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This Week's Citation Classic

Hruban Z, Spargo B, Swift H, Wissler R W & Kleinfeld R G. Focal cytoplasmic degradation. *Amer. J. Pathol.* **42**: 657-83, 1963.

An intracellular process consisting of the sequestration of cytoplasmic components followed by the formation of complex dense bodies, which correspond to the lysosomes of biochemists, is established by ultrastructural studies. This natural process is enhanced by cellular injury. The noxious agent codetermines the structure of the bodies. [The *SCI*® indicates that this paper has been cited 274 times since 1963.]

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"While studying the ultrastructural changes induced in hepatocytes and pancreatic acinar cells by phenylalanine analogs, I observed a series of changes which I interpreted as the stages of a process. The results presented at the Federation meetings and the American Association of Pathologists and Biologists meetings in 1961 brought encouragement from Drs. Hans Popper and W. Bernhard. Full length articles appeared the next year. The principal finding was that damaged organelles are sequestered by membranes and degraded. The observed structures were interpreted as stages of a process which is beneficial in repairing cellular injury, and as stages in the formation of lysosomes. This interpretation changed the static concept of the lysosome as a particle into the dynamic concept of a degradative process. Rather than particles causing injury, lysosomes became byproducts of the cellular reaction to injury. We realized that focal degradation (FCD) is a general reaction of the cell to injury (starvation, deficiency, hypoxis) and reported it in the 'Classic' article.

"The relation of focal degradation to atrophy **and** phagocytosis was presented in *Federation Proceedings* in 1964, in an article equally frequently quoted.[1] Morphologists and pathologists responded positively to the new concept, but the dynamic concept of the lysosome as a process remains foreign to some biochemists even today. The term FCD has since been replaced by the simpler term autophagy.

"The results of our early morphological studies at the University of Chicago confirmed our belief that sequential ultrastructural studies at short time intervals and the arrangement of the images in logical sequences open new avenues for a dynamic interpretation of physiological and pathological processes which can not be fully understood by biochemistry alone. The application of these principles to studies of cellular alterations, as originally described in the 'Classic,' led to the concept of myeloid bodies, which are lysosomes sequestering amphophilic drugs bound to membranes. Although the full description of myeloid bodies appeared in 1965, the basic idea of drug-induced lysosomal changes was accepted slowly and has only recently been considered in drug safety evaluation. Other dynamic concepts arising from morphological investigations are the concept of nonlysosomal cytoplasmic degradation intranuclear layered inclusion (topolysis) and the concept of altered membrane flow, which accounts for the formation of in-tracytoplasmic vacuoles, the invaginations of cell membrane and the formation of cytoplasmic bullae.

"Looking back on morphological research in general, we find that in recent years many morphologists have been eliminated from active basic research by the denial of research grants, while a quasi-supernatural power is often attributed to pure biochemistry. The article on focal cytoplasmic degradation should continue to remind us that morphological studies yield interpretations as dynamic as those of other disciplines."

REFERENCE

1. **Swift H & Hruban Z.** Focal degredation as a biological process. *Fed. Proc* **23**:1026-37, 1964.