THE PAPER THAT CHANGED MY LIFE

How leptin caused a paradigm shift in obesityrelated research

In the 1 December 1994 issue of Nature, I came across a research article which made the hairs on the back of my neck stand up. This paper transformed my thinking about the nature of a biological problem with huge clinical implications and sent my research down an avenue which has continued to be both productive and enjoyable more than a decade later.

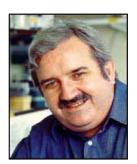
As a clinical endocrinologist who had studied diabetes for many years, I had long been comfortable with the idea that the control of blood glucose by insulin and its disruption in diabetes was essentially an endocrinological problem. However, I had given little consideration to the notion that the control of fat mass and its disruption in states of obesity could possibly be seen in the same way. Of course, this was based on my ignorance of a long-standing body of data obtained from studies in nutritionally manipulated, hypothalamically lesioned and parabiosed rodents, which strongly suggested that quantity of fat mass was somehow signalled to the brain via a blood-borne substance and that the brain responded to this signal with appropriate changes in appetite and subsequent food intake.

Even though some genetic forms of obesity in mice had begun to be better understood in the early 1990s, the physiology of energy balance lacked a tangible 'hormone' to whet the appetite of an endocrinologist. The 1994 paper from Jeffrey Friedman and colleagues (Zhang et al, 1994) changed all that. They discovered that the *ob/ob* mouse (homozygous for the mutant obesity gene) was genetically deficient in a circulating cytokine-like protein, leptin, which is normally expressed only by fat cells. In normal mice the amount of leptin produced was proportional to the amount of body fat.

In subsequent papers this team, and others, went on to show that administration of leptin to *ob/ob* mice reverses all of the abnormalities seen in these mice; that the signalling form of the leptin receptor is highly expressed in the hypothalamus; and that small doses of leptin administered centrally are just as effective as large doses given systemically in reversing the abnormalities of the *ob/ob* mice. Flier (Ahima et al, 1996), and others, elegantly demonstrated that the function of leptin in normal biology is to act as a signal to the brain regarding transitions between the adequately nourished and the starved states, and that leptin deficiency explains the amenorrhoea and other endocrinological disruptions seen in starvation.

We started to search for leptin deficiency among human patients with severe obesity and have found eight such individuals (from five families) to date. All of those treated with leptin have shown a dramatic reversal of the obese state. Defects in the downstream components of the leptin signalling pathways (leptin receptor, pro-opiomelanocortin, prohormone convertase-1 and melanocortin-4 receptor [MC4R]) have now been demonstrated in hundreds of obese people, with mutations in the MC4R being found in 5 % of severely obese children and 2.5 % of unselected obese European 18 year olds. Unfortunately, leptin did not turn out to be a panacea for common obesity. Leptin levels are usually high in obese people, indicating leptin resistance, and although increasing leptin levels from the very low to the normal range has dramatic effects, the dose—response curve flattens off rapidly. Nevertheless, there may be sub-groups of obese individuals who will respond beneficially to leptin given for weight loss or weight maintenance.

More importantly, leptin moved the field of energy balance and obesity from the periphery of the biomedical world to centre-stage. Before 1994, publications on scientific aspects of obesity were largely confined to specialist journals; soon after, the Institute of Scientific Information (ISI) documented obesity as the fastest-growing field in biomedical publishing. Before 1994, few pharmaceutical companies took a serious interest in obesity; now there is no major company which does not have a substantial obesity programme. We now know an enormous amount about the hypothalamic circuitry downstream of leptin signalling and it is only a matter of time before pharmacological manipulation of that circuitry leads to effective therapeutics. This paper launched a revolution and has already been cited almost 9000 times, a figure which reflects its paradigm-shifting impact.



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Ahima RS, Prabakaran D, Mantzoros C, Qu D, Lowell B, Maratos-Flier E, Flier JS (1996) The role of leptin in the neuroendicrine response to fasting. *Nature* **382**(6588): 250–53

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