# Correspondence

## Immunoresititution Disease in Relation to Infection with *Mycobacterium avium* Complex and to Leprosy

Cheng et al. [1] have reviewed the English-language literature on immunorestitution (or immune reconstitution) disease (IRD), which describes a total of 107 patients, some of whom were HIV-negative and some HIV-positive. There were 2 reports that described 10 cases of IRD due to atypical mycobacterial infection; all but 1 of these cases were infections with *Mycobacterium avium* complex. Not included were 10 other reports [2–11] that described 32 additional cases of mycobacterial IRD, which were due variously to *M. avium* complex (29 cases), *Mycobacterium genavense* (1 case), and unknown species (2 cases, for which smear results were positive but culture results were negative).

Cheng et al. [1] state that the diagnosis of IRD is one of exclusion. This is true for patients who are diagnosed with IRD due to an opportunistic infection for which treatment is initiated but whose signs and symptoms subsequently show "paradoxical worsening" at the time of immune reconstitution (e.g., tuberculosis). All 17 reported episodes of HIV-related IRD due to *M. tuberculosis* infection were recognized and partially treated prior to the onset of IRD, which underlines that it is important to search carefully for various possible causes for the apparent failure of antituberculous therapy. However, for 32 (84%) of the 38 reported cases of IRD due to infection with *M. avium* complex, the mycobacterial infection was unrecognized and usually subclinical prior to immune reconstitution. The "unmasking" of subclinical disease is a phenomenon associated with *M. avium* complex infection, but not with tuberculosis. This may be because *M. avium* complex infection is associated with a lower pathogenicity and, probably, a longer duration of subclinical disease than is tuberculosis [12].

In addition, a number of unusual features deserve mention that help distinguish infection with *M. avium* complex that is associated with IRD from the more usual disseminated disease in HIV-infected patients. These features include the following: disease that is frequently localized to lymph nodes coupled with blood culture results that are negative for mycobacteria; caseous necrosis of involved nodes and the development of draining sinuses (6 [75%] of 8 cases due to *M. avium* complex in one series [2]); the absence of wasting in most cases; a temporal association with an excellent virologic and immunologic response to antiretroviral therapy, reflected by a decreasing HIV plasma virus load and, usually, an increasing CD4 count; and much improved, long-term survival [13].

Given these observations, the recovery of *M. avium* complex from a lymph node of a patient who is undergoing immune reconstitution and who does not have a recently diagnosed case of mycobacterial disease establishes the diagnosis of IRD. Extensive investigations may not be necessary in this situation, unless prompted by unexplained clinical findings. Although it has been suggested that prophylaxis may prevent IRD, several cases of localized *M. avium* complex lymphadenitis have been reported in patients who received prophylactic treatment with azithromycin or clarithromycin [2].

Reports of IRD due to *M. tuberculosis* among HIV-negative patients were not included in the review of Cheng et al. [1]. They did not mention the condition associated with the largest number of reports of IRD, which is leprosy. Reversal reactions (lepra type I reactions) typically occur in patients with borderline leprosy during the first year that they are receiving antimycobacterial therapy, with or without concomitant immunotherapy [14]. Such reactions may be associated with clinical deterioration, including neuritis, inflammation of preexisting skin lesions, development of new skin lesions, and ulceration. These reactions are due to a significant increase in cell-mediated immunity to *M. leprae,* and are associated with a shift toward the tuberculoid end of the leprosy spectrum, in which, histologically, the predominant T cell is the CD4 rather than the CD8 lymphocyte. Leprosy reversal reactions have also been reported in HIV-positive patients [15].

*Varicella zoster* virus should be added to the list of viruses associated with IRD. A higher incidence of herpes zoster has been reported in a group of patients who had begun to receive highly active antiretroviral therapy that included protease inhibitors and that was associated with increases in CD8 counts [16].

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## Reply

Sir—We appreciated the effort of Dr. Phillips in searching out the remaining case series of HIV-positive patients who presented with symptomatic *Mycobacterium avium* complex infection after initiation of antiretroviral therapy [1]. These case series were not found in our literature search of the MEDLINE databases, which used the keywords "HIV," "highly active antiretroviral therapy," "immune reconstitution," "immune restitution," "immune recovery," "paradoxical," "opportunistic infection," "cytomegalovirus," and "tuberculosis." It is true that the recovery of the cellular immune system serves to "unmask" the subclinical diseases that are caused by *M. avium* complex. We believe that these patients were infected by *M. avium* complex when they were receiving antiretroviral therapy and when their immune systems were most deeply suppressed, rather than later, after their CD4 lymphocyte counts had recovered. However, we could not include all the additional case series because, in some reports, the restitution of cell-mediated immunity was only inferred by measurement of a cutaneous delayed-type hypersensitivity reaction [2, 3], and there was no objective serial measurement of CD4 lymphocyte counts [4, 5].

The development of a paradoxical reaction in HIV-negative patients who are infected with *Mycobacterium tuberculosis* and are being treated with antituberculous drugs has been well summarized in previous reviews [6–9]. In fact, this type of paradoxical reaction is not an entity of immunorestitution disease (IRD). According to our case definition, a diagnosis of IRD is basically a diagnosis of immunopathological damage associated with the reversal of immunosuppressive processes, such as withdrawal of corticosteroids, recovery of the neutrophil count after chemotherapy, engraftment after bone marrow transplantation, or highly active antiretroviral therapy (HAART) for AIDS [10]. A patient with IRD has experienced significant immunosuppression, and the subsequent immunopathological damage or paradoxical deterioration should be associated with a documented recovery of the immune system. Unlike the paradoxical response to *M. tuberculosis* infection in HIV-positive patients, which was temporally related to an increase in CD4 lymphocyte count, clinical deterioration of *M. tuberculosis* infection during antituberculosis therapy should not be regarded as IRD.

Similarly, patients with lepromatous leprosy who presented with reversal reactions were not included in our study. Although it has been suggested that *M. tuberculosis* and *M. leprae* infections are an immunosuppressive process and that the reversal of the immune system may occur after the mycobacterial load is reduced by antimicrobial therapy, the exact mechanism of immunosuppression has not been well defined [11, 12]. The serial change of absolute lymphocyte counts before and after antituberculosis therapy has never been emphasized. In contrast, HIV is an immunosuppressive agent that progressively destroys CD4 lymphocytes and reduces the CD4 count. Therefore, cases of IRD that were related to HAART were included in our analysis.

IRD is an important entity among clinical infectious diseases because the number of immunosuppressed patients is increasing as aggressive anticancer therapy and organ transplantation are more

widely used. Furthermore, as supportive treatment improves, patients who receive antimicrobial therapy, HAART, and/or appropriate use of colony-stimulating growth factors during the intense immunosuppressive phase of treatment are more likely to experience immunorestitution. Therefore, we expect that a greater spectrum of infecting microbes will be recognized in the setting of IRD. The aim of our study was to provide an introduction and stimulate further investigations in this emerging area in order to increase the understanding and improve the management of IRD.

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## Seroepidemiology of Pertussis in Senior Adults

Sir—We read with interest the article by Hodder et al. [1] regarding antibody responses to pertussis antigens in elderly community residents. Given the poor sensitivity of bacterial culture, serodiagnosis of pertussis is an attractive methodology to determine the burden of illness, and results of serodiagnosis have been used as evidence to support the need for pertussis immunization in various populations. However, there are no well-defined criteria for evaluating the results of serodiagnosis of pertussis. Hodder et al., in table 1 of their study [1], gave estimates of disease incidence that varied up to 6-fold, depending on the definitions they used. We agree with Hodder et al. that pertussis toxin (PT) is the most specific antigen for pertussis, and the measurement of levels of other single antigens for serodiagnosis will likely overestimate the incidence of pertussis.

Similar to Hodder et al. [1], we studied 100 healthy adults >60 years of age who were recruited from the Nashville, Tennessee, community for clinical vaccine trials at Vanderbilt University. Fifty-nine percent of the subjects were women, and 97% were white. Forty-seven subjects recalled having had pertussis ("whooping cough") in childhood. Twelve subjects reported a coughing illness that lasted >2 weeks during the previous year, and 35 subjects reported at least weekly contact with young children. The concentration of IgG antibodies to PT and filamentous hemagglutinin (FHA) were measured in serum samples by use of ELISA, according to the standard method of Manclark et al. [2]. Results are shown in figure 1, as are data on concentrations that were determined previously in our laboratory for serum samples obtained from younger persons in the same community [3]. Local regression (loess) analysis was used to estimate serological trends because the data did not conform to a single overall linear regression model.

The portion of the graph that shows data from the previous work illustrates that mean concentrations of antibody were significantly greater in subjects aged 4–6 and those aged 13–17 years. These peak concentrations are thought to correspond to a boost in the concentration of antibody after routine immunization, in children aged 4–6 years, and to reinfection, in children aged 13–17 years. In the current study, levels of PT and FHA for persons aged 60–90 years did not differ significantly from values obtained previously for persons aged >40 years. No subject in this study had serological evidence of recent pertussis infection, as defined by elevation of both PT and FHA titers above the 95th percentile. One subject, a 76-year-old man in good health with no recent history of coughing illness, met a less specific criterion for infection; namely, elevation of PT level alone that exceeded the 95th percentile.

Unlike the study by Hodder et al. [1], our serological survey cannot assess increases or decreases in antibody levels over time. However, the levels of IgG antibodies to PT and FHA in our cohort of senior adults are similar to the levels reported by Hodder et al. [1] among study subjects