bother to look for leptin receptors in the ovary, nor even to determine whether its administration raised plasma levels of pituitary gonadotropins in their animals (as expected if leptin's fertility-promoting action involved the brain).

The most recent blow to the theory that circulating leptin mediates weight homeostasis, and that it does so by activating a brain receptor coupled to eating behavior, was the finding by Levin *et al.* that, in genetically normal animals, leptin does not reduce weight by decreasing food intake[8]. Using a classic and simple pair-feeding paradigm, control animals were allowed to consume only as much food per day as other lean mice, which had lost weight after leptin administration, consumed electively. The pair-fed mice failed to lose weight. Hence the weight loss caused by leptin had to have resulted from some metabolic effect of the doses used, and not from an action, via the brain, on eating behavior. Because the leptin doses used were never shown to be physiologic, it cannot be assumed that the weight loss they produced bears any relationship to leptin's actual physiologic role, any more than hydrocortisone's ability to ameliorate the itch of poison ivy tells us anything about its actions when used as substitution therapy for Addison's disease, or more than the strong hungers produced by excessive, hypoglycemic doses of insulin tell us anything about the satiety produced by endogenous insulin released after carbohydrate consumption. It is still possible that very high doses of leptin will be found to reduce body weight in obese people by inducing a hypermetabolic state, much like the thyroid extracts and dinitrophenol used earlier in this century. However, these earlier agents stopped being used because physicians came to recognize that the induction of hypermetabolism was dangerous.

If we are to learn what leptin actually does, *in vivo*, investigators will have to start performing physiologic experiments in which we examine the consequences of varying plasma leptin levels within their normal dynamic range, or identify the factors that act directly on adipocytes to cause leptin's secretion after fat is consumed. Is most leptin secreted by peritoneal fat cells, perhaps perfused by the nutrient-rich blood of the portal circulation? Or by peripheral adipocytes, perhaps responding to circulating fatty acids, or even to other hormones released after fat consumption? Or perhaps to sympathetic nervous discharge, or to all of these? We also will have to recognize the limitations of extrapolating findings from experimental animals, like *ob/ob* mice, deprived of leptin or some other protein throughout their development, to normal animals or humans. It seems just as likely as not that leptin has a role in development, hence animals whose cells and regulatory systems have never been exposed to the hormone cannot be expected to respond the way "real" mice do when given it in adult life. Similar caveats apply to the use of other mutated or "knockout" mammals to learn about normal physiology.

Now let the search begin for what leptin really does . . . .

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Plasmin, fibrin degradation and angiogenesis

To the editor — In the March issue of *Nature Medicine*, Rømer and colleagues demonstrated that plasminogen is essential for normal repair by creating plasminogen-deficient mice that show poor wound healing[1]. However, neither they, nor Vasalli and Saurat's accompanying News & Views[2], make the connection between the failure of normal fibrin degradation by plasmin, and the failure of cell proliferation including angiogenesis. The missing link is the production of biologically active fibrin degradation products (FDP). We have shown that FDP are angiogenic both on the chick chorioallantoic test model[3], and when injected subcutaneously in mice and rats. FDP are abundant in experimental healing wounds[4]. The active component is fibrin fragment E, and the angiogenic effect of healing skin wound extracts is blocked by admixture with an anti-fragment E antibody[5].

Nevertheless, Rømer and colleagues did describe some limited healing in the deficient mice, and eventually fibrovascular granulation tissue developed and persisted. We agree with the authors' suggestion that to some extent the function of plasmin may be compensated by other factors, but rather than extracellular proteinases in general, we would suggest that the key to this lies in the non-plasmin, cathepsin-based fibrinolytic pathway of the macrophage[6], albeit less effective.

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