Leprosy and AIDS: A Review of the Literature and Speculations on the Impact of CD4+ Lymphocyte Depletion on Immunity to *Mycobacterium leprae*

The cultivatable mycobacteria were the first bacteria to be associated with opportunistic infections in individuals infected with human immunodeficiency virus 1 (HIV-1).[1, 2] Disseminated infection with *Mycobacterium avium* complex strains and an increased incidence of tuberculosis, often with unusual clinical manifestations, were noted very early in the course of the acquired immunodeficiency syndrome (AIDS) epidemic, but infections caused by *M. xenopi, M. kansasii, M. szulgai, M. asiaticum, M. flavescens, M. fortuitum, M. malmoense, M. bovis* BCG strain, *M. haemophilum, M. gordonae,* and *M. marinum* have subsequently been reported.[3-9] Given this level of interest in the interaction of HIV infection with mycobacterial disease, the paucity of reported cases of *M. leprae* infection in HIV-infected patients is striking. There are an estimated 12 million cases of leprosy in the world and an unknown, but undoubtedly large, number of people harboring subclinical infection with *M. leprae.*[10] Many of these infected individuals reside in regions of Africa suffering from epidemic rates of HIV infection.

The interaction of the causative agent of human leprosy, *M. leprae,* with the human immune system has fascinated immunologists for decades. The concept of a clinical disease spectrum derived from the variable individual response to the infecting organism, and which is reflected in the immunohistology of the skin lesions, is well established.[11, 12] Research on leprosy during the past decade has focused on various aspects of the immune response to *M. leprae,* but the specific determinants of protective immunity and of the clinical type of leprosy which develops in any single patient remain obscure. It is possible that the study of patients co-infected with HIV and *M. leprae* will provide valuable information on the role played by the CD4+ lymphocyte in the host-parasite interaction.

Leprosy and HIV infection—a review of the literature

A literature search performed a decade into the HIV epidemic (May 1991) on concurrent leprosy and HIV infection uncov-

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[2] Pitchenik, A. E., Cole, D., Russell, B. W., Fischl, M. A., Spira, T. J. and Snider, D. E., Jr. Tuberculosis, atypical mycobacteriosis, and the acquired immunodeficiency syndrome among Haitian and non-Haitian patients in South Florida. Ann. Intern. Med. **101** (1984) 641–645.

[3] American Thoracic Society. Mycobacterioses and the acquired immunodeficiency syndrome. Am. Rev. Respir. Dis. **136** (1987) 492–496.

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[5] Centers for Disease Control. Disseminated *Mycobacterium bovis* infection from BCG vaccination of a patient with acquired immunodeficiency syndrome. MMWR **34** (1985) 227–228.

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[7] Lambertus, M. W. and Mathisen, C. E. *Mycobacterium marinum* infection in a patient with cryptosporidiosis and the acquired immunodeficiency syndrome. Cutis **42** (1988) 38–40.

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[9] Sherer, R., Sable, R., Sonnenberg, M., Cooper, S., Spencer, P., Schwimmer, S., Kocka, F., Muthuswamy, P. and Kallick, C. Disseminated infection with *Mycobacterium kansasii* in the acquired immunodeficiency syndrome. Ann. Intern. Med. **105** (1986) 710–712.

[10] Bloom, B. R. and Godal, T. Selective primary health care: strategies for control of disease in the developing world. V. Leprosy. Rev. Infect. Dis. **5** (1983) 765–780.

[11] Ridley, D. S. and Jopling, W. H. Classification of leprosy according to immunity; a five-group system. Int. J. Lepr. **34** (1966) 255–273.

[12] Sansonetti, P. and Lagrange, P. H. The immunology of leprosy: speculations on the leprosy spectrum. Rev. Infect. Dis. **3** (1981) 422–469 (274 ref.).

ered four case reports,[13-15] three published epidemiologic surveys,[16-18] abstracts of an additional epidemiologic study,[19] an editorial,[20] and two studies in a primate model system.[21, 22]

Case studies. The first case reported was that of a 43-year-old homosexual with histologically diagnosed borderline tuberculoid leprosy.[15] He received dapsone and clofazimine with an excellent clinical response but subsequently developed Kaposi's sarcoma and pulmonary tuberculosis, and was positive for HIV. The leprosy never recurred.

The next case was a 28-year-old male from Martinique.[13] He had received triple therapy (dapsone, rifampin, clofazimine) for lepromatous disease, complicated by erythema nodosum leprosum (ENL), from 1976 through May 1985, with negative bacterial indices on skin biopsy from 1978 through 1986. In February 1987 he developed a reactive polyarthritis (believed secondary to chlamydial infection) but was found to have a 1+ bacterial index (BI), suggesting a relapse of his leprosy. He was also found to be HIV positive and to have chronic generalized lymphadenopathy.

The same authors reported a 27-year-old male who had been treated for "cutaneous leprosy" from 1978 through 1982. He presented in 1987 with a sensorimotor polyneuropathy and palpable nerve trunks. A skin biopsy showed a "tuberculoid infiltrate" and histologic changes suggestive of a reversal reaction. At the same time, he was found to have positive serology to HIV, candidal esophagitis, and a CD4/CD8 ratio of 0.3.

The final case was a 35-year-old, HIV-positive woman with an anesthetic macule clinically consistent with BT/BB leprosy.[14] The histopathology of the lesion, however, was more typical of downgrading BL disease. The cutaneous granulomas had a lymphocyte:histiocyte ratio of 3:1 and half of the lymphocytes were CD4+. The most unusual abnormalities were the absence of natural killer (NK) cells and interleukin-2 receptor positive cells in the granulomas and the lack of HLA-Dr expression by epidermal keratinocytes. Clincially, the patient had moderately advanced HIV disease (peripheral blood CD4 count was 300 with a CD4/CD8 ratio of 0.6), but her skin lesions responded rapidly to dapsone, rifampin and clofazimine.

There is little insight to be gained from the first two cases. In one the leprosy never recurred, and the evidence for recurrence in the second was limited to a BI of 1+ on skin biopsy. An occasional low positive BI is hardly unusual in lepromatous patients, even after years of therapy, and does not in itself imply relapse. The third case raises several interesting points. The first is that the patient relapsed with a histologic picture of tuberculoid disease despite having a reversed CD4/CD8 ratio and advanced HIV

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[17] Meeran, K. Prevalence of HIV infection among patients with leprosy and tuberculosis in rural Zambia. Br. Med. J. **298** (1989) 364–365.

[18] Tekle-Haimanot, R., Frommel, D., Tadesse, T., Verdier, M., Abebe, M. and Denis, F. A survey of HTLV-I and HIVs in Ethiopian leprosy patients. AIDS **5** (1991) 108–110.

[19] Pean, C., Pape, J. W., Deschamps, M.-M., Dambreville, M. and Johnson, W. D., Jr. Natural history of *M. leprae* and HIV co-infection. (Abstract) In: *Proceedings of the V International Conference on AIDS; the Scientific and Social Challenge, Montreal, June 4–9, 1989.* Ottawa: International Development Research Centre, 1989, p. 427.

[20] Turk, J. L. and Rees, R. J. W. AIDS and leprosy. (Editorial) Lepr. Rev. **59** (1988) 193–194.

[21] Baskin, G. B., Gormus, B. J., Martin, L. N., Murphey-Corb, M., Walsh, G. P. and Meyers, W. M. Pathology of dual *Mycobacterium leprae* and simian immunodeficiency virus infection in rhesus monkeys. Int. J. Lepr. **58** (1990) 358–364.

[22] Gormus, B. J., Murphey-Corb, M., Martin, L. N., Zhang, J., Baskin, G. B., Trygg, C. B., Walsh, G. P. and Meyers, W. M. Interactions between simian immunodeficiency virus and *Mycobacterium leprae* in experimentally inoculated rhesus monkeys. J. Infect. Dis. **160** (1989) 405–413.

disease. The second is that there was histologic evidence of a reversal or upgrading reaction. The final case demonstrated a discordance between the clinical and histologic staging. It is intriguing that CD4+ lymphocytes were well represented in the granulomas despite the deficiency in circulating CD4+ cells. The authors speculate, though, that functional defects in these CD4+ cells could have been responsible for the atypical aspects of the immunohistology which were noted above. All of the cases with clinical leprosy responded promptly to conventional therapeutic regimens.

Epidemiologic studies. A small study conducted in Zambia reported that 6 of 18 (33%) of newly diagnosed leprosy patients had antibodies to HIV, which was similar to the prevalence of seropositivity found in suspected tuberculosis cases (21/47, 45%) but significantly greater than that found in surgical patients (2/39, 5%) or blood donors (4/55, 7%) at the same hospital.[17] No details concerning the type of leprosy present in the patients was given, other than the comment that most had serious symptoms "such as paralysis or neuritis." This study suffers from its small size, potential bias in patient selection (those with mild cutaneous disease were presumably not seen at the hospital), and failure to confirm HIV seropositivity by immunoblotting.[23] Nonetheless, it does raise the possibility that co-infection with HIV could accelerate the development of clinical leprosy, or promote the development of significant neurologic disease in untreated patients infected with *M. leprae.* This study is also noteworthy in that it focused on newly diagnosed leprosy patients with active disease. It would be anticipated that the effects of HIV-induced immunosuppression on leprosy would be most evident in this population.

A much larger study conducted in the Ivory Coast, Congo, Senegal and Yemen found that the prevalence of antibodies to HIV-1 and HIV-2 was identical in leprosy patients and controls in each of the countries, although the rates differed between countries (from 0% HIV-1 seropositivity among both patients and controls in Yemen to 3.8% in patients and 5.2% in controls in the Congo).[16] All positive HIV serologies were confirmed by immunoblot. The prevalence of HIV-1 infection among patients with lepromatous (3.6%) and tuberculoid (3.7%) leprosy was identical. A similarly designed study conducted in Ethiopia by some of the same investigators[18] found antibodies to HIV-1 in 3.2% of the leprosy patients and 2.5% of controls (not significantly different). Of the 8 seropositive leprosy patients, 3 had multibacillary disease, 3 had paucibacillary disease, and 2 had indeterminate leprosy. None were clinically in reaction.

The final study was performed in Haiti between 1985 and 1988.[19] The HIV seropositivity rate was comparable for the 200 tuberculoid and 75 lepromatous patients studied (overall 18/275, 6.5%). New lesions developed during therapy in 4 of 14 (29%) seropositive tuberculoid patients, 0 of 4 seropositive lepromatous patients, and 2 of 257 (0.8%) seronegative patients. The patients who developed new lesions also became anergic to lepromin. The tuberculoid patients, even those without new leprosy lesions, were very likely to develop an HIV-associated illness during the follow-up period.

Summary of case reports and epidemiologic studies. No firm conclusions can be drawn from the limited data available at this time, but several patterns seem to be emerging. Concurrent HIV infection appears to result in anergy to lepromin. Relapses of leprosy, particularly of tuberculoid leprosy, may be more common in co-infected individuals. There is also the suggestion that concurrent tuberculoid leprosy can accelerate the progression of HIV-related disease, and that HIV co-infection may promote the development of clinical leprosy, or at least of severe neurologic complications of leprosy. There is no data indicating that concurrent HIV infection has any effect on the clinical classification (e.g., tuberculoid or lepromatous) of the leprosy which is present, either at the time of initial presentation or at relapse. Finally, there has been one case each of reversal and downgrading reactions in co-infected patients but erythema nodosum leprosum (ENL) has not been reported.

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[23] Miller, R. A., Collier, A. C., Buchanan, T. M. and Handsfield, H. H. Seroepidemiologic screening for antibodies to LAV/HTLV-III in Sri Lanka, 1980-1982. N. Engl. J. Med. **313** (1985) 1352–1353.

Primate model of co-infection with HIV and *M. leprae*. In the course of a study on experimental primate leprosy, five rhesus monkeys were inadvertently inoculated with bacilli harvested from a donor asymptomatically co-infected with simian immunodeficiency virus (SIV).[21, 22] Four of the five animals seroconverted to SIV and three (75%) developed clinical leprosy. Only 21% of the SIV seronegative monkeys receiving a comparable inoculum developed leprosy. All three animals with SIV and clinical leprosy developed other opportunistic infections consistent with advanced SIV infection and were humanely killed. At necropsy, two had evidence of borderline lepromatous disease and one had indeterminate disease with only scant numbers of bacilli. The one SIV-positive animal that did not develop leprosy also remained clinically free of SIV-related complications. Diminished or absent lepromin skin-test responses were seen in the SIV-positive animals that developed leprosy.

Of particular note was one animal that appeared to be resistant to *M. leprae*, having remained healthy while developing a strongly positive skin test response to lepromin and a humoral response to phenolic glycolipid-I (PGL-I) typical of resistant animals. This animal was reinoculated with bacilli unknowingly contaminated with SIV and 48 months later developed borderline lepromatous leprosy. The authors concluded that co-infection with SIV and *M. leprae* increases the susceptibility of the monkeys to leprosy despite an antibody response usually associated with resistance and, in at least one instance, an active cellular immune response as reflected by a positive lepromin skin test. It might also be argued that active infection with *M. leprae* led to accelerated SIV disease, since the only SIV-positive animal without clinical leprosy failed to show evidence of progressive immunodeficiency.

Role of CD4+ lymphocytes in immune response to *M. leprae*

The cellular immune response in leprosy is extraordinarily complicated, involving several lymphocyte subpopulations as well as other cell types.[24–26] CD4+ lymphocytes have been linked to classical delayed-hypersensitivity reactions[27] and to immune granuloma formation.[12, 27] CD4+ lymphocytes also have been postulated to be involved in protective immunity to *M. leprae* and in the immune interactions that determine what form of leprosy will develop in an individual destined to develop clinical disease,[28, 29] although other cell populations, in particular CD8+ (suppressor-T cells) lymphocytes, almost certainly play a role as well.[29–31]

The involvement of CD4+ lymphocytes in ENL and reversal reactions is controversial. There is indirect evidence consistent with increased CD4+ lymphocyte activity in ENL.[32, 33] Reversal reactions have long been attributed to an upgrading of the cellular immune response, specifically the CD4+ lymphocyte response, analogous to a systemic delayed-hypersensitivity reac-

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[29] Bloom, B. R. and Mehra, V. Immunological unresponsiveness in leprosy. Immunol. Rev. **80** (1984) 5–28.

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[32] Miller, R. A., Shen, Y.-Y., Rea, T. H. and Harnisch, J. P. Treatment of chronic erythema nodosum leprosum with cyclosporine A produced clinical and immunohistologic remission. Int. J. Lepr. **55** (1987) 441–449.

[33] Uyemura, K., Dixon, J. F. P., Wong, L., Rea, T. H. and Modlin, R. L. Effect of cyclosporine A in erythema nodosum leprosum. J. Immunol. **137** (1986) 3620–3623.

tion.[12, 34] However, thalidomide, which acts through suppression of helper T-cell activity, has no effect on reversal reactions.[35, 36]

Correlation of observations in co-infected individuals and populations with predictions: consistencies and surprises

Many of the published observations on co-infections have been in agreement with the postulated roles of CD4+ lymphocytes in the host response to *M. leprae.* In particular, the immunohistologic findings in the case reported by Kennedy, *et al.*,[14] the increased prevalence of clinical disease in co-infected primates,[22] and the apparently universal lepromin anergy in HIV/SIV-infected leprosy cases fit with predictions. The lack of reported cases of ENL among multibacillary leprosy patients with HIV infection and the occurrence of at least one case of reversal reaction in a co-infected patient are also consistent with involvement of CD4+ lymphocytes in ENL but not in reversal reactions, although it is hazardous to generalize given the small number of cases.

On the other hand, the absence of clinical evidence of downgrading, or of a shift in case distribution toward the lepromatous pole, is surprising. None of the epidemiologic surveys published to date has found a bias toward HIV seropositivity among multibacillary patients. It is also unexpected that the patients with tuberculoid disease who relapsed after becoming HIV seropositive relapsed with tuberculoid rather than multibacillary disease (although it is possible that the clinical/histologic discordance seen in one patient[14] may actually be a common phenomenon in this patient population, and that the "tuberculoid" relapses might have had multibacillary histology). Finally, if HIV-associated immunosuppression is associated with an increased incidence of clinical progression among patients with subclinical leprosy, one would predict an increasing incidence of leprosy in HIV-endemic areas, with the "excess" cases testing HIV positive. Only one of the epidemiologic studies[17] provides any support for this hypothesis.

Summary

The potent effects of HIV infection on the human immune system, the complexity of the host-parasite interaction in leprosy, and the paucity of current information on the natural history of co-infected patients makes this area a fertile ground for clinical and immunologic investigation. Several studies have now validated the prediction that there exists a large cohort of patients, particularly in Africa, who are concurrently infected with HIV and *M. leprae.* Sparse but tantalizing evidence suggests that infection with HIV may increase the incidence of leprosy among individuals with subclinical infection with *M. leprae,* either through shortening the incubation period or by increasing disease penetrance. Similarly, active mycobacterial disease may accelerate the course of HIV disease, as has been postulated to occur during concurrent infections with certain other viral and bacterial pathogens in HIV-positive patients. A subtle and complex interplay between HIV and leprosy may thus result which will impact the observed epidemiology of both illnesses in regions where both are prevalent. Possible effects of the HIV epidemic on leprosy control programs have been outlined by the World Health Organization and in an editorial by Turk and Rees.[20, 37]

The published experience provides few guidelines for the clinical care of co-infected patients. The initial response to conventional therapeutic regimens appears to be excellent, but no follow-up data have been included. The possible absence of ENL in these patients would simplify care for multibacillary disease, if this observation is confirmed in larger field studies. On the other hand, short-course treatment regimens, particularly the 6- to 12-month regimens recommended for selected cases of pauci-

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[35] Jacobson, R. R. Treatment. In: *Leprosy.* Hastings, R. C., ed. New York: Churchill Livingstone, 1985, pp. 193–222.

[36] Moncada, B., Baranda, M. L., Gonzales-Amaro, R., Urbina, R. and Loredo, C. E. Thalidomide—effect on T cell subsets as a possible mechanism of action. Int. J. Lepr. **53** (1985) 201–205.

[37] Abstract of a Special Meeting on "Interrelations of Tropical Diseases and HIV infection, UNDF-World Bank-WHO, Kenya, 1987." Lepr. Rev. **59** (1988) 277. TDR/GPA/TD-HIV/87.3.

bacillary disease, may be associated with unacceptable failure rates in HIV-positive individuals. The answers to these questions can only be provided by further work on the epidemiology, clinical manifestations, response to therapy, and immunologic responses of patients co-infected with *M. leprae* and HIV.

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