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INTIMATIONS RELATING TO PROTEIN FORMING DISEASES*

WILLIAM S. HAUBRICH, M.D.**

According to Webster, intimations are 'suggestions obscurely or indirectly made'. In this essay it is speculative suggestions, some obscure and some indirect, that I will attempt to relate to certain protein-forming diseases.

Increasing attention is being directed to the emergence of a group of disease states — of probably diverse etiologies, of diverse manifestations, and even of diverse courses — but which yet seems to share commonly the fact that each disease is constituted morphologically by the presence of ontogenetically similar cells which are capable of elaborating abnormal protein substances.

Because its clinical behavior and, particularly, its morphologic features have occupied our recent study¹, the condition which I submit as a prototype of these states is Whipple's disease.

HISTORICAL BACKGROUND

It is noteworthy that George H. Whipple, in his original report² of the disease for which his name is now the eponym, described in detail within the small intestine and mesentery a profusion of "peculiar cells with frothy cytoplasm" in addition to the more obvious anomalous accumulations of fats and fatty acids. It is these peculiar cells which we recognize now as the most significant feature of Whipple's disease.

The Henry Ford Hospital can claim an extraordinary share in the developing knowledge of Whipple's disease. Black-Schaffer, an alumnus of this hospital, provided a major breakthrough in 1949 by demonstrating the striking tinctorial response in tissue from Whipple's disease to the periodic acid-Schiff (PAS) technic³. Puite and Tesluk⁴, both members of the staff of this hospital at the time of their 1955 report, established the diagnosis of Whipple's disease by peripheral lymph node biopsy. In 1958 Sieracki, until recently associated with this hospital's department of laboratories, directed attention to the unusual configuration of the cytoplasmic inclusions in the "frothy cells" and coined the term "sickle-form particle containing" (SPC) cells⁵. Sieracki and Fine⁶ then catalogued the occurrence of these SPC cells in tissues representing all major anatomic systems thus confirming that Whipple's disease is a widespread, systemic affection. Involvement of the central nervous system was the subject of a special report by Sieracki, Fine, Horn, and Bebin⁷. Meanwhile, Eyler and Doub⁸ described the extraintestinal roentgen signs of Whipple's disease. It was in the physics department at the Edsel B. Ford Institute for Medical Research that the ultrastructure of the SPC cells and their cytoplasmic inclusions was first demonstrated by electron microscopy¹.

THE SPC CELLS

The characteristic cell of Whipple's disease is a large (average diameter: 20 μ to 30 μ), usually mononuclear cell. By the ordinary hematoxylin-and-eosin technic,

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the cytoplasm of these cells appears "frothy" because of numerous slightly basophilic particles faintly visible against a lightly eosinophilic background. In the cytoplasm of an occasional cell, a few droplets of fat may be seen, but the great bulk of the material is nonsudanophilic. The nucleus is relatively small, unilobular, and eccentric.

After treatment by the PAS technic, the intracytoplasmic particulate substance appears as a brilliant magenta (PAS-positivity). There is no doubt that the "peculiar cells with frothy cytoplasm" mentioned by Whipple² are identical with the SPC cells described by Sieracki⁵. This was proved when Mendeloff⁹ applied the PAS technic to tissue preserved from Whipple's original case and demonstrated precisely the tinctorial reaction and the morphologic configuration which we recognize as pathognomonic today.

Within the peculiar cells of Whipple's disease, the PAS-positive material occurs as sickle-form particles (averaging 2μ to 3μ) of varying density and also as amorphous clumps and strands (Figure 1). The true sickle-form configuration of these particles is best appreciated in imprints rather than in ordinary tissue sections. In imprints the particles are seen in their entirety rather than as random transverse or oblique sections. All solid tissues lend themselves to the imprint technic which we have found especially useful in applying to biopsies from peripheral lymph nodes and from the small intestine mucosa in Whipple's disease.

It is emphasized that PAS-positivity by itself does not confer distinction on the substance peculiar to Whipple's disease. A variety of glycoproteins or mucopolysaccharides react tinctorially with the PAS technic. In the normal intestinal mucosa, for example, PAS-positivity is exhibited by mucus adherent to the free border of the intestinal epithelial cell, by mucoïd substance in goblet cells, and by faint strands of mucoïd material in the lamina propria. It is the particulate configuration of the PAS-positive substance in abundant cells abnormally situated in the lamina propria which is unique in Whipple's disease.

Anatomic Occurrence of SPC Cells. Characteristic SPC cells invariably occur both in mesenteric and in peripheral lymph nodes. The latter provides a readily accessible site for biopsy, and this procedure has provided the diagnosis of Whipple's disease in 3 patients of our own series.

Equally abundant are the SPC cells in the lamina propria of the small intestine, but they are regularly found in all other segments of the gastrointestinal tract including the esophagus, stomach, and colon. With the newly developed technics for peroral biopsy of the small intestine mucosa, a diagnosis of Whipple's disease is promptly confirmed by the imprint technic (Figure 1) which we have successfully applied in 3 cases.

In the liver, SPC cells occur both in the portal and subendothelial spaces. It is noteworthy that the liver architecture is not distorted and, as in most other situations, there is no appreciable inflammatory reaction adjacent to collections of SPC cells.

In the spleen, SPC cells are distinct from morphologically similar cells containing only iron pigment. This suggests that SPC cells do not represent the ordinary tribe of macrophages which may perform only a simple phagocytic function.

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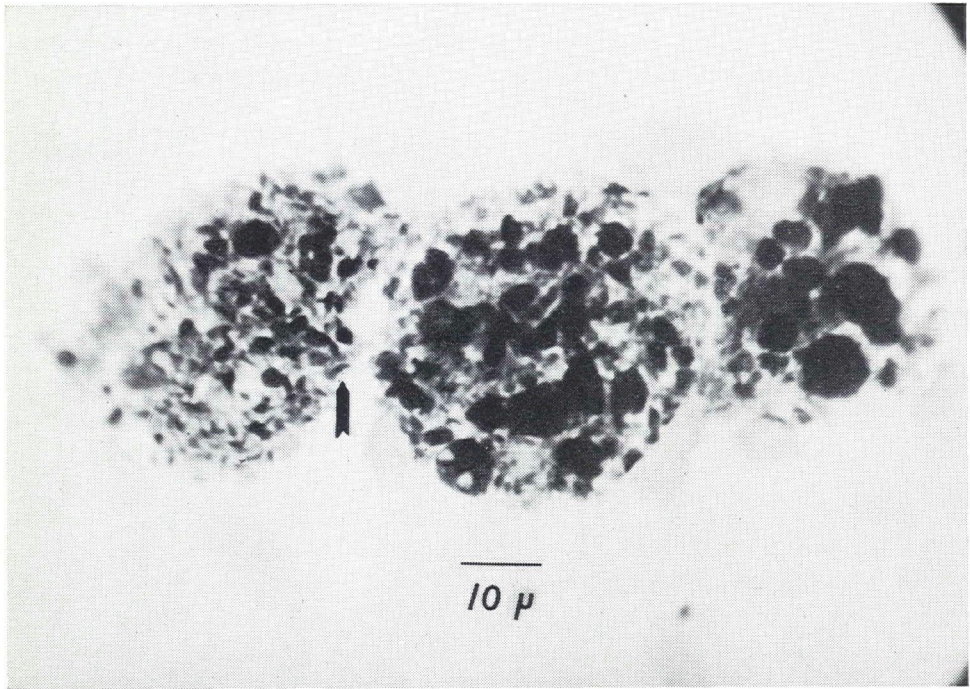


Figure 1

Three SPC cells aligned in an imprint from a peroral jejunal mucosa biopsy. The PAS-positive inclusions, actually a brilliant magenta, appear black in this reproduction. Arrow indicates a typical sickle-form particle in the cell at left. Larger, denser, amorphous clumps appear in cells at center and right. Periodic acid-Schiff, 1320x.

Clusters of SPC cells may occupy the connective tissues of the heart valves, the epicardium, and the myocardium. Endocardial vegetations, occasionally observed in Whipple's disease, are made up, in part, of agglomerations of SPC cells.

It is significant that, in the lung, SPC cells occupy the positions of the so-called "septal cells" which are histiocytes representing the reticulo-endothelial system in the interalveolar septa (Figure 2). SPC cells commonly are found in the pleura.

Surprisingly abundant are collections of SPC cells in the central nervous system where they occur as ependymal nodules and scattered in the glial tissues.

Anatomic evident recently compiled^{1,6} strongly supports the contentions that Whipple's disease is a widespread, multiple system disease.

Derivation of the SPC Cell. The ubiquity of the characteristic SPC cells of Whipple's disease suggests that they are derived from cellular elements normally present in tissues throughout the body. The alternative explanation by metastasis seems unlikely because the anatomic distribution of SPC cells fits neither that of lymphatic nor of hematogenous spread from a single focus.

The elemental cell system which includes all of the sites in which SPC cells have been identified is the reticulo-endothelial system. We suggest, in a manner of

speaking, that the forefather of the SPC cell is the reticulo-endothelial stem cell, that its cousins are plasma cells and lymphocytes, and that its better known siblings go by the names of histiocytes, macrophages, and clasmatocytes, among others.

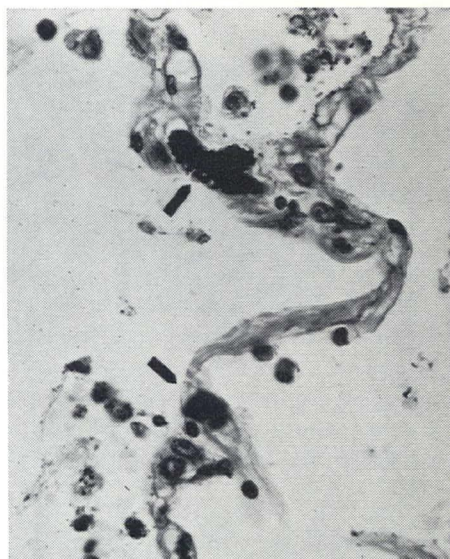


Figure 2

SPC cells (arrows) occupying the interalveolar septa of lung in Whipple's disease. Periodic acid-Schiff, 250x.

THE PAS-POSITIVE SUBSTANCE

In electron micrographs of SPC cells, the intracytoplasmic inclusions, which correspond to those reacting to the PAS technic at light microscopy, appear in 2 forms (Figure 3). The sickle-form particles are readily identified by their commensurate size and shape. Where by light microscopy these particles appear homogeneous, by electron microscopy they are seen to be made up of clusters of minute vesicles or labyrinthine networks surrounded by limiting linear densities or "membranes". The inclusions which appear as amorphous clumps or strands of PAS-positive material by light microscopy are seen in electron micrographs as innumerable, densely packed, minute, cylindrical bodies. The cores of these minute bodies appear relatively clear, *i.e.*, they exhibit little affinity for the osmium fixative, while their shells are dense and, hence, osmiphilic. Each cylindrical body is surrounded by a fine membrane. These observations, first made in this laboratory, have been subsequently confirmed by Cohen and his co-workers at the Massachusetts General Hospital¹⁰.

It is our supposition that the clusters of vesicles or reticula within the sickle-form particles represent the sites of synthesis of a protein-carbohydrate complex which then assumes the form of the densely packed, cylindrical bodies. This supposition implies that the PAS-positive substance of Whipple's disease occurs within the cells, not as a result of phagocytosis as generally believed, but rather that this substance is formed within the cytoplasm of the cells themselves.

The idea of proteinaceous elaboration by the peculiar cells of Whipple's disease was first conceived as a result of histochemical observations. In studies of the PAS-

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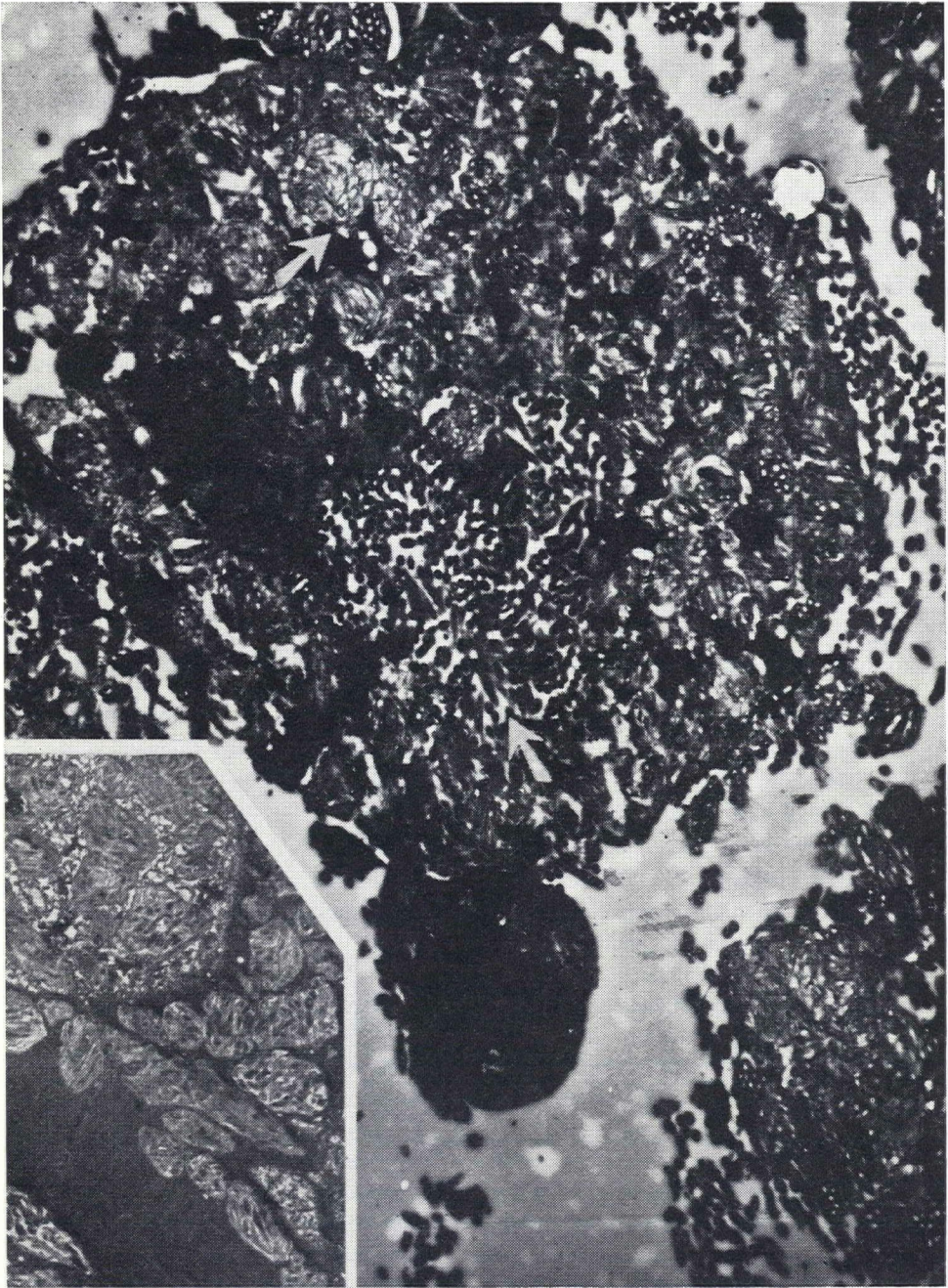


Figure 3

Electron micrographs of SPC cells illustrating the 2 forms in which the protein complex appears. The vacuolated clusters (*upper arrow* and *insert*) conform to the sickle-form particles. The aggregates of minute cylindrical bodies (seen in random sections at *lower arrow*) correspond to the amorphous cytoplasmic inclusions. Electron micrographs (about 7000x) by J. H. L. Watson, Ph.D., and Virginia Valentine of the department of physics, Edsel B. Ford Institute for Medical Research.

positive protein complex in the cytoplasm of plasma cells, Pearse¹¹ and later White¹² observed an inverse relation between the cytoplasmic content of ribonucleic acid (by pyroninophilia) and of the protein complex (by PAS-positivity). Teilum¹³ demonstrated a similar relation in the cytoplasm of reticulo-endothelial cells proliferating in response to a variety of stimuli. According to Teilum, pyroninophilia and PAS-positivity represent characteristic phases in the functional activity of these cells by which protein complexes are formed. Applying the same cytochemical technics, Taft, Liddelov, and Ralston¹⁴ in Australia reported a striking similarity in the staining reactions by the "frothy cells" of Whipple's disease to those observed in plasma cells by Pearse and by White and in reticulo-endothelial cells by Teilum. Taft *et al.* accepted this similarity as evidence that the PAS-positive substance of Whipple's disease is elaborated within the cytoplasm of the "frothy cells".

Accumulating evidence suggests, then, that the primary pathogenesis of Whipple's disease may be represented by the proliferation of peculiar SPC cells which are capable of elaborating within their cytoplasm an abnormal, PAS-positive, protein complex. The initial stimulus to this proliferation and elaboration remains unknown.

OTHER PROTEIN FORMING DISEASES

Pursuing further the concept of abnormal proteinaceous elaboration by cells derived from the reticulo-endothelial system, one can enumerate other diseases which may share this pathogenesis (Table I).

The commonest example of protein elaboration is that of antibody (globulin) formation by various cells of related origin, *i.e.*, by reticulo-endothelial cells, by plasma cells, and probably by lymphocytes, in response to infection or to antigen. In such instance, the elaboration is usually self-limited and, presumably, beneficial to the organism.

In other circumstances, the proliferation of abnormal cells and their elaboration of protein are often not controlled and represent a pathogenesis for disease. Macroglobulinemia furnishes an example in which abnormal protein substances are formed by cells proliferating, in some instances, autonomously (Mackay¹⁵). Myeloma is thought of as a neoplasm of plasma cells elaborating a type of globulin which may be deposited in visible quantities in the kidneys (Putnam,¹⁶ Sanchez and Domz¹⁷). Myeloma, in turn, has been related to primary systemic amyloidosis on the basis of the proteinaceous material deposited in various tissues (Kyle and Bayrd¹⁸). Pulmonary alveolar proteinosis (Rosen *et al.*,¹⁹ Harrison *et al.*²⁰) is a relatively newly described condition in which a copious proteinaceous substance may be formed by the interalveolar "septal cells" which, it has been noted, occupy the same situation where SPC cells have been identified in Whipple's disease. Other conditions in which a similar pathogenesis may pertain include the reticuloendothelioses, certain hemolytic anemias (Osgood,²¹ Sen Gupa *et al.*²²), Hurler's disease (Jermain *et al.*²³), and colonic histiocytosis in children (Rowlands and Landing²⁴).

Obviously these various disease states are not characterized by a proliferation of precisely the same cells or by elaboration of the same protein complexes. The very fact that the cellular proliferations and their products are distinctive makes more

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TABLE I

Suggested examples of protein forming diseases.

Protein Substance	Probable Source	Disease
Antibody globulin	R-E cells plasma cells lymphocytes	various infections
Macroglobulin	lymphoid cells	macroglobulinemia
Myeloma protein	plasma cells	myeloma
Amyloid	plasma cells	primary amyloidosis
A mucopolysaccharide	septal cells	pulmonary alveolar proteinosis
A mucopolysaccharide	SPC cells	Whipple's disease

attractive the applicability of certain features of Burnet's clonal selection theory²⁵ as a possible mechanism leading to specific disease. In this concept, stated briefly, a potential variety of cells exists, ultimately derived from the reticulo-endothelial system, any one of which is capable, under an appropriate antigenic stimulus, of proliferating as a peculiar "clone" and of elaborating a specific, abnormal, protein substance. As such, a variety of diseases — of diverse etiologies, of diverse manifestations, and of diverse courses — might conceivably share a common pathogenesis.

SUMMARY

Whipple's disease is submitted as a prototype of an emerging concept of disease which is characterized by the proliferation of peculiar cells, seemingly derived from the reticulo-endothelial system, and elaborating within their cytoplasm abnormal protein substances.

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