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of Porter's) confirm that Porter was correct in his intuition, if not his details. "The cytoplasm is 'Porterplasm'—a beautiful spongework with organelles suspended in it," says Heuser of his latest freeze-dried, frozen thin sections of cells. However, the soluble components are so densely packed that the overall structure is still difficult to discern.

Porter himself best described the EM conundrum: "In the strictest sense, of course, the content of the images is all artifact where the usual procedures are employed. The question is one of equivalence. To what extent do the images represent what was in the [cytoplasm] when the fixative was applied, and to what extent may these images be used to investigate the form and function of this part of the cell?" **KP**

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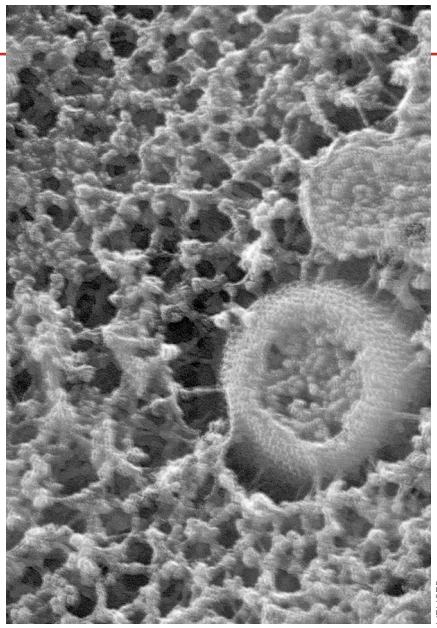
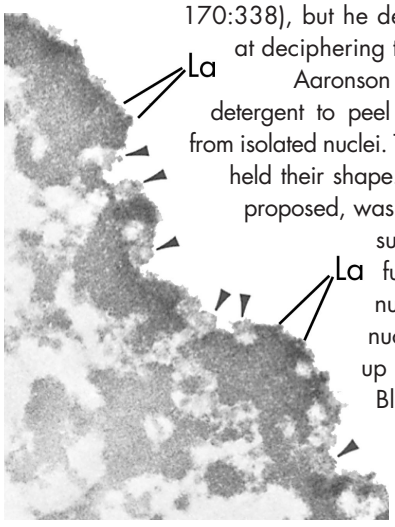


HEUSER

Heuser's more modern view of cytoplasmic structure.

The isolation of the nuclear lamina

The number of monikers early cell biologists attached to the nuclear lamina reflected their uncertainty about its function and architecture, and whether it was widespread or confined to a few specialized cells. Electron micrographs often disclosed a layer of varying thickness nestled against the backside of the nuclear membrane, which various researchers dubbed the "dense lamella," "fibrous lamina," "zona nucleum limitans," or just plain "lamina." Günter Blobel (Rockefeller University, New York, NY) had his mind on the signal hypothesis, for which he won the Nobel Prize in 1999 (see "Lost in translation: the signal hypothesis" *JCB* 170:338), but he decided to take a crack at deciphering the lamina.



BLOBEL

An immunoperoxidase stain that tags one lamina protein doesn't penetrate the nucleus ("La" indicates the lamina; arrows mark nuclear pores).

Aaronson and Blobel (1974) used detergent to peel away the membranes from isolated nuclei. The husks that remained held their shape. This sturdy layer, they proposed, was the lamina, and the results suggested two of its functions—bracing the nucleus and cradling the nuclear pores. Two follow-up studies (Aaronson and Blobel, 1975; Dwyer and Blobel, 1976) provided more evidence that the layer they had identified enclosed the nucleus and wasn't just part of the membrane.

Then Larry Gerace (Scripps Research Institute, La Jolla, CA), Blobel's first Ph.D. student, picked up the analysis. He wanted to definitively describe the lamina in part because of what he viewed as the erroneous conclusions of Berezney and Coffey (1977). They had proposed that proteins not only formed the lamina but also a "nuclear matrix" that extended throughout the nucleus and intermingled with the DNA. "Our localization was a riposte to their conclusions," Gerace says. He characterized three lamina proteins and created antibodies against them. Immunoperoxidase staining showed that the antibodies strongly labeled the rim of the nucleus; they didn't recognize anything in the interior (Gerace et al., 1978). Rather than a mesh that permeated the nucleus, the lamina was a protein polymer that hugged the nuclear membrane, the researchers concluded—and subsequent work has backed them up.

The proteins Gerace identified turned out to be lamins A, B_1, and C, three of the four major components that interweave to form the lamina. "We felt we had made a conclusive argument that lamins are primarily at the nuclear envelope, and the data have held up," says Gerace. Blobel describes this series of studies as one of the first examples of molecular cell biology. Instead of being content to identify new cellular structures, researchers were now breaking down these discoveries into their molecular components to elucidate their workings. **ML**

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