control study in rural Africa. Trans. R. Soc. Trop. Med. Hyg. **95** (2001) 481–483.

Selection bias, particularly of controls, is common in case-control studies and may materially affect the results. Methods of control selection should be tailored both for the risk factors and disease under investigation and for the population being studied. We present here a control selection method devised for a case-control study of tuberculosis in rural Africa (Karonga, northern Malawi) that selects an age/sex frequency-matched random sample of the population, with a geographical distribution in proportion to the population density. We also present an audit of the selection process, and discuss the potential of this method in other settings.—Trop. Dis. Bull.

Deps, P. D. How is the *Mycobacterium leprae* transmitted? Hansen. Int. **26** (2001) 31–36.

Hansen's disease occurs worldwide; however, the prevalence of disease is highly variable and is greatest in tropical countries. Transmission from infected nasorespiratory secretions is believed to be the most common mode of transmission between humans. The role of natural resevoirs and zoonotic transmission between other species and humans is not fully understood. This article reviews current knowledge concerning potential *M. leprae* reservoirs such as soil, vegetation, water, and arthropod, amphibian, and mammalian and their role in human disease.—Author's Abstract

Groenen, G. Trends in prevalence and case finding in the ALERT leprosy control programme, 1979–1999. Lepr. Rev. **73** (2002) 29–40.

From 1979 to 1999, the ALERT leprosy control programme has covered a well-defined area in central Ethiopia using standardized case finding strategies. During this period, the leprosy prevalence has decreased more than 30-fold, there has been a 3-fold decrease in case detection and a 6-fold decrease in the case detection rate. The

proportion of MB patients among new cases increased by around 80% and the proportion of children among new cases decreased by around 60%. Several factors may have contributed to these trends. The impact of the introduction of MDT and the shortening of the duration of the MB regimen are shown, but other factors are also discussed at length: an increase in the population of the area, cleaning up of the registers, changing case definitions, changes in staff motivation and fluctuations, even small ones, in case finding intensity and coverage. Do the observed trends reflect a reduction in the transmission of the leprosy infection? Because of the many confounding factors, it would be difficult to answer that question positively at present. Additional rigorous data collection and analysis is required.—Author's Abstract

Helene, L. M. F., Leão, V. M. and Minakawa, M. M. The social situation and the presents of physical disabilities among leprosy patients registered at a Public Health Center in São Paulo City. Hansen. Int. **26** (2001) 5–13.

This work was undertaken in order to get insight in the physical disabilities of active leprosy patients registered at a Public Health Center in São Paulo City. The goal was to determine the disability level and to identify the way in which that disability influences the social situation of the patient's family. In this study a total of 24 leprosy patients who attended a Health Center during the data collection period were included. After informed consent was obtained, the information collected was analysed with the Software EPI INFO 6. The results showed that the patients were between 45 to 60 years old with basic school level (equivalent to the 1st degree on the Brazilian scale); 58% were working and among them 78% had a regular salary, 64% were manual workers, and 71% working in a non qualified activity; 38% felt in risk for traffic accident or drugs. Among the patients 79% belonged to the multibacillary types and 87% presented physical disabilities, 46% of degree 2 and 37% of degree 1. The results show that the leprosy patients studied present physical disabilities and deformities and also clearly shows that some kind of prevention against those disabilities should be implemented in the service to the leprosy patients.—Authors' Abstract

Helene, L. M. F. and Salum, M. J. L. Social reproduction of Hansen disease: a case study in the city of São Paulo. Cad. Saúde Pública. **18** (2002) 101–113.

This study discusses the relationship between work and living conditions among leprosy patients enrolled in the São Paulo municipal public health system in 1996. Social patterns were studied based on the theory of social determination of the health-disease process. The main purpose of the study was to emphasize evidence of the disease determination network, seeking new knowledge to improve public policies on leprosy. Data were gathered from a sample of leprosy patients registered in the city's public health system. Although patients' families are characterized by a common social thread, different work/life possibilities allow for a classification of patients into three social groups. The majority belong to groups that are marginalized from social production, living in areas where social exclusion is more extreme, on the outskirts of the city. If the trends in this study persist, incident leprosy cases will result from the social exclusion of migrants from Brazil's Southeast and Northeast. The study also discusses the position of young people and female patients in the determination network of this infectious disease in the city of São Paulo.—Authors' Abstract

Thappa, D. M., Karthikeyan, K. and Jeevankumar, B. Changing face of leprosy in South India. Indian J. Lepr. **73** (2001) 276–278.

A total of 284 new cases of leprosy was recorded from 1995 to 2000 at the leprosy clinic hospital in Pondicherry, India. The mean age of the patients was 30.8 years (range, 5–79 years), and the male to female ratio was 2.7:1 The prevalence of leprosy cases during this period is tabulated.—Trop. Dis. Bull.

Rehabilitation

Cornielje, H., Nicholls, P. G. and Velema, J. P. Avoiding misperceptions: classifying rehabilitation projects using letters rather than numbers. Lepr. Rev. **73** (2002) 47–51.

A classification system proposed earlier of the many different known rehabilitation approaches and activities used a quantitative scoring system, thus giving the impression that projects with a higher score were better, more correct or more important than projects with a lower score. We therefore propose an alternative classification based on letters, so that a given combination of letters characterizes a particular type of project. The letters are derived from four dimensions: desired outcome of the intervention, participation of the clients in the rehabilitation process, the target group served and the services offered. Some examples are presented. The classification serves to analyze rehabilitation projects, to define policy and as a starting point for evaluation.—Authors' Abstract

El Hassan, L. A., Khalil, E. A. G. and El-Hassan, A. M. Socio-cultural aspects of leprosy among the Masalit and Hawsa tribes in the Sudan. Lepr. Rev. **73** (2002) 20–28.

Social and cultural factors influencing knowledge, attitudes and practices (KAP) towards leprosy in two communities in eastern Sudan were studied to determine their effects on treatment seeking and compliance. The study was qualitative using focus small group discussions, personal interviews and direct observation. The target populations were Masalit and Hawsa, the two main tribes in the area. Knowledge about the pathological cause of leprosy was lacking but the clinical manifestations were well recognized, particularly among the Masalit, in whom the disease is more common than the Hawsa. Among the Masalit there was a widely held belief that leprosy was caused by eating meat of the wild pig and a certain type of fish. The Hawsa, who are more devout Muslims, do not eat pig and associate leprosy with consumption of two types of fish. Between both tribes, the stigma of leprosy was not strong and the degree of rejection was more towards those with severe disease, particularly patients with ulcerated lesions and severe deformities. Patients were cared for by the family and lived in a separate hut within the families' housing compounds. In this remote area where medical services are scarce or nonexistent, those interviewed did not realize that leprosy was treatable by modern medicine. This influenced the treatment-seeking behavior of patients, who were often treated by spiritual healers and other traditional medicine practices. With the introduction of multidrug therapy and health education of patients and society, many more patients are now seeking medical treatment, indicating a change in health seeking behavior.—Authors' Abstract

Other Mycobacterial Diseases and Related Entities

Ara, M., de SantaMaria, C. S., Zaballos, P., Yus, C. and Lezcano, M. A. Sporotrichoid-like cutaneous infection with *Mycobacterium chelopae* in an immunocompetent patient. Actas Dermosifiliogr. **92** (2001) 498–501.

A 58-year-old woman consulted because of multiple cutaneous lesions developed on her right leg in an ascending pattern (sporotrichoid-like spread) up to the knee. Culture of the biopsy material was positive for *Mycobacterium chelonae*. She had no history of systemic immunosuppression. Closer questioning revealed that she had injured her right leg with a hammock on the beach one year before.—Authors' Abstract

Bariol, C., Meagher, A. P., Vichers, C. R., Byrnes, D. J., Edwards, P. D., Hing, M., Wettstein, A. R. and Fields, A. Early studies on the safety aand efficacy of thalidomide for symptomatic inflammatory bowel disease. J. Gastroenterol. Hepatol. **17** (2002) 135–139.

BACKGROUND AND AIM: Thalidomide is clinically effective in the treatment of graft versus host disease in bone marrow transplantation and aphthous ulceration in HIV infection. It appears to exert a selective effect on tumor necrosis factor-alpha (TNF-alpha) production. Tumor necrosis factor-alpha is implicated in the pathogenesis of inflammatory bowel disease (IBD). The aim of this study was to assess the efficacy and safety of thalidomide in symptomatic IBD. METHODS: Eleven patients (nine males, mean age 33 years, range 20–77 years) with chronic inflammatory bowel disease (six Crohn's disease (CD), four ulcerative colitis (UC), one indeterminate colitis (IC)) who were symptomatic despite standard medical therapy were administered a daily dose of thalidomide for 12 weeks in an open-labeled protocol. Their response was assessed by using clinical, colonoscopic, histological, and immunological methods. RESULTS: Two patients withdrew at 3 weeks because of mood disturbances. Of the remaining nine patients, eight (five CD, two UC and one IC) had a marked clinical response, while one patient with CD had no response. The mean stool frequency decreased from 4.3 to 2.3 per day ($p = 0.0012$), and the stool consistency increased from 2.1 to 1.2 ($p = 0.02$). The mean Crohn's Disease Activity Index decreased from 117 to 48 ($p = 0.0008$). Endoscopic inflammatory and histological grade, C-reactive protein and erythrocyte sedimentation rate (ESR) all decreased significantly ($p = 0.011$, $p = 0.03$, $p = 0.023$ and $p = 0.044$, respectively). However, the serum TNF-alpha levels did not change. Side-effects included mild sedation, xerostomia and skin dryness in all, constipation in three, and minor abnormalities in nerve conduction in one patient. CONCLUSION: These data strongly suggest that thalidomide is an effective short-term treatment for symptomatic IBD.—Authors' Abstract

Chambers, M. A., Stagg, D., Gavier-Widen, D., Lowrie, D., Newell, D. and Hewinson, R. G. A DNA vaccine encoding MPB83 from *Mycobacterium bovis* dissemination to the kidneys of mice and is expressed in primary cell cultures of the European badger (*Meles meles*). Res. Vet. Sci. **71** (2001) 119–126.

Nucleic acid (DNA) vaccination against tuberculosis in the European badger (*Meles meles*) is one approach to addressing the escalating problem of bovine tuberculosis in Great Britain. The aim of vaccination is to reduce the burden of tuberculosis within the badger population and the shedding of *Mycobacterium bovis* to levels that would break the transmission of infection to cattle. To this end, the vaccine would be required to limit the amount of disseminated tuberculosis in the badger, especially dissemination to the kidney from where *M. bovis* can be shed in the urine. A promising candidate DNA vaccine encoding a 26 kDa major antigen (MPB83) of *M. bovis* was evaluated in a mouse model of disseminated *M. bovis* infection. Using the DNA vaccine, protection against infection of the kidney was found to be greater than that achieved with the current live vaccine, Bacille Calmette-Guerin (BCG). Kidney tissue and skeletal muscle from the badger was used to derive primary cell cultures in which to examine the expression of MPB83 following transfection with the DNA vaccine. Kidney cortex gave rise to a monotypic culture of epithelial cells whilst the muscle gave rise to a mixed culture of fibroblasts and myoblasts. During culture the myoblasts differentiated into multinucleated myotubes, verified by immunofluorescent detection of mammalian desmin. Successful expression of MPB83 by transfected epithelial and myotube cells was confirmed by immunofluorescence using a monoclonal antibody specific to the protein. These observations fulfil the early requirements for the development of a DNA vaccine for badger tuberculosis.—Authors' Abstract

Chambers, M. A., Williams, A., Hatch, G., Gavier-Widen, D., Hall, G., Huygen, K., Lowrie, D., Marsh, P. D. and

Hewinson, R. G. Vaccination of guinea pigs with DNA encoding the mycobacterial antigen MPB83 influences pulmonary pathology but not hematogenous spread following aerogenic infection with *Mycobacterium bovis*. Infect. Immun. **70** (2002) 2159–2165.

Protection of cattle against bovine tuberculosis by vaccination could be an important control strategy in countries where there is persistent *Mycobacterium bovis* infection in wildlife and in developing countries where it is not economical to implement a tuberculin test and slaughter control program. The main aim of such a vaccination strategy would be to reduce transmission of infection by reducing the lung pathology caused by infection and preventing seeding of the organism to organs from which *M. bovis* could be excreted. Recent reports of successful DNA vaccination against *Mycobacterium tuberculosis* in small-animal models have suggested that DNA vaccines act by reducing lung pathology without sensitizing animals to tuberculin testing. We therefore evaluated the ability of vaccines consisting of DNA encoding the mycobacterial antigens MPB83 and 85A to reduce lung pathology and prevent hematogenous spread in guinea pigs challenged with a low dose of aerosolized *M. bovis*. Vaccination with MPB83 DNA reduced the severity of pulmonary lesions, as assessed by histopathology, and resembled *M. bovis* BCG vaccination in this respect. However, unlike BCG vaccination, MPB83 DNA vaccination did not protect challenged guinea pigs from hematogenous spread of organisms to the spleen. In contrast, vaccination with antigen 85A DNA, a promising DNA vaccine for human tuberculosis, had no measurable protective effect against infection with *M. bovis*.—Authors' Abstract

Chan, K., Knaak, T., Satkamp, L., Humbert, O., Falkow, S. and Ramakrishna, L. Complex pattern of *Mycobacterium marinum* gene expression during long-term granulomatous infection. Proc. Natl. Acad. Sci. U.S.A. **99** (2002) 3920–3925.

During latent infection of humans with *Mycobacterium tuberculosis*, bacteria persist in the asymptomatic host within granulomas, organized collections of differentiated macrophages, and other immune cells. The mechanisms for persistence remain poorly understood, as is the metabolic and replicative state of the microbes within granulomas. We analyzed the gene expression profile of *Mycobacterium marinum*, the cause of fish and amphibian tuberculosis, during its persistence in granulomas. We identified genes expressed specifically when *M. marinum* persists within granulomas. These granuloma-activated genes were not activated *in vitro* in response to various conditions postulated to be operant in tuberculous granulomas, suggesting that their granuloma-specific activation was caused by complex conditions that could not be mimicked *in vitro*. In addition to the granuloma-activated genes, the bacteria resident in granulomas expressed a wide range of metabolic and synthetic genes that are expressed during logarithmic growth in laboratory medium. Our results suggest a dynamic host-pathogen interaction in the granuloma, where metabolically active bacteria are kept in check by the host immune system and where the products of granuloma-specific bacterial genes may thwart the host's attempt to completely eradicate the bacteria.—Authors' Abstract

Chatterjee, D. and Khoo, K. H. The surface glycopeptidolipids of mycobacteria: structure and biological properties. Cell. Mol. Life Sci. **58** (2001) 2018–2042.

One of the most important opportunistic pathogens associated with acquired immunodeficiency syndrome (AIDS) is the *M. avium* complex. *M. avium* infections are found in up to 70% of individuals in advanced stages of AIDS. It is apparent that *M. avium* can replicate in host macrophages and persist for long periods. This group of mycobacteria are distinguished by the presence of unique, highly antigenic, surface-located lipids known as the glycopeptidolipids (GPLs). The GPLs are the chemical basis of the 31 distinct serovars of the *M. avium* complex, and have also been identified in

some other species. The *M. avium* lipids are immunosuppressive and can induce a variety of cytokines that affect general host responses. Despite extensive chemical characterization of the structures of these GPLs, much work is needed to elucidate the molecular mechanism involved in this complex glycosylation pathway and its genetic basis. The challenges for the future lie in explaining the roles of these copious products in the intracellular life and infectivity of mycobacteria. The intention of our review is to offer a concise account of the structures of the *M. avium* lipids, their putative roles in the host responses, bacterial physiology and pathogenesis, particularly in immunocompromised patients such as those infected with human immunodeficiency virus (HIV). Advances in chemical synthesis of the various haptenic oligosaccharides are also given to demonstrate how these have helped to define the immunogenic determinants. We believe that future research should involve the creation of conditional mutants defective in these lipids for both functional and biosynthesis studies which will complement biological assays using chemically defined or modified neoglycoconjugates.—Authors' Abstract

Collins, H. L. and Kaufmann, S. H. Prospects for better tuberculosis vaccines. Lance Infect. Dis. **1**(2001) 21–28.

Tuberculosis remains one of the top three infectious disease killers. Treatment is long and expensive and drug resistant strains of *Mycobacterium tuberculosis* are already on the rise. The current vaccine, BCG, is ineffective in parts of the world where the disease is most widespread and, therefore, the search for a novel, more effective vaccine is paramount. In this review we discuss the current state of vaccine research, including the identification of candidate antigens and the current methods used for their evaluation.—Authors' Abstract

Domenech, P., Pym, A. S., Cellier, M., Barry, C. E. and Cole, S. T. Inactivation of the *Mycobacterium tuberculosis* Nramp orthologue (mntH) does not affect virulence in a mouse model of tuberculosis. FEMS Microbiol. Lett. **207** (2002) 81–86.

Mycobacterium tuberculosis is an intracellular pathogen which can survive and multiply within the phagosomal compartment of the macrophage, and in doing so has to withstand the various macrophage defense mechanisms, which include limitation of iron and other metals. Analysis of the complete genome sequence of *M. tuberculosis* revealed an extensive array of cation transporters, including mntH, an orthologue of the eukaryotic Nramp (natural resistance-associated macrophage protein) gene, that encodes a proton-dependent divalent metal transporter. To assess the effect of this transporter on intracellular survival and pathogenesis, an mntH knock-out mutant of *M. tuberculosis* H37Rv was created and assayed in bone marrow-derived macrophages and in a murine model of tuberculosis. In neither of these systems was any loss of fitness associated with inactivation of mntH, demonstrating that Nramp orthologues are not important determinants of mycobacterial virulence.—Authors' Abstract

Foley, J. E., Borjesson, D., Gross, T. L., Rand, Ca., Needham, M. and Poland, A. Clinical, microscopic, and molecular aspects of canine leproid granuloma in the United States. Vet. Pathol. **39** (2002) 234–239.

Leproid granulomas from seven dogs in the United States were evaluated. Gross characteristics included nodular and ulcerated dermal and subcutaneous lesions primarily on the caudal aspects of the pinnae and to a lesser extent on the muzzle, face, and forelimbs. In all except one dog, there was complete regression of the lesions within 6 months, either with no therapy or after surgical resection. Cytology or histopathology revealed pyogranulomatous inflammation with few to many acid-fast mycobacterial bacilli within macrophages. The organisms could not be cultivated *in vitro*. DNA sequencing of part of the 16S ribosomal RNA gene region revealed 99–100% homology among fragments from five of

these dogs and fragments from dogs in the south Pacific. This syndrome occurs in dogs in North America and the prognosis is excellent, in contrast to the prognosis for rapid-growing or tuberculous mycobacteriosis.—Authors' Abstract

Geisler, W. M., Harrington, R. D., Wallis, C. K. and Harnisch, J. P. Broad spectrum of dermatologic manifestations caused by *Mycobacterium haemophilum* infection. Arch. Dermatol. **229** (2002) 229–230.

Mycobacterium haemophilum typically infects superficial tissues in immunocompromised persons and can lead to systemic illness. Its natural habitat is unknown, although most cases have been reported from cities near large bodies of water. No cases have been previously reported from the northwestern area of the United States. We report two cases of *M. haemophilum* infection that demonstrate the broad spectrum of dermatologic manifestations in varied clinical settings; both cases occurred in the state of Washington.—Authors' Abstract

Hashimoto, Y. Structural development of biological response modifiers based on thalidomide. Bioorg. Med. Chem. **10** (2002) 461–479.

Thalidomide (N-alpha-phthalimidoglutarimide) is a teratogenic hypnotic/sedative agent which was used widely in the late 1950s and the early 1960s. In spite of its withdrawal from the market because of its severe teratogenicity, there has been a resurgence of interest in the drug in recent years due to its potential usefulness for the treatment of various diseases, including acquired immunodeficiency syndrome (AIDS) and various cancers. It has been revealed that thalidomide elicits pleiotropic effects and is a multi-target drug. Our structural development studies of thalidomide, focusing on tumor necrosis factor-alpha (TNF-alpha) production-regulating activity, anti-androgenic activity, puromycin-sensitive aminopeptidase-inhibiting activity, alpha-glucosidase-inhibiting activity, and inhibitory activities toward some other enzymes, are reviewed in relation to the pharmacological effects of thalidomide.—Author's Abstract

Kanga, J. M., Dion-Laine, M., Kacou, D. E. and Menan, E. I. H. Observation of the therapeutic use of heparin in the treatment of Buruli ulcer. Bull. Soc. Pathol. Exot. **94** (2001) 32–35.

Medical treatment of Buruli ulcer is often ineffective, despite the susceptibility of *Mycobacterium ulcerans* to antibacterial drugs. This may be due to a bacterial toxin that causes endarteritis followed by thrombosis of the dermal vessels, causing an ischaemia that prevents antibiotics from reaching the infected area. Removal or prevention of the thrombosis may improve the efficacy of drugs. To test this hypothesis, combination therapy with standard heparin (at 500 UI/kg repeatedly administered by a syringe releasing 1 ml/h) for its activity on thrombosis and rifampin (at 300 mg/day) for its bactericidal activity was used in a case of oedematous Buruli ulcer on the face of a 16-year-old girl from Côte d'Ivoire. The facial oedema began to decrease on day 15 of treatment and had disappeared by day 30, and a small area of the ulcer dried. However, the use of standard heparin was stopped on day 37 with the occurrence of *Klebsiella oxytoca* septicaemia at the permanent administration site. Rifampin was continued at the same dose. The facial oedema quickly reappeared, followed by full closure of the eyelids and further ulceration. Standard heparin was substituted by low MW heparin (enoxaparin) administered at 40 mg twice daily by the subcutaneous route. After 45 days the oedema had decreased and the ulceration did not develop further. After 90 days, signs of progressive mycobacterial infection had disappeared and the use of enoxaparin was discontinued; rifampin was continued until the ulceration healed after 12 months of treatment. There was no recurrence after 16 months follow up. It was concluded that heparin combined with antimycobacterial drugs can provide an effective treatment for Buruli ulcer.—Trop. Dis. Bull.

Kanga, J. M. and Kacou, E. D. Epidemiology of Buruli ulcer in Côte d'Ivoire:

results of a national survey. Bull. Soc. Pathol. Exot. **94** (2001) 46–51.

Buruli ulcer caused by *Mycobacterium ulcerans* is characterized by large skin ulcerations which can lead to debilitating sequelae. The disease occurs in swampy areas in tropical regions. West Africa has been affected for 20 years with a significant increase in cases in the last 10 years. In Côte d'Ivoire, 2246 cases were reported between 1991 and 1994. In 1995, the cumulative number of cases was 5000, distributed throughout the forested and marshy areas in the south of the country. To assess the magnitude and severity of the disease in Côte d'Ivoire and to collect data necessary for developing a control programme, the National Programme of Buruli Ulcer Control (PNUM) conducted an extensive cross-sectional nation-wide survey. The results showed a total of 10 382 cases distributed throughout the country. The number of active cases was 4642, equivalent to a prevalence rate of 0.32 per 1000. Buruli ulcer is the second most prevalent mycobacteriosis in Côte d'Ivoire after tuberculosis and before leprosy. From 1996, the average annual incidence exceeded 2000 cases. The main risk factor was the presence of a nearby watering point. Children were affected at a rate of 57% with male predominance; in adults, the rate was higher in females. Children and women enjoyed the highest recovery rates. Ulcerated cases represented 89.5% of active cases compared with 6.5% for oedematous cases and 4% for nodule cases. Sequelae (scarring, ankylosis or amputation) were more frequently observed in children with no difference between the sexes. It was concluded that Buruli ulcer is endemic in Côte d'Ivoire and is characterized by the severity of the lesions.—Trop. Dis. Bull.

Khan, M., Walley, J., Witter, S., Imran, A. and Safdar, N. Costs and cost-effectiveness of different DOT strategies for the treatment of tuberculosis in Pakistan. Health Policy Plan **17** (2002) 178–186.

An economic study was conducted alongside a clinical trial at three sites in Pakistan to establish the costs and effectiveness of different strategies for implementing directly observed treatment (DOT) for tuberculosis. Patients were randomly allocated to one of three arms: DOTS with direct observation by health workers (at health centers or by community health workers); DOTS with direct observation by family members; and DOTS without direct observation. The clinical trial found no statistically significant difference in cure rate for the different arms. The economic study collected data on the full range of health service costs and patient costs of the different treatment arms. Data were also disaggregated by gender, rural and urban patients, by treatment site and by economic categories, to investigate the costs of the different strategies, their cost-effectiveness and the impact that they might have on patient compliance with treatment. The study found that direct observation by health center-based health workers was the least cost-effective of the strategies tested (US$310 per case cured). This is an interesting result, as this is the model recommended by the World Health Organization and International Union against Tuberculosis and Lung Disease. Attending health centers daily during the first 2 months generated high patient costs (direct and in terms of time lost), yet cure rates for this group fell below those of the non-observed group (58%, compared with 62%). One factor suggested by this study is that the high costs of attending may be deterring patients, and in particular, economically active patients who have most to lose from the time taken by direct observation. Without stronger evidence of benefits, it is hard to justify the costs to health services and patients that this type of direct observation imposes. The self-administered group came out as most cost-effective ($164 per case cured). The community health worker sub-group achieved the highest cure rates (67%), with a cost per case only slightly higher than the self-administered group ($172 per case cured). This approach should be investigated further, along with other approaches to improving patient compliance.—Authors' Abstract

Lucas, S. The pathology of HIV infection. Lepr. Rev. **73** (2002) 64–71.

The acquired immunodeficiency syndrome (AIDS) is the result of a human im-

munodeficiency virus (HIV) infection damaging the cell-mediated immune system. A wide range of opportunistic infections (OI) and tumours develop; additionally, HIV directly damages some organs. The patterns of opportunistic diseases (OD) are different in different parts of the world, depending on the local prevalence of latent and acquired infections and on the survival of HIV-infected patients. OD patterns change as people migrate. Recently introduced highly active anti-retroviral chemotherapy prevents many of the common OIs, but also introduces a new range of toxic pathological damage. Longer survival permits development of new HIV-related diseases. The pathology of HIV/AIDS is not static but changing.—Author's Abstract

Malik, R., Hughes, M. S., James, G., Martin, P., Wigney, D. I., Canfield, P. J., Chen, S. C., Mitchell, D. H. and Love, D. N. Feline leprosy: two different clinical syndromes. J. Feline Med. Surg. **4** (2002) 43–59.

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 cases 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 localized 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 domicile 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.—Authors' Abstract

Nunez, G. M. A., Estrade I. and Calderon-Aranda, E. S. DDT inhibits the functional activation of murine macrophages and decreases resistance to infection by *Mycobacterium microti*. Toxicology **174** (2002) 201–210.

DDT is still widely used in several parts of the world to control malaria, typhoid and dengue vectors, even though its use was banned in many countries based on toxicity data in wild life species. DDT has been shown to have immunotoxic effects in mice and to increase susceptibility to intracellular pathogens such as *Mycobacterium leprae*. However, little is known about the mechanisms underlying this effect. Activated macrophages play an important defensive role against intracellular pathogens, therefore our objective was to evaluate the effect of *in vitro* exposure to technical grade DDT (a mixture of three forms: 1,1,1-thricloro-2,2-bis(p-chlorophenyl)ethane (p,p′-DDT) (85%), o,p′-DDT (15%) and o,o′-DDT (trace amounts)), p,p′-DDT, 1,1-dicloro-2,2-bis(p-chlorophenyl) ethylene (p,p′-DDE) and 1,1-dichloro-2,2-bis(p-chlorophenyl)′ ethane on the functional activation of J774A.1 macrophages and their capability to limit growth of intracellular pathogens, using *Mycobacterium microti* as a model. We evaluated cytotoxicity and the effect on cell proliferation of 2.5, 5.0 and 10 &mgr;g/ml of DDT compounds. Functional macrophage activity (NO(&z.rad;) and 0(2) (-) production, and mRNA expression of TNF-alpha, IL-1beta and iNO synthase) and the ability of treated cells to limit infection by *M. microti* in IFN-gamma-activated macrophages were evaluated in cells exposed to 2.5 &mgr;g/ml of DDT compounds. Doses of 5 and 10 &mgr;g/ml induced direct cytotoxic effects precluding meaningful analysis of the above parameters, whereas 2.5 &mgr;g/ml of all DDT compounds inhibited macrophage activity and reduced their ability to limit the intracellular growth of *M. microti* without inducing cytotoxicity. Technical grade DDT and p,p′-DDE were the more potent compounds. Therefore, exposure to DDT compounds could represent an important risk for infection development by those intracellular pathogens against which NO (&z.rad;) and/or O(2) (-) production represent the main immune protective mechanism.—Authors' Abstract

Oliver, S. J., Kikuchi, T., Krueger, J. G. and Kaplan, G. Thalidomide induces granuloma differentiation in sarcoid skin lesions associated with disease improvement. Clin. Immunol. **102** (2002) 225–236.

Sarcoidosis, a chronic granulomatous disease of unknown etiology, is treated with immune suppressive drugs such as corticosteroids. Sarcoidosis patients have been reported to benefit clinically from treatment with thalidomide. We administered thalidomide for 16 weeks to eight patients with chronic skin sarcoidosis and evaluated the drug's effects before and with treatment. After thalidomide treatment, all skin biopsies showed decreases in granuloma size and reduction in epidermal thickness. We also observed extensive T cell recruitment into the granulomas, the appearance of multinucleated giant cells, and increased numbers of dermal Langerhans cells (CD1a(+)) and mature dendritic cells (CD83(+) or DC-LAMP(+)). Plasma IL-12 levels increased and remained elevated during the treatment period. We noted increased HLA-DR expression on peripheral blood lymphocytes and a corresponding drop in the naïve T-cell marker CD45RA. Our data suggest that thalidomide treatment of sarcoidosis results in granuloma differentiation to a Th1-type cellular immune response usual associated with protective immunity to tuberculosis and tuberculoid leprosy.—Authors' Abstract

Palendira, U., Kamath, A. T., Feng, C. G., Martin, E., Chaplin, P. J., Triccas, J. A. and Britton, W. J. Coexpression of interleukin-12 chains by a self-splicing vector increases the protective cellular immune response of DNA and *Mycobacterium bovis* BCG vaccines against *Mycobacterium tuberculosis*. Infect. Immun. **70** (2002) 1949–1956.

More effective vaccines against *Mycobacterium tuberculosis* may contribute to the control of this major human pathogen. DNA vaccines encoding single mycobacte-

rial proteins stimulate antimycobacterial T-cell responses and induce partial protection against *M. tuberculosis* in animal models. The protective efficacy of these vaccines encoding a single antigen, however, has been less than that afforded by the current vaccine, *Mycobacterium bovis* bacillus Calmette-Guerin (BCG). The heterodimeric cytokine interleukin-12 (IL-12) potentiates the induction and maintenance of the type 1 helper T-cell response. We have developed a novel self-splicing vector based on the 2A protein of foot-and-mouth disease virus that permits the coordinate expression of both chains of IL-12 (p2AIL12). Coimmunization with this vector and DNA expressing *M. tuberculosis* antigen 85B or MPT64 enhanced the specific lymphocyte proliferative response and increased the frequency of specific gamma interferon-secreting T cells against the whole protein and a defined CD8 (+) T-cell epitope on MPT64. Further, coimmunizing with p2AIL12 significantly increased the protective efficacy of DNA-85 in the lung against an aerosol challenge with *M. tuberculosis* to the level achieved with BCG. Therefore, codelivery of an IL-12-secreting plasmid may be a potent strategy for enhancing the protective efficacy of vaccines against *M. tuberculosis*.—Authors' Abstract

Richardson, P., Hideshima, T. and Anderson, K. Thalidomide: emerging role in cancer medicine. Annu. Rev. Med. **53** (2002) 629–657.

Thalidomide—removed from widespread clinical use by 1962 because of severe teratogenicity—has antiangiogenic and immunomodulatory effects, including the inhibition of tumor necrosis alpha factor. It has now returned to practice as an effective oral agent in the management of various disease states including erythema nodosum leprosum, for which it was approved by the U.S. Food and Drug Administration in 1998, and more recently certain malignancies, including multiple myeloma. Although thalidomide's mechanism of action remains incompletely understood, considerable insight has been generated by extensive preclinical studies in multiple myeloma. Moreover, clinical trials have confirmed benefit in relapsed disease, and the role of thalidomide in treating newly-diagnosed patients is currently under study. Its use in other tumors is under evaluation, with promise in renal cell carcinoma, prostate cancer, glioma, and Kaposi's sarcoma. Activity has also been demonstrated in chronic graft-versus-host disease and in symptom relief as part of palliative care.—Authors' Abstract

Shleeva, M. O., Bagramyan, K., Telkov, M. V., Mukamolova, G. V., Young, M., Kell, D. B. and Kaprelyants, A. S. Formation and resuscitation of "non-culturable" cells of *Rhodococcus rhodochrous* and *Mycobacterium tuberculosis* in prolonged stationary phase. Microbiology **148** (2002) 1581–1591.

After growth of *Rhodococcus rhodochrous* in Sauton's medium, and further incubation for about 60 h in stationary phase, there was a transient (up to 5 log) decrease in the c.f.u. count, whereas the total count remained similar to its initial value. At the point of minimal viability, the most probable number (MPN) count was 10 times greater than the c.f.u. count. This difference was further magnified by 3–4 logs (giving values close to the total count) by incorporating supernatant taken from growing cultures. A small protein similar to Rpf (resuscitation-promoting factor of *Micrococcus luteus*) appeared to be responsible for some of the activity in the culture supernatant. The formation of 'non-culturable' cells of the 'Academia' strain of *Mycobacterium tuberculosis* was similarly observed following growth in Sauton's medium containing Tween 80 in sealed culture vessels, and further incubation for an extended stationary phase. This resulted in the formation, 4–5 months post-inoculation, of a homogeneous population of ostensibly 'non-culturable' cells (zero c.f.u.). Remarkably, the MPN count for these cultures was 10^5 organisms ml (-1), and this value was further increased by one log using supernatant from an actively growing culture. Populations of 'non-culturable' cells of *Mycobacterium tuberculosis* were also obtained by the filtration of 'clumpy' cultures, which were grown in the absence of Tween 80. These small cells could only be grown in liquid medium

(MPN) and their viability was enhanced by the addition of culture supernatant or Rpf. The 'non-culturable' cells that accumulated during prolonged stationary phase in both the *R. rhodochrous* and the *Mycobacterium tuberculosis* cultures were small ovoid an coccoid forms with an intact permeability barrier, but with undetectable respiratory activity. The authors consider these non-culturable bacteria to be dormant. The observed activity of culture supernatants and Rpf with 'non-culturable' bacterial suspensions invites the speculation that one, or more, of the cognate *Mycobacterium tuberculosis* Rpf-like molecule(s) could be involved in mechanisms of latency and reactivation of tuberculosis *in vivo*.—Authors' Abstract

Soruri, A., Schweyer, S., Radzun, H. J. and Fayyazi, A. Mycobacterial antigens induce apoptosis in human purified protein derivative-specific alphabeta T lymphocytes in a concentration-dependent manner. Immunology **105** (2002) 222–230.

The morbidity and lethality of tuberculosis is partially the result of an ineffective delayed-type hypersensitivity reaction which causes caseating granulomas in the lung and other organs. Recently we showed that during caseation besides macrophages numerous Fas+ FasL+ lymphocytes undergo apoptosis and postulated that this phenomenon may be due to activation-induced cell death (AICD) as a consequence of T-lymphocyte reactivation via bacillary antigens. As purified protein derivative of *Mycobacterium tuberculosis* (Mtb-PPD) provokes caseation in tuberculosis patients, the question arose as to whether bacillary antigens are responsible for AICD within caseous areas. In the present study Mtb-PPD-specific T helper 1 (Th1)-differentiated T lymphocytes were generated *in vitro*. Reactivation of these cells with Mtb-PPD resulted in a concentration-dependent hyporesponsiveness, which was due to an increase in apoptosis of gammadelta+, alphabeta+ CD9+ as well as alphabeta+ CD8+ T lymphocytes as assessed by the demonstration of the apoptosis-associated mitochondrial membrane protein 7A6 and DNA fragmentation. Blocking experiments demonstrated that Mtb-PPD antigens exploited the Fas/FasL system to induce apoptosis in Mtb-PPD-specific T lymphocytes. These results may support the hypothesis that in tubercle granulomas with caseation T lymphocytes undergo AICD following reactivation by bacillary antigens, thus contributing to the persistence of tuberculosis.—Authors' Abstract

Stienstra, Y., Graaf, W. T. A. van der, Meerman, G. J. Te, The, T. H., Leu, L. F. de, and Werf, T. S. van der. Susceptibility to development of *Mycobacterium ulcerans* disease: review of possible risk factors. Trop. Med. Int. Health **6** (2001) 554–562.

Mycobacterium ulcerans disease, also known as Buruli ulcer (BU), is a disease of subcutaneous fat tissue. BU is prevalent in riverine and swamp areas of the tropical zone in Africa, Asia and South America, and a few scattered foci in Australia. The mode of transmission of *M. ulcerans* has not been fully elucidated, but inoculation into the subcutaneous tissues probably occurs through penetrating skin trauma. BU has not been linked with HIV infection. Antimycobacterial drug treatment is ineffective, and treatment is surgical. Patients eventually develop scars and contractures, with resulting disabilities, and the disease imposes a large burden on affected populations. The incidence of BU has dramatically increased in West African countries over the last decade. There is an urgent need for research into host and environmental risk factors for BU in order to develop effective strategies to combat this disease. We review possible genetic host susceptibility factors for BU that are relevant in other mycobacterial diseases: natural resistance-associated macrophage protein-1 (*NRAMP-1*), HLA-DR, vitamin D_3 receptor, mannose binding protein, interferon-gamma (IFN-γ) receptor, tumour necrosis factor alpha (TNF-α), interleukin (IL)-lα, 1β and their receptor antagonists; and IL-12. *Schistosoma haematobium* infection is highly endemic in many BU foci in West Africa, with a striking increase in transmission after river dams were constructed. This observation, and the observations from interaction of schistosomiasis and tuberculosis, have fuelled our hy-

pothesis that schistosomiasis is a risk factor for BU by driving the host immune response towards a predominantly Th-2 pattern, away from a Th-1 preponderant protection against mycobacterial infection. If the latter hypothesis is confirmed, enhanced schistosomiasis control should impact on BU.—Trop. Dis. Bull.

Tobin, E. H. and Jih, W. W. Sporotrichoid lymphocutaneous infections: etiology, diagnosis and therapy. Am. Fam. Physician **63** (2001) 326–332.

Sporotrichoid lymphocutaneous infection is an uncommon syndrome that is often misdiagnosed and improperly treated. Of the several hundred cases seen each year in the United States, the majority are caused by *Sporothrix schenckii, Nocardia brasiliensis, Mycobacterium marinum* or *Leishmania braziliensis*. The "sporotrichoid" disease begins at a site of distal inoculation and leads to the development of nodular lymphangitis. Systemic symptoms are characteristically absent. By recognizing the distinct pattern of nodular lymphangitis and focusing on the diverse but limited etiologies, the physician can obtain the appropriate histological and microbiological studies, and start targeted antimicrobial therapy. Therapy is generally continued for two to three months after the resolution of cutaneous disease.—Trop. Dis. Bull.

Waage, A. and Seidel, C. Thalidomide—a dreaded drug with new indications. Tidsskr Nor Laegeforen **121** (2001) 2954–2957. (in Norwegian)

BACKGROUND: Thalidomide was introduced as a non-toxic sleeping pill in 1957 and was prescribed in more than 20 countries. In 1961 the link between congenital limb defects and thalidomide use in pregnancy was proven, resulting in withdrawal of the drug. MATERIAL AND METHODS: On the basis of literature searches and personal experience we review the effects and use of thalidomide today. RESULTS: *In vitro*, thalidomide has immunoregulatory properties. This has led to the administration of thalidomide in many immunological diseases. In 1964 it was discovered that thalidomide was effective against erythema nodosum leprosum. Thalidomide also has effect on aphthous stomatitis and Behcet's disease. The effect is more uncertain in graft-versus-host-disease, rheumatoid arthritis and Crohn's disease. Thalidomide reduces angiogenesis in experimental animals, and this has led to several studies of thalidomide as a possible anticancer drug. Advanced or resistant multiple myeloma may be a new target for thalidomide; at least 30% of these patients obtain response during treatment. Results indicate that patients with breast cancer and glioma do not benefit from treatment with thalidomide. INTERPRETATION: Thalidomide has proven to be effective in the treatment of erythema nodosum leprosum and aphthous stomatitis. It is also effective in advanced multiple myeloma, but not in other cancers.—Authors' Abstract