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# The Beginnings of an Endocrinologist

During my graduate studies I never had courses in endocrinology and pharmacology. Expressions such as "dose-response," "desensitization," "agonist/antagonist," in fact, all expressions relating to physiology were alien to my ears. I was a biochemist bred to believe in the reductionist philosophy of science, still much in vogue today. Grind, extract, purify, and reconstruct were the keys words in my lexicon. Nature, in all its mystery, was at my feet waiting to be dismembered into its constitutive parts and, as with any organic chemistry problem, reassembled as proof of one's unerring biochemical skills. That philosophy for me was dramatically altered several years later when I attempted to investigate whether fat cells were the source of lipoprotein lipase present in adipose tissue. I discovered that fat cells, which float because of their fat content, could be isolated from other cells by treatment with commercial preparations of collagenase (1). The fat cells contained lipoprotein lipase. My good fortune was that Bernardo Houssay, the great Argentine physiologist and Nobel Laureate was visiting my lab the day of the first successful experiment. "How do you know these are viable cells?", he queried. "Of course they are, just look under the microscope," I replied. "No," he said, "I will not be satisfied unless you can demonstrate that they are subject to the actions of hormones, such as insulin, that are known to act on adipose tissue." Down the hall I went to ask Sid Chernick and Bob Scow how to determine the actions of insulin. Two days later I had devised a means of collecting radioactive $CO_2$ released by the metabolism of glucose-1-$^{14}$C and demonstrated that insulin strikingly increased the amount released. I was nonplussed. Dr. Houssay was ecstatic. Apparently, this was the first demonstration that insulin acts on individual cells. Practically overnight I had become an endocrinologist; of sorts, that is. It was the guidance and inspiration of Robert Williams, the head of the Department of Endocrinology at the University of Washington, who inspired me to rethink my strategies in exploring the living process. No more grinding, extraction, and purification. Treatment of cells with phospholipases and other enzymes, preparation of fat cell "ghosts," and purification of cell membranes were the cautious, step-by-step means of exploring at what level of cell dismemberment insulin's actions remained. By 1967 I knew that the plasma membrane had to be the initiating site of action, but there my investigative prowess ended. The next momentous change for me came when Sutherland lectured at NIH about the enzyme adenyl cyclase (now adenylate or adenylyl cyclase). Aided by an assay of the enzyme's activity developed by Gopal Krishna, Lutz Birnbaumer, my first post-doc, and I discovered that the adenyl cyclase system in rat adipocytes was activated by several different hormones, acting through distinctive receptors, on what appeared to be a common enzyme (2). Moreover, the hormones increased the affinity of the system for Mg ions (3). Intrigued by these findings, we considered it likely that there is some common, Mg-dependent element that intervened between the receptors and enzyme and which could accommodate a system having so many "angels on a pinhead." At this point, Oscar Hechter entered into my life with long, wonderful discussions about cybernetics. Out of this came the transduction model of hormone action (4). Experimental evidence for the model came when Michiel Krans, while studying the binding of $^{125}$I-glucagon to purified rat liver plasma membranes found that glucagon binding was a slow process that was essentially irreversible, in contrast to the rapid and reversible effects of the hormone on adenyl cyclase activity found by Lutz Birnbaumer and Steve Pohl. But the medium used for the hormone-binding studies was devoid of most of the ingredients employed for the adenyl cyclase studies. By the standard biochemical technique of adding and deleting each of the ingredients, we found that ATP was the culprit. However, I knew from experience in my graduate studies that one cannot rely on the purity of commercial ATP. We tested every known purine and pyrimidine nucleotide and subsequently discovered that GTP affected the binding of glucagon to its receptors and, as importantly, was necessary for glucagon to activate adenyl cyclase (5, 6). Since those discoveries more than 20 yr ago, transduction has become a key concept for explaining the actions of hormones and drugs on membrane processes. But, as I have learned over these many years, nature cannot simply be fathomed by knowing its chemical and physical composition. The living process has evolved far beyond our knowledge of physics and chemistry. Understanding the organization and integration of

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all cellular information processing systems presents challenges that certainly will not be met in my lifetime, and perhaps never. But, at the very least, I have become, if not officially, at least in practise a full-fledged endocrinologist.

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