Is There an Immune Deficit in Whipple's Disease?

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There is controversy as to the role of immune deficiency, if any, in Whipple's disease. This report summarizes published data in regard to immune function in this disease. Thirty-two publications during the past ten years offer varying amounts of immunological data in 61 patients—50 males, 6 females, and 5 patients in whom the sex was not reported. There is no evidence for humoral immune deficiency in these patients. Secretory immunoglobulins are within normal limits. Intestinal mucosal plasma cells are decreased before treatment, but are normal after treatment. There are no abnormal deposits of complement or immunoglobulins within the intestinal mucosa. There is no evidence for autoantibody production. These patients invariably have lymphocytopenia prior to treatment and have a decreased percentage of T cells both before and after treatment. There is decreased responsiveness of lymphocytes to the mitogens PHA and Con A, before and after treatment. The cutaneous response to antigens is clearly diminished before treatment, improves somewhat after treatment, but is still significantly less than that seen in normal controls. There may be an increased association with HLA B27, which suggests that an abnormality in the cellular immune system promotes susceptibility to the Whipple bacillus.

Whipple's disease is a systemic illness, largely reported from North America and continental Europe in which the great majority of the patients are middle-aged, white males. The major histological involvement is that of macrophage infiltration of the lamina propria of the small intestine and of its lymphatic drainage. The presence of periodic acid-Schiff-positive macrophages has also been shown in most organ systems. The consistent presence of bacilli in the small intestine, lymph nodes, and other tissues of these patients prior to treatment has been repeatedly confirmed. The structural characteristics of the organisms in the untreated patient, their absence after antibiotic therapy, and the uniformly good clinical results with antibiotics leads one inescapably to regard Whipple's disease as a bacterial disease (1). That this apparent bacterial organism has not been cultured nor the disease reproduced in laboratory animals represents a major challenge. The necessity for successful culture of the bacterial organism is becoming increasingly apparent. Whipple's disease in the absence of apparent intestinal involvement has been identified (2–5). Thus, one can no longer rely entirely upon intestinal biopsy in order to make a diagnosis of this disease. Recent reports of Whipple's disease presenting as a central nervous system illness in the absence of intestinal symptoms provides increasing impetus to culture the apparent etiologic organism, hopefully permitting development of a serological assay for the diagnosis of this disease (6, 7).

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HISTORICAL ASPECTS

Patients with Whipple's disease are not unusually susceptible to ordinary viral and bacterial infections. However, there may be an unusual host susceptibility to the Whipple organism. The marked

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TABLE 1. SERUM IMMUNOGLOBULINS (MG/ML)*

	Before			After		
	A	*G*	*M*	*A*	*G*	*M*
Barbier (16)	7.80	6.80	0.43	5.40	10.50	0.50
Berens (17)	3.40	14.75	0.15			
Bloch (19)	2.20	8.50	0.50			
Buchholz (20)				2.22	12.10	0.90
Cerf (10)	10.40	10.40	3.00			
	2.10	7.50	0.50			
	10.00	12.60	0.80			
	5.00	15.00	0.60			
Clancy (39)	7.70	10.00	3.90	3.00	6.00	2.60
Cornet (24)	1.94	5.50	0.50			
Douglas (25)	8.00	1.50	1.45			
Groll (11)	15.00	18.50	1.20	5.90	10.00	3.00
Haeney (27)	3.58	15.20	0.48	1.90	7.20	1.42
Kirkpatrick (12)	3.10	14.50	0.43			
LeBodic (30)	9.50	15.00	1.60	3.24	14.13	1.35
	4.60	13.00	0.80	1.40	4.00	5.80
	2.40	6.89	0.15			
Lukacs (31)	3.00	12.00	0.80			
Maas (32)	3.10	9.00	0.32			
Myre (34)				3.90	18.50	0.26
Pastor (35)	0.56	5.80	0.70	0.64	1.50	2.93
Total	103.38	202.44	18.31	26.60	83.93	18.76
Mean	5.44	10.65	0.96	3.07	9.33	2.08
SD	±3.82	±4.37	±0.97	±1.77	±5.27	±1.73

*Results of serum immunoglobulins (mg/ml) in patients with Whipple's disease as reported by various authors. The reference is in parentheses. The data are tabulated in relation to treatment, either before or after. When multiple serum immunoglobulin analyses were done after treatment, only the last reported result is recorded above.

paucity of plasma cells within the intestinal lamina propria of untreated patients with this disease was first emphasized in 1967 (8). In 1968, Maxwell showed decreased lymphocyte responsiveness to phytohemagglutinin (PHA) in a patient following treatment (9). This observation suggested that these patients had a cell-mediated immune (CMI) deficit rather than a humoral immune deficit. In 1970, it was suggested independently by two groups that the presumed cell-mediated immune defect might relate to defective macrophage processing of the bacterial antigen (1, 10). This observation was based upon morphological data, and no functional studies were done to support the morphological observations. In 1972, Groll proposed that a disorder of cellular immune function permitted the rod-shaped organism to gain a foothold in tissues and proliferate until a state of specific immunological tolerance developed (11). In 1978, Kirkpatrick found no evidence for CMI deficiency in a single patient but further supported the possibility of immunological tolerance when he noted the absence of antibody in the patient's convalescent serum to the PAS-positive material in his own tissues (12). In 1979, Keren reported extensive immunological studies in three patients with Whipple's disease and found minimal evidence for cell-mediated deficiency (13). Feurle tested the cellular immune system in nine patients with Whipple's disease and found evidence (normal mitogenic response of lymphocytes to phytohemagglutinin and pokeweed mitogen but decreased response to concanavalin) suggesting a defect of a subclass of T-cells, a defect that was more severe in patients with active disease than in treated patients (14).

The major challenge today is still to successfully culture the apparent etiologic organism. The second challenge is to define the role of immune deficiency, if any, in these patients. A summary of current published data in regard to immune function in Whipple's disease should be helpful in deciding whether there is consistent evidence for immune deficiency in these patients and, if so, in providing direction for future studies in order to further clarify the immune status of these patients. Thirty-two publications during the past ten years offer varying amounts of immunological data in 61 patients—50 males, 6 females, and 5 patients in whom the sex was not reported (3, 9–39). Most of these reports have appeared since the publication of our comprehensive review of this disease (1).

HUMORAL IMMUNITY

Table 1 lists the patient immunoglobulin levels derived from reports. Using mean values ±1 standard deviation from the laboratory of Dr. T.A. Waldmann of the NIC, NIH (IgG 12.1 ± 2.6, IgA 2.6 ± 1.1, and IgM 1.4 ± 0.6 mg/ml), it can be seen that IgG and IgM are normal before treatment, while IgA is high. Immunoglobulin levels were normal after treatment. Immunoglobulin levels were said to be "normal" in four patients studied before and in nine patients studied after treatment (9, 15, 22, 29, 33). There is one report of Whipple's disease in a patient with common variable hypogammaglobulinemia (23).

Normal levels of secretory IgA were found in saliva and in intestinal secretions in all nine patients tested for this secretory immunoglobulin (10, 11, 25, 30). Normal levels of secretory component bound to IgA were found in parotid and intestinal secretions of the single patient tested for this, and free secretory component was found to be present in the intestinal secretions of the same patient (11). Immu-

nofluorescent studies utilizing fluorescent-labeled antibodies to IgA, IgG, and IgM to quantitate plasma cells within the intestinal lamina propria are reasonably consistent (9–11, 16, 20, 27, 28, 30, 37, 38). Before treatment, intestinal mucosal plasma cells were decreased in 12 patients, normal in 5, and increased in 1. After treatment, intestinal mucosal plasma cells were reported to be decreased in only 4 patients and to be normal in 7 patients. No consistent abnormalities in the relative proportions of the 3 classes of plasma cells were noted. Faint deposits of complement (C3) below the epithelial basement membrane were noted by Buchholz (20), and faint deposits of IgG in the same location were reported by Haeney (27). Serum complement levels (C3 in all reports, C4 in three) were found to be normal in 5 patients prior to treatment and in 10 other patients studied after treatment (20, 21, 27, 31, 33, 38, 39). Very slightly decreased C3 levels were noted in a single patient after treatment, and immunofluorescent staining of the intestinal biopsy of this patient showed faint deposits of C3 below the epithelial basement membrane (20).

Serum antibodies were detected in normal titers to streptococci, *Salmonella* species, *E. coli, Hemophilus influenza* type B, pneumococci, *Vibrio cholera,* diphtheria, and tetanus when tested in a small number of patients (9, 11, 20, 30, 31). A single patient had absence of serum hepatitis B surface antigen (HB_sAg) prior to treatment, but was found to have presence of HB_sAg in blood, serum, saliva, and intestinal secretions after treatment, at which time the liver biopsy showed evidence of subsiding hepatitis (27). Rheumatoid factor, antinuclear antibody (ANA), antimitochondrial antibody (AMA), anti-smooth-muscle antibody were found to be absent (9, 18, 20, 30, 31, 33, 36). Clancy found low titers (1 : 10) of anti-smooth-muscle antibody and of AMA in one patient before treatment. ANA was absent in this patient, and all assays for autoantibodies were negative after treatment (39). LE cells have not been detected (20, 36). Antibodies to thyroid microsomes, thyroglobulin, parietal cells, and salivary tissues were absent (9, 31). Isohemagglutinin titers were normal (20). Serological assays for influenza, coxsackie, and psittacosis viruses were reported to be negative in one patient (18).

CELLULAR IMMUNITY

Lymphocytopenia has almost invariably been present prior to treatment, with the lymphocyte levels returning to low normal levels after treatment. The mean of T lymphocytes was 41% in 11 patients prior to treatment and the mean was 45% in 12 patients after treatment (12–14, 16, 27, 30, 39). A reasonable normal mean for human peripheral T lymphocytes is 60% with a standard deviation of 10 (13, 14). Thus, the percentage of T lymphocytes, both before and after treatment, was consistently low. The percentage of B lymphocytes was normal before and after treatment in five patients (12, 16, 27, 28, 39). The mitogenic response of peripheral blood mononuclear (PBM) cells (lymphocyte response) to phytohemagglutinin (PHA) was a mean of 69% of normal in 15 patients studied before treatment (10–12, 14, 16, 27, 30, 31, 38, 39) and was a mean of 65% of normal after treatment in 25 individuals (9, 11, 13, 14, 16, 27, 30, 33, 35, 38).

It should be kept in mind that this testing was done in a variety of laboratories, utilizing various amounts of the mitogen, generally ranging from 2.0 to 10.0 μg/ml, and testing the mitogenic response usually after 3 days but sometimes after 4 and 5 days. Nevertheless, all of the responses were expressed as percent of normal mean for each laboratory. The data suggest a consistently diminished responsiveness of lymphocytes, both before and after treatment, to the mitogen PHA.

Other lectins, concanavalin A (Con A), and pokeweed mitogen (PWM) were tested in a very few patients. Similar to the findings with PHA, there was generally a decreased responsiveness of lymphocytes to these mitogens (12–14, 27, 30, 38). Three reports bear closer scrutiny. Martin found a significantly decreased response ($P > 0.001$) of PBM to PHA in 7 patients with treated Whipple's disease and in 1 patient studied during treatment, when compared with the response in 11 healthy adults (33). Keren emphasized that he was able to find minimal evidence for cell-mediated immune deficiency in the three treated patients that he studied. His data show decreased responsiveness of lymphocytes in these three patients to PWM, PHA, and Con A. If one merely compares the means of the results of 36 analyses in these 3 patients to the mean normals reported from his laboratory, 31 of the 36 responses were decreased. If one further analyzes this data in relation to a difference of one standard deviation, then 27 of the 36 responses were below the normal means for his laboratory (13). Feurle reported data on 9 patients, three untreated and six following treatment (14). Considering entire groups (treated and untreated together), only the response to Con A was significantly depressed ($P < 0.02$),

TABLE 2. CUTANEOUS RESPONSE TO ANTIGENS*

	Before treatment	*After treatment*
Tuberculin	5/21	7/26
Candida	2/16	6/15
Trichophyton	0/8	2/17
Histoplasmin	1/5	1/10
Mumps	0/8	5/14
SKSD	1/7	1/11
DNCB	1/4	1/3
Total	10/69 13%	23/96 24%

*Tabulation of reported skin test responses in patients with Whipple's disease in relation to treatment. The numerator represents number of positive responses while the denominator represents the total number of patients tested.

while Con A stimulated the patients in remission significantly less ($P < 0.04$) than the controls. He pointed out that the differing responses to PHA and Con A may be due to differing action of the mitogens on suppressor and helper T cells. He interpreted these results to be compatible with evidence that there is a persistent defect of T lymphocytes in Whipple's disease and that this impairment resides in a subclass of T lymphocytes (14).

Most of the reports cited give some information in regard to the cutaneous response to antigens. Thus, the data will not be referenced but are summarized in Table 2. The data in Table 2 suggest that there is a defect in cutaneous reactivity to several antigens both before and after treatment, but control data in several studies are lacking. In two controlled studies the findings were as follows: Feurle assessed skin test antigen (trichophyton, *Candida,* tuberculin, SKSD) responses in 21 male inpatients with disease not associated with impaired delayed hypersensitivity, a group that was matched for age and sex with the 9 patients he studied. He found a positive response of 33/81 (41%) in this group of controls, no response in 3 untreated patients, and only 4 positive responses to 24 skin tests (17%) in 6 treated patients in remission (14). Martin assessed cutaneous hypersensitivity in 7 patients with treated Whipple's disease utilizing 23 different antigens and compared the results to those found in 138 control patients (3). Delayed hypersensitivity reactions were significantly depressed, when compared to control, in all 7 patients tested and 5 of the patients exhibited no delayed reactions to all 23 of the antigens. Skin graft rejection was tested in a single patient (11). A homograft applied before treatment was accepted for over 4 months and a second graft placed after 3 months of treatment was also rejected slowly (11). Thus, there appears to be a significant degree of cutaneous anergy in patients with Whipple's disease, both before and after treatment.

HLA typing was done in 15 patients (3, 11, 12, 14, 19, 21, unpublished). Six of the 15 (40%) patients were B27 positive. Only 10% of the general population is B27 positive (14). The association of Whipple's disease with HLA B27 may be further evidence that an abnormality in the cellular immune system promotes susceptibility to the Whipple organism.

The histopathological response in Whipple's disease is generally described as an infiltrative one in which macrophages are predominant. Sometimes the inflammatory reaction is granulomatous in nature (6, 15, 19, 22, 24, 25, 32, 36, 40) and in two patients has been described as "sarcoid-like" (15, 36). A granulomatous response to injury, whether bacterial or otherwise, has been taken as an indication of alteration in cell-mediated immune function.

Phagocytic activity by PMN leukocytes and by macrophages, and lymphokine production by lymphocytes is an area that has been generally neglected in studies of Whipple's disease. Lukacs found a slightly decreased index of PMN and macrophage phagocytosis in one patient studied before treatment (31). Intracellular killing of fungi by PMN leukocytes was also shown to be 56% of normal (31). No studies were done after treatment. Tytgat studied one patient after treatment and showed that PMN chemotaxis was minimally diminished, that PMN phagocytosis of *Staphylococcus aureus* was within normal limits, and that PMN killing of the same organism was slightly diminished (38). Barbier showed low secretion of migration inhibitory factor (MIF) by lymphocytes in response to SKSD in one patient before treatment, but showed a normal MIF response one year after treatment (16). Decreased macrophage adherence to glass was reported in one patient with Whipple's disease (22). Clancy demonstrated normal neutrophil function and normal serum opsonizing capacity in a single patient (39).

CONCLUDING REMARKS

The evidence supporting immunodeficiency obtained in patients prior to treatment must be discounted. Severe malnutrition and partial obstruction of intestinal mucosal lymphatics could account for all of the observed changes in immune function in the untreated patient. Further, transient anergy is the normal immune response to some infections

(41). There may be a subtle defect of cell-mediated immune function in the treated patient. The Whipple bacillus may be an intracellular pathogen, similar to *Listeria monocytogenes,* salmanellae, and brucellae. Unlike pyogenic bacteria, which after phagocytosis are rapidly digested by the macrophage, intracellular pathogens survive inside the macrophage, unless the macrophage is activated. The immune response to intracellular pathogens requires interaction between T cells and macrophages, resulting in production of lymphocyte mediators requiring a two-stage interaction (42). Exploration of this aspect of macrophage-lymphocyte interaction may be a fruitful area for investigation in Whipple's disease. Production of lymphokines, especially macrophage activating factor, should be explored. If there is indeed an abnormality in cellular immune function in these patients, it may reside in a subset of T cells as pointed out by Feurle (14). The function of immunoregulatory T cells should be studied (43), and the role of T cell regulation of the immune response as it relates to the mucosal immune system should be explored (44).

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