

**This Week's Citation Classic™**

**Hales C N & Randle P J.** Effects of low-carbohydrate diet and diabetes mellitus on plasma concentrations of glucose, non-esterified fatty acid, and insulin during oral glucose-tolerance tests. *Lancet* 1:790-4, 1963.  
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A preceding paper<sup>1</sup> described the "glucose-fatty acid cycle" and included the concept that the oxidation of lipid fuels inhibits the degradation of glucose in muscles. This paper describes investigations of normal subjects on a low-carbohydrate diet and of non-insulin-dependent diabetics, the results of which were compatible with such a mechanism operating in these two situations *in vivo*. A new possibility was suggested that the primary event in the development of diabetes could be excessive release of fatty acids in adipose tissue and muscle. [The SCJ<sup>2</sup> indicates that this paper has been cited in over 275 publications since 1963.]

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This is the third of three papers that I authored while a graduate student in the Department of Biochemistry at Cambridge. Surprisingly, all three have been featured in the *Citation Classics* series.<sup>1,2</sup> The present paper together with the one on insulin radioimmunoassay<sup>2</sup> represents the work I carried out for my PhD as a graduate student working under the supervision of Philip Randle. I was very fortunate to be a member of Randle's research group at a particularly exciting time. Hal Coore and Randle also devised the simple system that opened up the study of insulin secretion. I should point out, as there seems to be a danger of its being overlooked in these pages, that they showed for the first time epinephrine inhibition of glucose-stimulated insulin secretion.<sup>3</sup>

The present paper's frequent citation is probably due to its being the early *in vivo* evidence for the glucose-fatty acid cycle. The cycle seems likely to be important in some states of diabetes. I followed three main themes from this work. The first, in

1964, with Laughton Miles, a graduate student, was the production of new immunological assay methods. We used labelled antibodies to assay soluble polypeptides as a possible improvement on radioimmunoassay. Our approach proved successful and led us also to propose the use of alternatives to radioisotopic labels including the now popular use of enzyme labels.<sup>4</sup> Further developments of this system, for which we introduced the now widely used term immunoradiometric assay ("IRMA"), included a two-site (with Michael Addison) and an indirect method (with Peter Beck). The former has been rendered technically simple by the advent of monoclonal antibodies and is becoming widely used in clinical assays.

The second line of research followed the idea of fatty acid oxidation and insulin resistance. In 1965, Chris Dawson and I turned our attention to the liver and the control of the insulin-sensitive enzyme, glucokinase. We found that by administering steroids, the enzyme could be reduced in activity despite elevated insulin concentrations. We suggested that this reduction of activity was due to inhibition by fatty acyl CoA,<sup>5</sup> thus extending the tissue range of the glucose-fatty acid cycle. This work has recently been repeated by others (1982). The third line of research, still active, is the ionic basis of the regulation of insulin secretion. Our initial studies of this area, with another graduate student, David Milner, led us to propose that the  $\beta$ -cell membrane had a potassium-dependent membrane potential and that depolarisation could lead to insulin secretion. Last year, while on sabbatical with Ed Krebs in Seattle, I was privileged also to collaborate with Dan Cook in discovering an ATP-sensitive  $K^+$  channel in cells. We believe this is an important component of the regulatory mechanism.<sup>6</sup>

[Awards related to this work are: British Diabetic Association R.D. Lawrence Lectureship, the European Association for the Study of Diabetes Minkowski Prize, and the Medal of the British Endocrine Society.]

1. 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. [See also: Randle P J. Citation Classic. *Current Contents:Life Sciences* 24:31:24, 3 August 1981.]
2. Hales C N & Randle P J. Immunoassay of insulin with insulin-antibody precipitate. *Biochemical J.* 88:137-46, 1963. [See also: Hales C N & Randle P J. Citation Classic. *Current Contents:Life Sciences* 23:49:10, 8 December 1980.]
3. Coore H & Randle P J. Regulation of insulin secretion: studies with pieces of rabbit pancreas incubated *in vivo*. *Biochemical J.* 93:66-79, 1964. (Cited 640 times.)
4. Miles L E M & Hales C N. Labelled antibodies and immunological assay systems. *Nature* 219:186-9, 1968. (Cited 110 times.)
5. Dawson C M & Hales C N. The inhibition of rat liver glucokinase by palmitoyl-CoA. *Biochim. Biophys. Acta* 176:657-9, 1969.
6. Cook D L & Hales C N. Intracellular ATP directly blocks  $K^+$  channels in pancreatic B-cells. *Nature* 311:271-3, 1984.