This Week's Citation Classic™ CC/NUMBER 50 DECEMBER 10, 1984

Kahn C R, Flier J S, Bar R S, Archer J A, Gorden P, Martin M M & Roth J.
The syndromes of insulin resistance and acanthosis nigricans. Insulin-receptor disorders in man. *N. Engl. J. Med.* **294**:739-45, 1976.
[Diabetes Branch, Natl. Inst. Arthritis, Metabolism, and Digestive Dis., NIH, Bethesda, MD and Dept. Pediatrics, Georgetown Univ. Sch. Med., Washington, DC]

Six patients are described representing two syndromes of insulin resistance associated with acanthosis nigricans. The Type A patients are young females with virilization and have insulin resistance due to a decrease in the number of insulin receptors on cells. The Type B patients have an autoimmune syndrome with autoantibodies to the insulin receptor. [The *SCI*® indicates that this paper has been cited in over 345 publications since 1976.]

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August 15, 1984

"Although the concept of specific cellular receptors for hormones and drugs dates back to the turn of the century, direct measurement of the receptor for peptide hormones did not become possible until 1969. When I arrived as a clinical associate at the National Institutes of Health in July 1970, most of the effort of what was then a small section on diabetes, under the direction of Jesse Roth and Phil Gorden, was devoted to defining these receptors. A colleague and I were actually assigned to work on the problem of ACTH receptors, but this proved impossible to master, moving my interest into the area of insulin receptors and driving my colleague into dermatology!

"As soon as it became apparent that insulin receptors could be defined by direct binding studies, we turned our attention to possible abnormalities in disease states. We were able to demonstrate defects in insulin binding to liver membranes from obese mice. But for human studies we were restricted to the study of circulating blood cells, and the significance of insulin receptors on these cells was uncertain.

"As the medical community recognized our interest in diseases associated with defects in insulin action, we were gradually referred several patients with syndromes of extreme insulin resistance—some requiring thousands of units of insulin per day. These were clinically challenging cases, but even more interesting in that they provided a way to test the importance of the insulin receptor. As we had hoped, when insulin binding to its receptor was measured using circulating monocytes from these patients, there was a marked decrease. Jeffrey Flier recognized the importance of the immune features in some of these patients and developed an assay to directly measure anti-receptor antibodies.

"Although the syndromes of insulin resistance and acanthosis nigricans are quite rare (about 12 cases of the Type A and 30 cases of the Type B syndrome have been identified), they are now well recognized as discrete forms of diabetes. They have also provided important insights into insulin action. The Type A patients have been shown to have a series of genetic defects in the insulin receptor molecule or its biosynthesis. The Type B patients have provided a source of anti-receptor antibodies that have been valuable probes of receptor structure and function. Thus, this is another example in which studies of a rare disease have shed light on both normal physiology and the physiology of many disease states.

"As a result of this and related studies of insulin receptors, the diabetes section grew into a large branch, and many of the fellows involved in these studies now head independent diabetes clinical and research groups at several university hospitals. This body of work has also been recognized by a number of awards given to the investigators involved, and the field of insulin receptors has grown to a size large enough for several international meetings and many written reviews."[1-3]

1. **Kahn C R.** The insulin receptor and insulin. The lock and key to diabetes. *Clin. Res.* **31**:326-35, 1983.
2. **Bar R S, Harrison L C, Muggeo M, Gorden P, Kahn C R & Roth J.** Regulation of insulin receptors in normal and abnormal physiology in humans. *Advan. Internal Med.* **24**:23-46, 1979.
3. **Olefsky J M & Kolterman O G.** Mechanisms of insulin resistance in obesity and noninsulin-dependent (Type II) diabetes. *Amer. J. Med.* **70**:151-68, 1981.

