PATHOGENESIS OF GIARDIASIS

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General pathogenesis

The pathogenesis of giardiasis is complex and conditioned by several co-existing factors. The basic factor initiating the pathogenic effect involves the mechanical attachment of the a ventral disc of the Giardia trophozoite to the microvillus border of the enterocyte. This is well documented for the mouse model (Erlandsen & Chase, 1974; Erlandsen & Feely, 1984), but is not frequently seen in human biopsy specimens. Observations (Barbieri et al., 1970; Poley & Rosenfield, 1982) have proven that the thick layer of mucoid material in the human intestine may restrict the attachment of trophozoites to the microvillus border. Structural alterations of microvilli have rarely been observed (Brooks et al., 1969; Tubbs & Hawk, 1976; Kociecka et al., 1984). Still, experimental (Gillon et al., 1982) and clinical data (Tewari & Tandon, 1974; Tubbs & Hawk, 1976; Swiatkowska et al., 1984) exist which indicate that, despite insignificant structural changes of the villi, disaccharidase deficiency and lactose intolerance occur. Dysfunction of enterocytes has been indicated by several authors, but analysis of their data has shown that no correlation between clinical and biochemical disturbances on the one hand and structural alterations of enterocytes on the other are present in the majority of giardiasis patients (Zamcheck et al., 1963; Hoskins et al., 1967; Barbieri et al., 1970; Tandon et al., 1974; Hartong et al., 1979).

Pathogenic mechanisms (Immunopathology)

The disturbed function of mucosal epithelium in the small intestine may be explained by the action of cytopathic toxins released by Giardia and by release of antigenic substances. The cytopathic toxins of Giardia have been demonstrated in experimental studies in tissue culture (Radulescu et al., 1980). Not all elements of the problem have been clarified. Antigen released by Giardia leads to cell-mediated or humoral responses of variable intensity. The cellular cytotoxic mechanism has been shown to participate in the host response to the parasite. Experimental studies have shown that Giardia is a target for both spontaneous cell-mediated cytotoxicity by monocytes and for antibody-dependent cellular toxicity by granulocytes. Monocytes/macrophages isolated from the blood of giardiasis patients have been shown to be spontaneously cytotoxic for G. intestinalis trophozoites and this may be a major mechanism of the first level defence, responsible for eliminating Giardia out of the intestine. Granulocytes become the second line of defence against Giardia (Smith et al., 1982). In light of the data, the statement of Smith et al. (1982) that reduced...
cellular cytotoxicity of the host toward Giardia may be significant for the persistence of immunopathological process and for prolongation of the invasion, seems well based. Therefore, the phenomenon should taken into account in appraising patients with chronic giardiasis. In experimental studies on mice infected with Giardia muris (Owen et al., 1979), the submucosal layer has demonstrated a prevalence of lymphocytes and their migration in the intercellular spaces toward enterocyte microvilli, close to the villous base. Moreover, a phenomenon of lymphocyte adherence to the dorsal surface of Giardia trophozoites has been noted. On the grounds of the observations it seems highly probable that the effector T cells do cross the epithelium to attack the Giardia within lumen of the intestine. Moreover, it has been noted (Owen et al., 1981) in electron microscopy that Giardia trophozoites in mucosal breaches are engulfed by macrophages. Thus, the intraepithelial lymphocytes seem to play a leading role in cell-mediated immune response of the host and to participate in the final clearance of the invasion. Clinical reports on the subject are few (Ferguson et al., 1976; Wright & Tomkins, 1977; Rosekrans et al., 1981; Chapoy et al., 1982; Kociecka et al., 1984) but they constitute valuable confirmation of experimental findings.

Howat and Ferguson (1981) suggest that T cells react vigorously to an antigen by releasing enteropathic lymphokines which damage enterocytes. It has also demonstrated (Gillon et al., 1982) that enteropathic lymphokines act directly on the epithelial cells and stimulate mitosis and mucous secretion by goblet cells (McDonald & Ferguson, 1978). The hypothesis has been supported by the work of Thelwall and Mitchel (1978) who have shown that the villus-crypt ratio in Giardia-infected athymic mice were augmented when the mice were reconstituted with lymphoid cells from non-infected donor mice. Damaged enterocytes are being substituted by new immature ones, proliferating in the crypt region, as noted in experimental and clinical work (Wright & Tomkins, 1977; Ridley & Ridley, 1976; Gillon et al., 1982; Kociecka et al., 1984). Walker (1976) suggests that immature epithelial cells absorb molecules of antigen by pinocytosis and histological features in giardiasis, with malabsorption (shortening of villi with increased mitosis of crypt cells) are consistent with increased rate turnover in response to enhanced epithelial cell loss from the villi. Sequelae of disturbances in enterocyte kinetics involve not only the altered villous architecture, but primarily their disturbed function (resorption, transport) which induces malabsorption symptoms and diarrhea of variable intensity, reflecting the epithelial lesions.

Within the local immune defence reaction, in the course of giardiasis, an important role is being ascribed to IgA antibodies produced by sublayer plasma cells. IgA antibodies diffuse up to the epithelial surface and attach to the surface of Giardia trophozoites, but in some cases may be shed from the parasite membrane without inducing injury. Thus, IgA antibody may prevent implantation of Giardia in the intestine by agglutinating or impairing motility of the trophozoite or by interacting with surface components involved in adhesion. On the grounds of the experimental data, the hypothesis of Zinneman and Kaplan (1972) that IgA deficiency in the intestinal juice augments susceptibility to Giardia infection seems well based. On the other hand, the notion does not always find confirmation in broader clinical studies in patients. Observations of patients with immunoglobulin deficiency or with variable immunodeficiency syndromes indicate that Giardia infection in such cases is usually asymptomatic, with malabsorption and shows a tendency to a chronic course (Ament & Rubin, 1972; Hughes et al., 1971; Brown et al., 1972; Ochs et al., 1972; Popovic et al., 1974).

The detailed mechanisms of the host immune response in giardiasis are far from being completely defined. Circulating antibodies (IgA, IgM, IgC) also develop (Ridley & Ridley, 1976; Nuriev et al., 1979; Winiecka et al., 1984), but their biological role is unclear. Immunoglobulin E, mast cells and substances released by them play an essential role in local hypersensitivity phenomena of the intestinal mucosa (Belot et al., 1980; Brown et al., 1975; Budzynska, 1984). The presence of mucosa mast cells in the lamina propria in the course of human giardiasis has been demonstrated (Gustowska et al., 1983; Kociecka et al., 1984). Both histamine and serotonin released from the mast cells have been cited as potential mediators in mucous release from epithelial cells (Trier et al., 1981). Tutton et al. (1974) have shown that serotonin released from mast cells influences crypt cell renewal rate in the jejunum and stimulates net fluid and electrolyte secretion by epithelium of the intestine (Kisloff et al., 1976). Vasoactive intestinal polypeptide (VIP), also secreted by mast cells (Cutts et al., 1978), is a potent inducer of c-AMP-mediated NaCl secretion by intestinal epithelium. Considering its neurotransmitter function, VIP should be regarded as playing a significant role in the control of intestinal wall physiological functions, and may be important in giardiasis.
Pathology and clinical symptoms

In descriptions of jejunal mucosa pathomorphology in the course of giardiasis, the lack of correlation between spread and intensity of lesions on the one hand and the frequency and as well as the intensity of clinical symptoms on the other hand is striking. Therefore, discussion on pathogenesis of giardiasis cannot bypass the role of intestinal enzymes and hormones secreted by enterochromaffin cells at the base of Lieberkuhn crypts. Intestinal enzymes and hormones control motor and secretory function of the intestine as well as of the stomach, gall-bladder and pancreas. In this way, they shape a parasite's microenvironment and affect interrelationships in the host-parasite system. Intestinal secretin and 5-hydroxy-tryptamine inhibit small bowel motility, while gastrin, cholecystokinin-pancreozymin, vasoactive intestinal polypeptide (Buffa et al., 1977) and prostaglandin E increase small bowel motility. Moreover, secretin and pancreozymin control the intestinal phase of digestion by stimulating secretion of bicarbonates and pancreatic enzymes, thus regulating the pH of the intestinal microenvironment (Trier et al., 1981; Lipkin et al., 1981). Disturbed synthesis and secretion of the enzymes, resulting from Giardia invasion, manifest themselves by a wide spectrum of clinical symptoms (diarrhoea or constipation, abdominal pain, nausea) which cannot be attributed solely to atrophy of villi in the small bowel. The point has been supported by clinical studies (Chawla et al., 1975; Gupta & Mehta, 1973), who demonstrated decreased activity of pancreatic enzymes in patients with malabsorption symptoms or diarrhoea observed in the course of giardiasis.

Hypoacidity represents another factor influencing disturbances in giardiasis. Disturbed secretion by the gastric mucosa in patients with giardiasis may be primary or secondary. The frequency of hypoacidity in giardiasis in children and young adults and its reversibility after elimination of the parasite suggest a relation between Giardia invasion and disturbed secretion of gastric mucosa (Giebiski, 1965; Haas & Buecken, 1967; Planeta-Malecka et al., 1971; Kociecka et al., in press). From the clinical viewpoint, hypoacidity may lead to disturbed digestion and be associated with multiple symptoms. Hypoacidity in the course of giardiasis makes patients prone to penetration by pathogenic bacteria or fungi, thus causing chronic recurrent intestinal disorders. This seems to be indicated by several authors who have studied various aspects of the problem (Alkiewicz et al., 1969; Brown et al., 1972; Tandon et al., 1977; Tomkins et al., 1978). The view of some authors (Yardley et al., 1964; Drasar et al., 1969; Slomim et al.) that patients either with hypoacidity or after gastrectomy are particularly prone to Giardia intestinalis invasion is not fully explained and documented. The development of Giardia intestinalis invasion in patients with excessively high hydrochloric acid secretion indicates that a low pH of the gastric juice does not prevent the invasion (Balashova, 1978; Kociecka et al., in press).

Thus, the multiplicity of immunopathologic and physiopathologic factors induced by Giardia intestinalis invasion explains to a significant extent the variable clinical pattern of giardiasis which may range between an asymptomatic course and spontaneous extinction of the parasite or, on the other hand, marked symptoms, chronicity and a tendency to relapse. A comprehensive approach to the pathogenic mechanisms occurring in giardiasis should facilitate understanding the problem by clinicians.

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