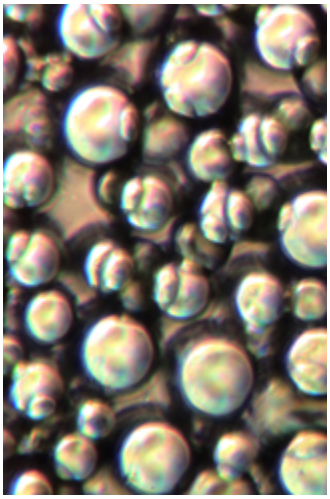
Rodbell First Step

The First Step: Isolating Single Cells

In the mid-1960s, Rodbell was studying enzymes. At that time, the only test medium available was crude chunks of fat tissue. To get more precise results, Rodbell developed a method for isolating single fat cells from the fat tissue. Because fat floats, Rodbell first put the minced tissue in a liquid and then treated the floating cells with a substance called collagenase to separate the fat cells from other cells.

> *"Great," he shouted, but are they viable cells?"*
>
> - *–Bernardo Houssay*

Martin Rodbell, 1966 Courtesy of the Rodbell Family



Fat cells isolated by Rodbell's method. Courtesy of Dr. May-Jan Zarnowski and Dr. Joseph Brzostawski, NIDDK

This Week's Citation Classic

CC/NUMBER 45
NOVEMBER 10, 1980

Rodbell M. Metabolism of isolated fat cells. I. Effects of hormones on glucose metabolism and lipolysis. *J. Biol. Chem.* 239:375-80, 1964.
[Laboratory of Nutrition and Endocrinology, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, MD]

A homogeneous preparation of isolated fat cells was prepared by treating adipose tissue with collagenase. The isolated fat cells were very sensitive to the actions of insulin on glucose metabolism and responded to a variety of lipolytic hormones with increased production of fatty acids. [The *SCI*® indicates that this paper has been cited over 1,485 times since 1964.]

Martin Rodbell
Laboratory of Nutrition
and Endocrinology
National Institute of Arthritis,
Metabolism, and Digestive Diseases
National Institutes of Health
Bethesda, MD 20014

October 14, 1980

"This paper was a turning point in the direction of my research career. Prior to this study, I had been concerned principally with the structure of lipoproteins and the mechanism by which chylomicrons were metabolized by liver and adipose tissue. It was during a sabbatical year with Brachet and Gaillard that I became interested in the metabolism and differentiation of animal cells in culture. From that experience I learned how important it was to have a single cell type and a chemically defined medium for such studies.

"From previous experience, I realized that adipose tissue was appropriate material for two reasons. Firstly, the metabolism of adipose tissue was known to be affected by a number of hormones. Secondly, adipose cells, being laden with fat, should be easily separated from other tissue cells since they should float to the surface once liberated from the tissue. On returning to NIH, my first task was to find some means of dispersing the tissue in a manner that would release the cells without affecting their normal behaviour toward hormones. I knew from earlier cytochemical studies that adipose cells were embedded in a matrix of collagen fibers, which suggested that digestion of the collagen might liberate fat cells. Fortunately, a commercial preparation of crude collagenase was available for testing purposes (fortunately, also, that it was a crude enzyme since later studies showed that purified collagenase doesn't work).

"I recall vividly the first experiment, since Houssay was visiting the laboratory that day and observed with me the gradual digestion of the tissue and the release of the pearl-like objects of my desire. 'Great,' he shouted, 'but are they viable cells?' I replied by suggesting that the effects of insulin on glucose metabolism should be an excellent test of their viability. This was demonstrated a short time later. Immediately I recognized the importance of this finding since, until then, the actions of insulin were observed only with intact tissues. Moreover, the isolated cells were responsive to extraordinarily low concentrations of the hormone. From that time onward I have remained committed, for better or for worse, to investigate the molecular basis by which hormones interact with cell surface receptors and thereby alter the physiology and structure of their target cells.

"Peculiarly, the rat fat cell responds to numerous types of hormones. Thus, it is virtually a 'gold mine' for studies of hormone action. Moreover, unlike its tissue counterpart, the isolated fat cell is exposed directly and uniformly to ingredients in the incubation medium, thus providing the means of testing the effects of various agents on cell surface receptors. Undoubtedly, these are the primary reasons why the isolated fat cell preparation has been employed so often in studies of hormone action.

"Naturally, I am gratified by the response to this paper. With hindsight, it was a simple, straightforward exercise. Apparently, it often happens that a simple idea can engender consequences that are far beyond the intent."

© 1980 by ISI®

Rodbell's 1980 commentary on his 1964 paper, which became a "Citation Classic."
Reproduced with Permission from ISI (R). Original material published in Current Contents, Number 45, November 10, 1980

To confirm for the Nobel laureate Bernardo Houssay, who was visiting Rodbell's laboratory, that these cells were viable, Rodbell showed that the cells reacted normally to the hormone insulin. This was a turning point in his career—Rodbell's focus shifted from studying the metabolism of fat to examining the actions of hormones.

> *"Apparently, it often happens that a simple idea can engender consequences that are far beyond the intent."*
>
> - *–Martin Rodbell*

The procedure for isolating fat cells was a boon to hormone research, because fat cells respond to a wide variety of hormones. No one before had been able to study hormones' effects on cells this way. Many researchers began using Rodbell's method, making his paper "The Metabolism of Isolated Fat Cells" one of the most widely cited in the field.

Rodbell's Inspiration: Sutherland's Second Messenger