CC/NUMBER 15
APRIL 13, 1981

This Week's Citation Classic

Weissmann G. Lysosomes and joint disease. *Arthritis Rheum.* **9**:834-40, 1966. [Department of Medicine, New York University, School of Medicine, New York, NY]

The hypothesis is presented that lysosomal constituents are released from phagocytic cells following direct injury or endocytosis of immune complexes. Lysosomal enzymes, chiefly proteases, provoke acute inflammation and degrade extracellular structures, including the proteoglycans of cartilage. This view implies that tissues such as the joint destroy themselves by a 'final common pathway' under stimuli that vary from disease to disease. [The ***SCI***® indicates that this paper has been cited over 165 times since 1966.]

Gerald Weissmann
Department of Medicine
School of Medicine
New York University Medical Center
New York, NY 10016

March 18, 1981

"This article was a summary of work carried out at New York University (with Lewis Thomas), and the Strangeways Research Laboratory in Cambridge (with John Dingle and Honor B. Fell). By 1966, we had con-cluded that lysosomes could play a role in tissue injury, although we were ignorant of the exact means whereby their corrosive intracellular ferments were extruded from cells. In this review, the hypothesis was first articulated that cells such as granulocytes, macrophages, or synovial lining cells might release lysosomal enzymes consequent to their encounter with immune complexes or urate crystals.

"It has required another decade of experimental work to validate this youthful restatement of Metchnikoff's contention, that 'the organism digests materials which it encounters outside the gastrointestinal tract by means of an inflammatory reaction.'[1] But, I presume that the heuristic value of this 1966 article was due to the encapsulation, for the clinician, of the previous decade's analysis of the lysosomal apparatus, by Christian de Duve, Alex Novikoff, Zanvil Cohn, and James G. Hirsch.[2] It carried, as a long footnote, definitions of such lysosomal neologisms as 'endocytosis,' 'autophagy,' 'heterophagy,' 'phagolyso-some,' and 'residual body.' It was also suggested that anti-inflammatory steroids, by interacting with biomembranes, would diminish extrusion of lysosomal contents.

"The major hypothesis elaborated in this review has since been appropriately tested in our own, and other, laboratories. Indeed, phagocytic cells exposed to particulate invaders or immune complexes secrete lyso-somal enzymes by a process now termed 'regurgitation during feeding,' whereas their encounter with crystals such as monosodium urate leads to 'perforation from within' the intracellular gastrointestinal tract. The interaction of *neutral* proteases from lysosomes (elastase, cathepsin G) with circulating, inflammatory materials (complement, kinin, and clotting cascades) has become partially elucidated. Finally, the role of these proteases in degrading extra-cellular matrices has been carefully documented.

"It is surprising that this speculative review, in a journal devoted to my clinical subspecialty, has proved useful to so many. Especially, I might add, for younger investigators, since Dingle and I had submitted a similar hypothesis to the same journal five years earlier. It was rejected with the (proper) advice that we do more experiments, and the (improper) suggestion that the lysosome was an artifact of the biochemical literature. Claude Bernard once compared the process of science to a progression from a warren of dark and busy kitchens to an occasional, brilliantly-lit hall. Busy in the kitchen of the 1970s, it is reassuring to have once passed fairly close to a bright salon.

"Although I have been informed that the most highly cited paper from my laboratory is 'Studies on lysosomes,'[3] it was not until 1966 that it became possible to extend this experimental work in rabbits to an analysis of human disease. A recent summary of these developments has been published by J.E. Smolen, H.M. Korchak. and myself."[4]

1. **Metchnikoff E**. *Immunity in infective diseases.* London: Johnson Reprint Co. (reprinted from Cambridge Univ. Press, 1905 edition), 1968. p. 210.
2. **de Duve C**. The lysosome in retrospect. (Dingle J T & Fell H B, eds.) *Lysosomes in biology and pathology.* Amsterdam: North Holland, 1969. Vol. I. p. 3-42.
3. **Weissmann G & Thomas L.** Studies on lysosomes. I. The effect of endotoxin, endotoxin tolerance, and cortisone on the release of acid hydrolases from a granular fraction on rabbit liver. *J. Exp. Med.* **116**:433-50, 1962. [The *SCI*® indicates that this paper has been cited over 385 times since 1962.
4. **Weissmmn G, Smolen J E & Korchak H M.** Release of inflammatory mediators from stimulated neutrophils. *N. Engl. J. Med.* **303**:27-34, 1980.