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This Week's Citation Classic

Randle P J, Garland P B, Hales C N & Newsholme E A. The glucose fatty-acid cycle: its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. *Lancet* **1**:785-9, 1963. [Department of Biochemistry, University of Cambridge, Cambridge, England]

The 'glucose fatty-acid cycle' describes the reciprocal relationship between the catabolism of glucose and lipid fuels in animals. Evidence was given that release and oxidation of lipid fuels inhibits metabolic degradation of glucose in muscles, and conversely that metabolic effects of glucose inhibit release of lipid fuels and thereby facilitate uptake and oxidation of glucose. The physiologic and pathologic significance of this concept is discussed. [The *SCI*® indicates that this paper has been cited over 800 times since 1963.]

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"My collaborators were all graduate students in the department of biochemistry at Cambridge. They have each made distinguished careers. **Peter** Garland is head of the department **of** biochemistry in Dundee, Nick Hales is head of the department of clinical biochemistry at Cambridge, and Eric Newsholme is lecturer in biochemistry and fellow of Merton College in Oxford

"As a graduate student at Cambridge, I had worked on the rat diaphragm assay for insulin and anti-insulin factors in blood plasma. This experience convinced me that the route to an understanding of the factors which modify the action of insulin in muscle was through identification of rate-limiting reactions in the tissue and of the biochemistry of their regulation. The pioneer of this general experimental approach was the late E.W. Sutherland [1]

In 1956, I had the good fortune to observe that glucose uptake and glycolysis in diaphragm muscle are in-Creased by anoxia and (provided insulin **was added) decreased by ketone bodies. Studies of the effects of anoxia between 1956 and 1961 identified membrane transport, hexokinase, and phosphofructokinase as rate-limiting reactions for glucose uptake and glycolysis in** *in vitro* **preparations of heart and diaphragm muscles. Work in the latter half of 1961 and early 1962 showed that metabolism of fatty acids (and ketone bodies) inhibited these reactions and additionally pyruvate dehydrogenase. The effects of fatty acids (and ketone bodies) were quantitatively very similar to the changes effected by starvation or induction of alloxan-diabetes in the rat.**

"In consequence, much of 1962 was taken up with obtaining evidence for increased intracellular provision of fatty acids in heart and diaphragm muscles of diabetic or starved animals. By the end of 1962, we were convinced that we had sufficient evidence to justify writing a conceptual paper on regulatory interactions between glucose and fatty-acid metabolism and their physiologic and pathologic significance. This paper was written in January 1963.

"Perhaps this paper has been cited frequently because it summarised, at an opportune moment, a phase in the development of understanding of the process of fuel selection in mammalian muscle. I hope that it adequately represented and **acknowledged the contribution of colleagues in other laboratories. The main controversy over the glucose fatty-acid cycle since then has** been **its applicability to** skeletal muscle, and **its quantitative** importance in the **whole animal.** However, recent **work by M.J. Rennie** and J. O. Holloszy has **shown its applicability** to red **skeletal muscle and re-**emphasised its importance *in vivo.*[2] **Much** of my own **work since 1963 has** been **concerned with detailed biochemical mechanisms relevant to the** general concept."

1 **Sutherland E W.** The effect of the hyperglycaemic factor of **the** pancreas and of epinephrine on **glycogenolysis.** *Recent Progr Hormone Res* **5-441**-59, 1950.

2 Rennle M J & Hollozy J O. Inhibition of glucose uptake and glycogenolysis by availability of oleate in well-oxygenated perfused skeletal muscle *Biochemical J.* ***168***:16l-70, 1977.