ANIMAL MODEL OF HUMAN DISEASE

Menetrier's Disease

Pre-Type II and Type II Ostertagiosis in Cattle

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MENETRIER'S DISEASE is an uncommon condition in man characterized by marked increase in the size of the mucosal rugae of the stomach with a marked increase in numbers of superficial mucosal cells of the stomach which frequently extend in tortuous ducts into the fundic glands. Protein-losing gastropathy, hypoproteinemia, anemia, abdominal pain, vomiting, normo or achlorhydria and mucosal inflammation with lymphocyte and plasma cell infiltration are characteristic of the condition.[1,2]

Biologic Features

Ostertagia ostertagi is a trichostrongylid nematode with a five stage direct life cycle which infects the abomasum of cattle.[3] Natural infections have been observed in cattle and occasionally in goats and sheep with experimental infections reported for cattle, goats, sheep and rabbits. Two disease syndromes have been identified in cattle.[4] Type I ostertagiosis is characterized by a rapid and massive accumulation of infective third stage larvae from forage. These larvae mature within 16–18 days and can produce acute gastric dysfunction. The Type II ostertagiosis is more complex and involves poorly defined epidemiologic factors.[5,6] In this syndrome infective third stage larvae are exposed to adverse environmental conditions, usually seasonal chilling, which induces a state of arrested development of the early fourth stage larvae within the gastric mucosa. The arrested development phase, which serves as an effective over-wintering survival mechanism, lasts for 4 to 6 months. Identified as pre-Type II ostertagiosis, this phase is terminated by a sudden maturation of arrested larvae within 1–3 weeks. The result is Type II ostertagiosis in which severe gastric dysfunction often produces death.[7] Associated with *Ostertagia ostertagi* infection is elevation of plasma pepsinogen which has application in cattle as a diagnostic procedure.[8–10]

Significant pathological changes in ostertagiosis are limited to the abomasum and produce clinical signs of gastrointestinal disease. Type I ostertagiosis is characterized by larval infection and growth within gastric glands, principally of the fundus and corpus, with glandular dilatation and destruction of glandular epithelium.[11,12] This and pressure atrophy of adjacent glands result in the loss of parietal cell function with increased gastric pH. Marked plasma protein loss through the damaged mucosa results in hypoproteinemia. Accompanying the maturation of larvae there is mucosal congestion and severe submucosal edema. Residual lesions include mucous cell invasion of the crypts with focal to diffuse infiltration of lymphocytes, plasma cells, and eosinophils and increased numbers of globule leukocytes. Ultrastructural studies have demonstrated recovery of the parietal cell population numbers within 48 hours in the Type I syndrome[13,14].

The lesions of Type II ostertagiosis differ signifi-

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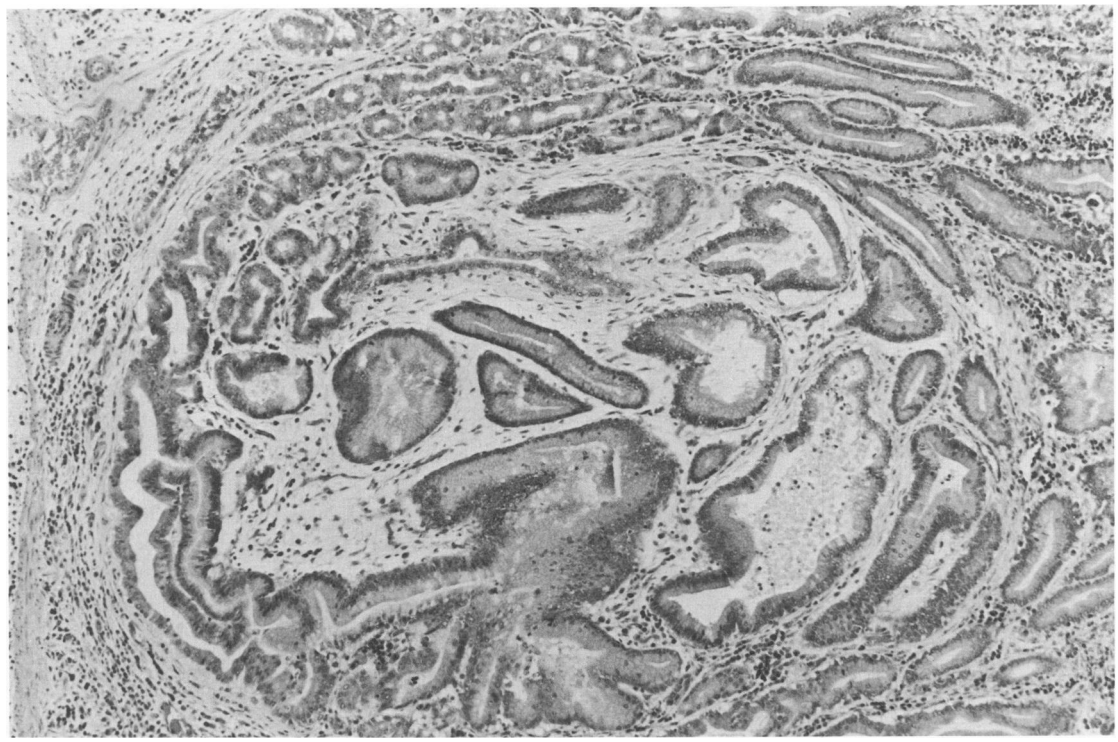

Figure 1 — Ostertagia-induced nodular hyperplasia and cystic dilatation of the mucus glands in the fundic region of the abomasum. The cellular infiltrate is admixed lymphocytes and eosinophils. (H&E, ×260)

cantly in that during the pre-Type II phase there is a gradual increase in focal and diffuse lymphocyte accumulation with slight to marked, focal to diffuse eosinophil and plasma cell infiltration and slight to marked focally diffuse globule leukocyte hyperplasia in the lamina propria. This has been related to an intramucosal migration of the early fourth stage larvae while in arrested development.[10] The cellular infiltrations replace the functional gastric mucosa which, with the sudden maturation of large numbers of larvae, severely compromises gastric function. There is dedifferentiation of glandular epithelium with mucous cell metaplasia followed by mucous cell hyperplasia in the infected glands (Figure 1).

Studies of Type II ostertagiosis have been limited by the lower and unpredictable incidence of the natural disease. Through the use of chilled (4° C for several weeks) third stage larvae workers in the United Kingdom have been able to induce experimental larval arrest which persists for a time period similar to that observed under natural conditions but have not reported the gastric lesions.[7] In another study, the use of an infection schedule which included a single large larval inoculation followed by increasing serial larval inoculations reproduced the gastric lesions observed in naturally occurring pre-Type II ostertagiosis.[10] The influences of potential *O. ostertagi* population differences and the host inflammatory and immune response in the pathogenesis of the disease have not been clarified.

Comparison With Human Disease

Like Menetrier's disease, pre-Type II and Type II ostertagiosis have an increased gastric pH[15] with protein losing gastropathy, hypoproteinemia,[16] anemia, inflammatory changes of the stomach mucosa and hyperplasia of mucosal cells. Differences include the presence of eosinophils in the reaction in the bovine gastric mucosa and the known etiologic agent, which is not recognized in the human disease.

Usefulness of the Model

The elucidation of the mechanisms of irritation and the probable role of the immune system in this disease could produce useful information to be applied in the study of Menetrier's disease in man. The interaction of hormone receptors with immunoglobulins and the possibility of a blocking role for the hormonal stimulation of acid secretion should be evaluated and compared. Hypergastrinemia with decreased

acid secretion has been observed in some cases of Menetrier's disease[2] as has been documented for ostertagiosis.[15] This contrasts with a similar condition, hypertrophic hypersecretory gastropathy, in which there is hypersecretion in addition to hypergastrinemia and a gastropathy with some similarities to Menetrier's disease. Parietal cell autoantibodies have been demonstrated in hypochlorhydric, hypergastrinemic gastropathies[17] as well as in a patient with protein losing hypersecretory, hypergastrinemic gastropathy.[18]

Information obtained in this animal model could contribute to further elucidate the complex set of pathophysiological events occurring in Menetrier's disease in man.

Availability

A method for producing pre-Type II Ostertagia infections in cattle has been published. The lesions described above have been reproduced in a recently concluded project sponsored by the Louisiana State Board of Regents (82-LBR/054-B35) using the method previously described.[10]

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