INTRODUCTION

Although chemotherapy of tuberculosis has resulted in a dramatic decrease in the number of new and active cases in the United States, relatively little improvement has been made in the treatment of diseases caused by nontuberculous mycobacteria. Depending on the type of hospital and population served by the hospital, the incidence of "atypical" mycobacteria may be as high as 30% of all mycobacterial infections (1). Aside from the clinical importance and economic consequences of these infections, these chronically ill patients provide a valuable source of new information concerning cellular defense mechanisms and resistance to chronic infectious diseases. Unlike patients with chronic fungal infections who commonly develop disease during early childhood, patients with "atypical" mycobacterial diseases are usually well during early childhood and adolescence (2). Thus, to explain the predisposition of individuals to infections with these organisms, one would predict an abnormality of immunoregulatory mechanisms rather than a failure to develop immunocompetent lymphoid cells.

Our laboratory has been investigating cell-mediated immune responses in patients with chronic "atypical" mycobacterial infections. The frequency with which these patients demonstrated negative responses to skin tests with tuberculin and other antigens suggested that the patients were immunologically impaired. Subsequent experiments which examined in vitro T-cell proliferation in response to antigens and a mitogen revealed that although these responses were subnormal, marked enhancement and, in some cases, normalization was observed when the T-cells were cultured...
in media containing indomethacin. This finding prompted a systematic study of the relationship of arachidonic acid metabolites to T-cell proliferation in response to antigens and a mitogen.

MATERIALS AND METHODS

Nine patients with culturally proven, clinically active "atypical" mycobacterioses were studied. The controls, consisting of four healthy males and two healthy females, three of whom had delayed hypersensitivity to PPD and others were negative, were assayed over the 8 month period during which the patients were studied.

Cultures of Ficoll-Hypaque prepared peripheral blood mononuclear cells received one of the following inhibitors of arachidonic acid metabolism: indomethacin (final concentration 10^{-7} M and 10^{-6} M), a preferential inhibitor of cyclooxygenase; nordihydroguaiaretic acid (NDGA) (3x10^{-7}, 3x10^{-6}, 3x10^{-5} M), a preferential inhibitor of lipoxygenase, and phenidone (3x10^{-7}, 3x10^{-6}, 3x10^{-5} M), an inhibitor of both enzymes. Control cultures received no inhibitor. Dose response relationships were obtained for the mitogen (phytohemagglutinin 0.33 μg/ml; PHA) and antigens (PPD, 10 μg/ml and Candida, 10 μg/ml; CAN) which were used to stimulate T-cell proliferation, which in turn was monitored by thymidine incorporation.

RESULTS

The studies with healthy control subjects confirmed the findings of others; tuberculin-sensitive subjects responded to PPD with marked T-cell proliferation while tuberculin-insensitive subjects did not. These findings were in contrast to those in patients with "atypical" mycobacterial infections. Even though they had known exposures to mycobacterial antigens, all 9 patients were hyporesponsive to PPD both by skin testing and by T-cell proliferation. The extent of the hyporesponsive state was illustrated by the finding that 5 patients were also hyporesponsive to CAN and 3 of 3 patients were poorly responsive to PHA.

In most instances, addition of indomethacin to the cells of the hyporesponsive patients enhanced and, in some cases, even normalized the T-cell proliferative responses to the microbial antigens and to PHA. Lymphocytes from 6 of 9 patients demonstrated significant (p < .05) improvement of thymidine incorporation in response to PPD (Figure 1); 3 of 9 patients had a significant (p < 0.01) improvement of proliferative responses to CAN, and 1 of 3 patients had significant (p < 0.01) improvements in responses to PHA. In contrast, inhibition of the lipoxygenase