GASTRIC AUTOIMMUNITY IN ADDISONIAN PERNICIOUS ANEMIA AND STUDIES OF HUMAN INTRINSIC FACTOR SECRETION

by

Robert Geoffrey Strickland, M.B., B.S. (Adel.) M.R.A.C.P.

Division of Gastroenterology, Department of Medicine

Stanford University School of Medicine, California. 94305. U.S.A.

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THESIS SUMMARY

Of all the diseases of man in which autoimmune phenomena occur pernicious anemia offers perhaps the best opportunities for correlated studies of the presence of antibodies in serum, glandular secretion, and tissue with morphology and secretory activity of the involved organ, namely the stomach.

Such a study is presented in this thesis and has established that in addition to circulating gastric autoantibodies, local gastric autoimmune phenomena occur with high frequency in this disease. A higher incidence of intrinsic factor antibodies in gastric juice than in serum and a striking incidence of IgA parietal cell antibody in gastric juice compared to serum, together with the presence of gastric autoantibody containing cells in the gastric mucosa strengthen the possibility that an immunodestructive gastritis forms the basis of pernicious anemia. Comparison of these phenomena with structural and functional data has not provided sufficient evidence to implicate the autoantibodies themselves directly in the evolution of the disease.

A case study of two adults with pernicious anemia and polyendocrine deficiency in addition to emphasizing the clinical interrelationships between gastric and endocrine disease has demonstrated the probable interplay between immunologic and genetic

factors in the pathogenesis of these disorders and has indicated that the evolution of autoimmune organ damage may be extremely prolonged.

A study of the effect of corticosteroids in pernicious anemia confirms the results of investigations published in the course of the present studies. The influence of these drugs in restoring vitamin B_{12} absorption to normal levels has been shown to be specific to patients with advanced atrophic gastritis as no effect on vitamin B_{12} absorption or intrinsic factor secretion was observed in normal subjects or in those with chronic superficial gastritis, taking prednisolone. Though regeneration of parietal cells was seen in some patients such changes could not always be linked to the improvement in vitamin B_{12} absorption. A unique series of short term studies of the influence of prednisolone in pernicious anemia disclosed that the improvement in vitamin B_{12} absorption took at least one week to appear and contrary to other reports was not invariably accompanied by enhanced intrinsic factor output. The first study of the influence of corticosteroids on gastric juice intrinsic factor antibodies is presented. Despite a correlation between functional improvement and the existence of serum or gastric juice intrinsic factor antibodies an immunosuppressive effect in gastric juice could not be demonstrated.

Acid secretion was shown to be significantly enhanced in normal subjects taking oral prednisolone but the mechanism of this effect could not be discerned from this study.

Physiological studies of the gastric secretion of vitamin B_{12} binding proteins in man have established that proteolysis indeed has a marked depressive effect on the quantitation of these components as measured by the widely used immunoassay procedure.

A method of overcoming intragastric proteolysis yet retaining the capacity to measure actual secretion rates of macromolecular constituents has been developed and successfully applied to a study of the secretion of vitamin B_{12} binding proteins and pepsinogen in normal subjects.

Demonstration of the pattern of secretion of these components under maximal stimulation has been thereby achieved under optimal conditions. The results lend strong support for the gastric parietal cell being the cell of origin of intrinsic factor in man.

Several noteworthy methodological advances have resulted from these studies. A method for quantifying gastric juice constituents by the use of inorganic phosphate as a volume marker whilst maintaining the gastric juice pH close to pH 7.0 by <u>in vivo</u>

neutralization is described and may have wider application in the study of gastric juice macromolecular components. Improved techniques for the collection and handling of pernicious anemia gastric juice for immunological testing, a modification of the guinea pig mucosal homogenate method for detecting gastric juice intrinsic factor antibodies and a technique using labelled crude gastric antigens to localize antibody producing cells to these antigens are described.