LIPID DROPLETS

Lipid droplets (LDs) are neutral lipid-containing structures that play an essential role in energy storage and also have additional functions. In addition to being a major structural component of adipocytes (cf. Figs. 164 and 165), they are ubiquitous organelles and their number and size in non-adipocyte cell types can vary greatly. For instance, in liver hepatocytes they are impressively increased following nutritional overload, tissue hypoxia, and poisoning.

By conventional electron microscopy, lipid droplets (LD) are observed as spherical bodies with a rather homogenous content (panel A). Depending on cell type, the core of the lipid droplets consists of varying ratios of triglycerides and cholesterol and of diacylglyceride. Lipid droplet phospholipids are phosphatidylcholine and lysophosphatidylcholine, phophatidylethanolamine and lysophophatidylethanolamine, and phosphatidylinositol. Lipid droplets are limited by a single phospholipid layer, as shown in panel B from cryo-electron microscopic analysis of isolated lipid droplets and as schematically depicted in panel C. Hence, no distinct limiting membrane can be observed by conventional electron microscopy. This is in contrast to other cytoplasmic organelles that are surrounded by a phospholipid bilayer (panels D and E), which can be seen as a double-layered unit membrane. It is generally assumed that the proteins of lipid droplets such as perilipin, adipocyte differentiation-related protein (ADRP), and TIP47 (named PAT proteins) as well as caveolin-1 and a variety of other proteins are embedded in their surface.

For the biogenesis of lipid droplets, various models have been proposed. It is generally agreed that the endoplasmic reticulum is the site of lipid droplet formation, although the initial stage of formation has not convincingly demonstrated by electron microscopy. Panel F illustrates the intimate relationship between the two organelles. The endoplasmic reticulum (ER) forms what is called an ApoB-crescent (arrowheads in panel F) upon immunohistochemical localization of adipocyte differentiation-related protein (ADRP) and apolipoptotein B-100. The ApoB-crescent should not be confused with contact sites between endoplasmic reticulum and lipid droplets (cf. Fig. 97). Panel G depicts schematically two proposed models of lipid droplet biogenesis. They have in common the presence of a tiny lipid ester droplet between the inner and outer phospholipid leaflet of the ER membrane. This lipid droplet leaves the ER either by a budding-fission process, which is currently widely accepted, or by hatching. In either case, the cytoplasmic phospholipid leaflet forms the surface phospholipid layer of the lipid droplet.

Figures A–G from Fujimoto et al. (2008) Histochem Cell Biol 130:263.

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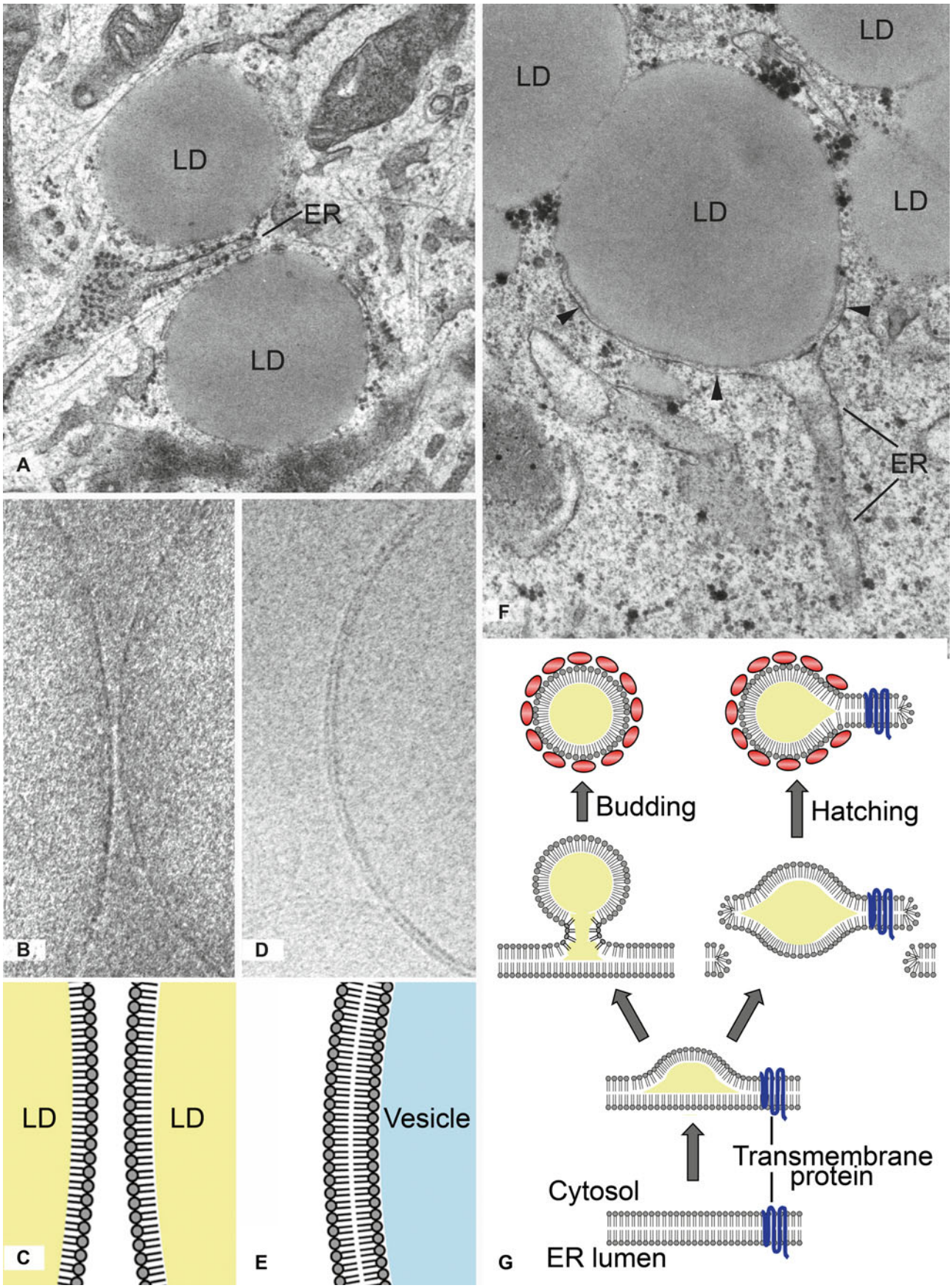
Magnification: ×45,000 (**A**); ×300,000 (**B**, **D**); ×32,500 (**F**)


LD
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Budding
Hatching
Transmembrane protein
Cytosol
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GLYCOGEN

Glucose is an important source for energy, and glycogen is its cellular storage form, which is most abundant in liver and muscle. Glycogen is found in the cytoplasm in the form of granules ranging from 10 to 40 nm in diameter, the so-called β particles, which are typical for muscle cells. In hepatocytes, the β particles assemble to form characteristic rosettes of glycogen, the α particles (arrows). The α particles do not consist solely of glycogen but additionally contain various enzymatic proteins involved in the synthesis of glycogen, hence the name glycosomes. During glycogen synthesis, glycogenin, which initiates the synthesis, and glycogen synthase, which elongates the glucose chain, form a complex with glucose.

The glycosomes are often closely related to the smooth endoplasmic reticulum. The smooth endoplasmic reticulum contains glucose-6-phosphatase, which is involved in the final step of breakdown of glycogen and hydrolyses glucose-6-phosphate to glucose and phosphate. Remarkably, this enzyme is present in high levels only in liver, kidney, and the insulin-producing pancreatic beta cells. Inherited deficiency of this enzyme results in a glycogen storage disease (see below).

M: mitochondrion; PO: peroxisome

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GLYCOGENOSIS TYPE I

As has been described, the biosynthesis and breakdown of glycogen are complex. Equally multifaceted are the inherited disorders of glycogen metabolism, of which more than 12 disease types are presently known.

The type I glycogen storage disease (glycogenosis type I, glucose-6-phosphatase deficiency, von Gierke's disease) is an autosomal recessive trait that is caused by deficiency of glucose-6-phosphatase activity. The disease may be caused by a partial or complete deficiency of the catalytic enzyme subunit or the entire enzyme. The gene coding for the enzyme has been mapped to chromosome 17q21 and that for the translocase to chromosome 11q23. Mutations that affect the transmembrane domain of glucose-6-phosphatase cause more severe reduction in enzyme activity than mutations in one of the two luminal loops. Interestingly, ethnic-specific mutations have been found.

By electron microscopy, the glycogen deposits are observed as glycogen particles in the cytosol of the hepatocytes (panel B). These deposits are massive and fill most of the cytoplasm of the hepatocytes. Structurally similar cytosolic glycogen depositions occur in the other types of glycogen storage diseases, with the exception of one lysosomal glycogen storage disease (cf. Fig. 73A). The accumulation of glycogen occurs in liver, kidney, and intestinal mucosa and causes hypoglycemia and lactic acidosis. The treatment is directed to establish and maintain normal blood glucose concentrations by special nutritional regimen.

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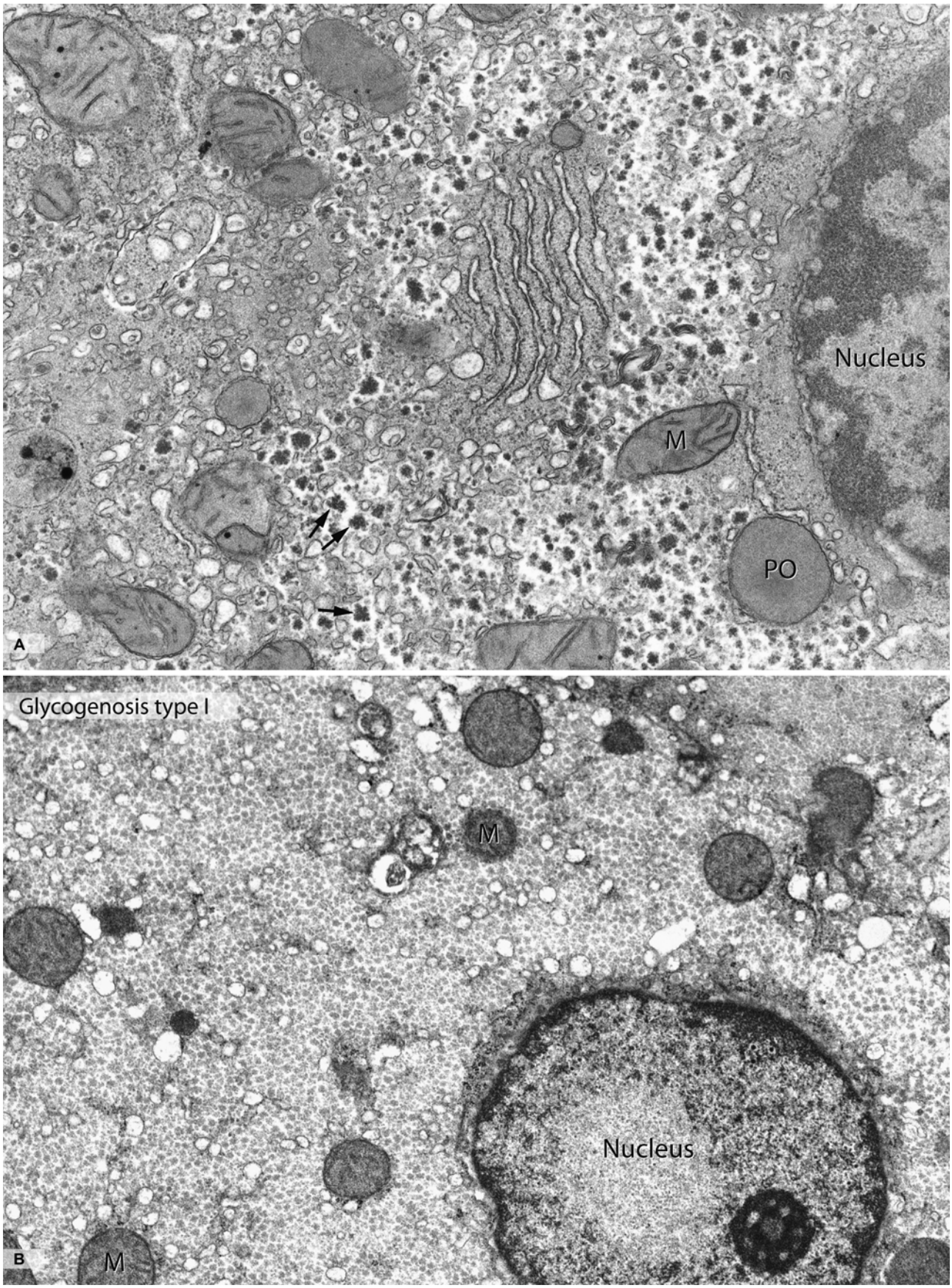
Magnification: ×23,500 (**A**); ×7,200 (**B**)


Nucleus
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Glycogenosis type I
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ERYTHROPOIETIC PROTOPORPHYRIA

This is an autosomal dominant disease in which a partial deficiency of the enzyme ferrochelatase is the causative defect. Ferrochelatase is present in the inner mitochondrial membrane and is the last acting enzyme in the heme biosynthesis. It inserts the iron into protoporphyrin IX to yield the heme. The gene locus coding for the enzyme is at chromosome 18q23.1 and a whole spectrum of disease-causing mutations has been detected in all 11 exons. In patients, protoporphyrin accumulates in the erythroid cells of bone marrow and circulating erythrocytes, is elevated in the plasma, bile, and feces, and can cause cutaneous photosensitivity.

The liver is affected in a minority of patients, giving rise to characteristic hepatobiliary complications. By electron microscopy, numerous starburst, crystalline inclusions of varying sizes (arrows) are found in the cytoplasm of hepatocytes. These characteristic inclusions are composed of a filamentous crystalline material. They are also present in Kupffer cells, bile ductal epithelia, and ductal lumen as well as bile canalicular lumens.

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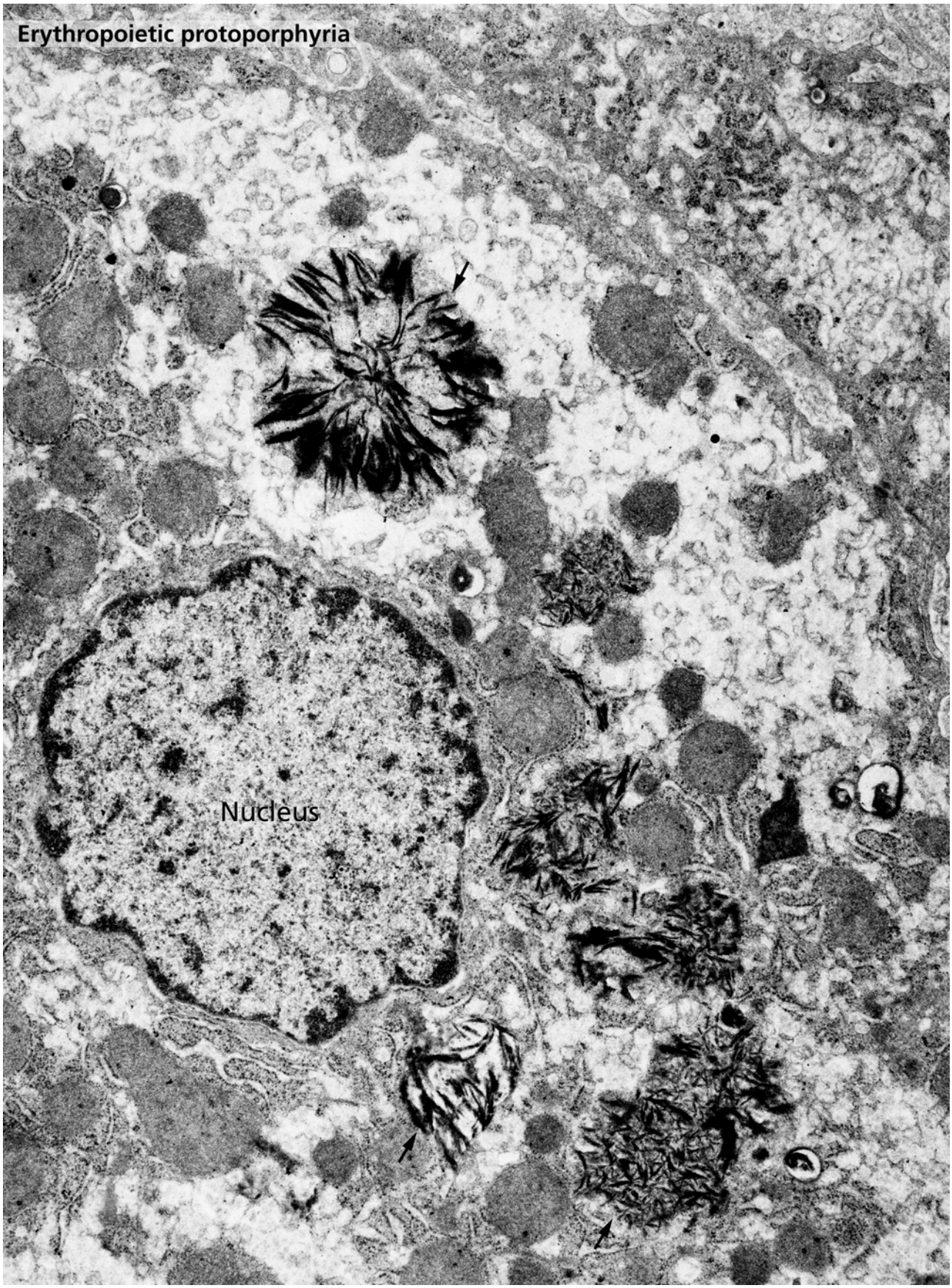
Erythropoietic protoporphyria
Nucleus