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This Week's Citation Classic

Waldmann T A, Steinfeld J L, Dutcher T F, Davidson, J D & Gordon R S, Jr.
The role of the gastrointestinal system in "idiopathic hypoproteinemia." *Gastroenterology* **41:**197-207, 1961. [Metab. Serv. and Pathological Anat. Br., Nat. Cancer Inst., and Lab. Cell. Physiol. and Metab., Nat. Heart Inst., Bethesda, MD)

A new syndrome we termed 'intestinal lymphangiectasia' was described in patients previously diagnosed as 'idiopathic hypoproteinemia.' Intestinal lymphangiectasia is characterized by a generalized disorder of lymphatic channels including dilated small intestinal lymphatics that leads to excessive gastrointestinal protein loss and to hypoproteinemia and edema. [The *SCI*® indicates that this paper has been cited over 215 times since 1961.]

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"Shortly after the NIH Clinical Center opened, investigators from different institutes joined in a study of patients with 'idiopathic hypoproteinemia.' Frederic Bart ter followed the fate of IV human albumin in these patients by metabolic balance techniques and found several cases with increased catabolism. Jesse Steinfeld using radioiodinated proteins then showed that hypoproteinemia in many patients was due to shortened protein survival rather than decreased synthesis.[1] Citrin at SUNY Upstate Medical Center using IV ^{131}I-albumin demonstrated loss of albumin into the gastric secretions in a patient with Menetrier's disease.[2] However, no practical test for protein loss was available until Robert S. Cordon, Jr.'s development of radioiodinated polyvinylpyrolidone (PVP),[3] a macromolecule that is unaffected by mammalian enzymes and is not absorbed from the intestine. The hypoproteinemic patients excreted excessive quantities of IV PVP into their feces demonstrating that their hypoproteinemia was due to excessive gastrointestinal loss. We then joined in a study of 18 patients to define the cause of the protein losing enteropathy demonstrated in patients who did not have a previously described gastrointestinal disease.

"Three new syndromes defined in these patients formed the basis for the cited publication. One patient had transient protein loss, two protein loss secondary to constrictive pericarditis, and 15 a previously undescribed disease we termed 'intestinal lymphangiectasia.' A generalized disorder of lymphatic channel development was suggested by chylous effusions and asymmetrical edema observed in many of these patients. The suspected disorders of small intestinal lymphatics were demonstrated on peroral biopsies. The disorder of intestinal lymphatics leads to excessive protein loss, hypoproteinemia, edema, and chylous effusions.

"This description of a new syndrome and pathophysiologic mechanism led to the numerous citations and to the reproduction of this paper in the silver anniversary issue of *Gastroenterology.*[4] We subsequently developed new macromolecules, including ^{51}Cr albumin, to quantitate gastrointestinal protein loss.[5] In addition, we demonstrated a new immunodeficiency state characterized by hypogammaglobulinemia, lymphocytopenia, skin anergy, and impaired homograft rejection in patients with intestinal lymphangiectasia.[6] These defects were due to excessive gastrointestinal loss of immunoglobulins and lymphocytes through the disordered lymphatic channels.

"Thus, studies of patients with the ill defined disorder 'idiopathic hypoproteinemia' led to the discovery of a new common cause of hypoproteinemia, protein losing enteropathy, to the identification of a new disease, intestinal lymphangiectasia, and to the definition of an associated immunodeficiency with a previously unrecognized pathogenic mechanism leading to disordered immunity."

1. **Bartter F C, Steinfeld J L, Waldmann T A & Delea C S.** Metabolism of infused serum albumin in hypoproteinemia of gastrointestinal protein loss and in analbuminemia. *Trans. Assoc. Amer. Phys.* **44:**180-94, 1961.
2. **Citrin Y, Sterling K & Halsted J A.** Mechanisms of hypoproteinemia associated with giant hypertrophy of gastric mucosa. *N. Eng J. Med.* **257:**906-12, 1957.
3. **Gordon R S, Jr.** Exudative enteropathy: abnormal permeability of the gastrointestinal tract demonstrable with labelled polyvinylpyrolidone. *Lancet* **1:**325-6, 1959.
4. **Waldmann T A, Steinfeld I L, Dutcher T F, Davidson J D & Gordon R S, Jr.** The role of the gastrointestinal system in "idiopathic hypoproteinemia." *Gastroenterology* **54:**794-6. 1968.
5. **Waldmann T A.** Gastrointestinal protein loss demonstrated by ^{51}Cr-labelted albumin. *Lancet* **2:**121-3, 1961.
6. **Strober W, Wochner R D, Carbone P P & Waldmann T A.** Intestinal lymphangiectasia. a protein losing enteropathy with hypogammaglobulinemia, lymphocytopenia and impaired homograft rejection. J. *Clin. Invest* **46:**1643-56. 1967.