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This Week's Citation Classic

Bruni C & Porter K R. The fine structure of the parenchymal cell of the normal rat liver. I. General observations. *Amer. J. Pathol.* 46:691-755, 1965.
[Biological Laboratories, Harvard University, Cambridge, MA]

A group of observations, described for the first time in this report, is taken to indicate that liver secretory proteins are segregated by the membranes of the rough endoplasmic reticulum (RER). After transfer into the smooth endoplasmic reticulum (SER) and, subsequently, into the Golgi system, they are finally carried to the space of Disse by way of Golgi-released vacuoles. [The SCI® indicates that this paper has been cited in over 370 publications since 1965.]

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"This electron microscopic study of the normal mature rat hepatocyte, carried out in Porter's laboratory at Harvard University, was in part generated by our interest in searching for morphological expressions of the transport of liver secretory proteins into the bloodstream. For instance, according to biochemical studies,[1] liver albumin was synthesized by the ribosomes of the rough microsome fraction, but before final extrusion became associated with the smooth microsome fraction. Prior to 1965, very little work had, however, been published to clarify this transitional step at the level of cell fine structure.

"First, we saw that the lumen of the cisternae of the rough endoplasmic reticulum (RER) contained two kinds of substances, interpreted by us as proteins that had been synthesized by the membrane-associated ribosomes: one substance was in the form of highly electron dense spherical particles (30-100 nm in diameter), the other in the form of less dense fine fibrils. Second, the two types of substances detected within the RER were also detected within vesicles of the smooth endoplasmic reticulum (SER) and within the peripheral portions of the cisternae of the Golgi system. In this latter location, however, the granules often appeared to be remarkably more numerous than in the elements of the ER. This observation was in accordance with the concept that the Golgi apparatus plays a role in packaging proteins for export. Subsequently, granule-containing vacuoles were seen to lose continuity with the Golgi complex and to make contact with the hepatocyte plasma membrane at the space of Disse. Finally, this space was found to contain granules identical to those seen within membranous systems in the cytoplasm. Several blood proteins are known to be formed in the liver. It was not possible, however, to determine which proteins were segregated within the membranous cytoplasmic systems in our study, as we had used electron microscopic techniques alone. Nevertheless, it was speculated that the granules were representative of aggregates of albumin, but other possible interpretations were not ruled out.

"After publication of our report, investigations from other laboratories, using electron microscopy in conjunction with biochemical or immunological procedures to identify the products of liver secretory activity, were led to recognize that the granular material represented very low density lipoproteins[2] rather than aggregates of albumin. It was, however, similarly recognized and recently confirmed[3] that liver secretory proteins, both simple, like albumin,[3,4] and complexed either to lipids or carbohydrates,[5] all follow the pathway of transport formed by the RER, SER, and Golgi apparatus. We therefore think that a reason for the frequent citation of our report is that it clearly illustrated for the first time the basic fine structural aspects of the transport of blood liver proteins into the bloodstream. Other reasons were that the report enlarged on the role of the Golgi apparatus in separating proteins for export from proteins for intracellular use and that it presented both a description of additional previously unreported findings in the rat hepatocyte and an extensive review of earlier fine structural studies of this cell type."

1. **Peters T, Jr.** The biosynthesis of rat serum albumin. II. Intracellular phenomena in the secretion of newly formed albumin. *J. Biol. Chem.* 237:1186-9, 1962.
2. **Jones A L, Ruderman B B & Herrera M G.** Electron microscopic and biochemical study of lipoprotein synthesis in the isolated perfused rat liver. *J. Lipid Res.* 8:429-46, 1967.
3. **Yokota S & Fahimi H D.** Immunocytochemical localization of albumin in the secretory apparatus of rat liver parenchymal cells. *Proc. Nat. Acad. Sci. US—Biol. Sci.* 78:4970-4, 1981.
4. **Peters T, Jr., Fleischer B & Fleischer S.** The biosynthesis of rat serum albumin. IV. Apparent passage of albumin through the Golgi apparatus during secretion. *J. Biol. Chem.* 246:240-4, 1971.
5. **Jamieson J C & Ashton F E.** Studies on the acute phase of proteins of rat serum. IV. Pathway of secretion of albumin and α_1-acid glycoprotein from liver. *Can. J. Biochem.* 51:1281-91, 1973.