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This Week's Citation Classic™

Bierman E L, Dole V P & Roberts T N. An abnormality of nonesterified fatty acid metabolism in diabetes mellitus. *Diabetes* 6:475-9, 1957.
[Hospital of the Rockefeller Institute and New York Hospital, New York, NY]

This paper demonstrated for the first time that insulin deficiency causes elevated levels of nonesterified fatty acids (NEFA), reversible with insulin treatment. In patients with ketoacidosis, injection of insulin caused a dramatic drop of NEFA levels paralleling the fall in blood glucose and preceding by several hours the elimination of ketone bodies. It was also demonstrated that diabetics tend to have elevated fasting NEFA levels and abnormally delayed responses to hyperglycemia induced by oral glucose or injection of glucagon. [The *SCI*® indicates that this paper has been cited in over 330 publications since 1957.]

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"This work represents one of my earliest major research papers, emerging from the first year of my research apprenticeship in the laboratory of Vincent P. Dole at the Rockefeller Institute for Medical Research (now Rockefeller University). I was offered the position there toward the end of my internship across the street at New York Hospital. Dole had just worked out a simple method for measuring the tiny concentration of nonesterified fatty acids (NEFA) in plasma,[1] and he theorized that NEFA was indeed the long sought-after high-energy fuel released from fat tissue. A single preliminary study suggested that NEFA levels were elevated in a patient with uncontrolled diabetes and that NEFA might be the precursor of ketone acids (and hence involved in the pathogenesis of diabetic ketoacidosis).

"Because of my interest in diabetes and metabolism, a research career, and temporary postponement of military service, and despite my appalling prior lack of knowledge about fat metabolism, I accepted the challenge of defining abnormalities of NEFA metabolism in diabetes. My first task was to follow the course of NEFA levels before and during treatment of patients with diabetic ketoacidosis entering the emergency room. I did the analyses myself at any hour of the day or night that the blood became available. This included laborious analyses of plasma bicarbonate levels performed on one of the early hand-operated mercury machines, developed and built by Donald D. Van Slyke and left over in the lab as part of his legacy.

"The excitement of following the decline of NEFA levels coincident with insulin treatment, and preceding the fall in blood glucose, can only be imagined. These results led directly to our animal studies demonstrating that insulin inhibits fatty acid release from fat tissue stores. The additional finding that the fall in NEFA levels after a glucose or glucagon-induced hyperglycemic challenge is impaired in diabetics not in ketoacidosis is a major topic of the cited paper. An abstract of this work was presented at the plenary session of the American Society for Clinical Investigation, and the paper generated much interest.[2]

"I think that this publication is so frequently cited because it was the first documentation that insulin deficiency causes fatty acid mobilization and elevated NEFA levels, reversible with insulin treatment. It also raised the level of awareness that the abnormal metabolic state of the diabetic patient reflected in the circulation consists of more than hyperglycemia and, in fact, suggested that abnormal regulation of fat mobilization plays an important role. These results have been amply confirmed and have stood the test of time. Furthermore, they opened up a new area of research focus in diabetes in many laboratories, and led directly to the discovery of insulin regulation of a new enzyme, hormone-sensitive lipase, in adipose tissue.[3] The fact that NEFA mobilization is an early step in the pathogenesis of ketoacidosis is now well established."[4,5]

1. **Dole V P.** A relation between non-esterified fatty acids in plasma and the metabolism of glucose. *J. Clin. Invest.* **35**:150-4, 1956. (Cited 3,710 times since 1956.)
2. **Dole V P, Bierman E L & Roberts T N.** Plasma NEFA as an index of carbohydrate utilization. (Abstract.) *J. Clin. Invest.* 36:884, 1957. (Cited 35 times since 1957.)
3. **Rizack M A.** An epinephrine-sensitive lipolytic activity in adipose tissue. *J. Biol. Chem.* **236**:657-62, 1961. (Cited 260 times.)
4. **Kreisberg R A.** Diabetic ketoacidosis: new concepts and treatment. *Ann. Intern. Med.* **88**:681-95, 1978.
5. **Foster D W & McGarry J D.** The metabolic derangements and treatment of diabetic ketoacidosis. *N. Engl. J. Med.* **309**:159-69, 1983.

