Adipose tissue metabolism and calorie balance

By T. M. CHALMERS, *Department of Medicine, The Middlesex Hospital,*
London, W.1

Adipose tissue can no longer be regarded simply as an inert storage site in which fat formed in the liver or derived directly from the diet is deposited, and from which during fasting fat is 'mobilized' and 'burned' in the liver for energy. The use of substrates labelled with radioactive isotopes has established that these fat 'stores' are, in fact, constantly being turned over, and that most of the fat is synthesized from glucose within the tissue itself. Some of the reactions involved in the synthesis and release of fatty acids by adipose tissue are shown in Fig. 1 which is redrawn from the
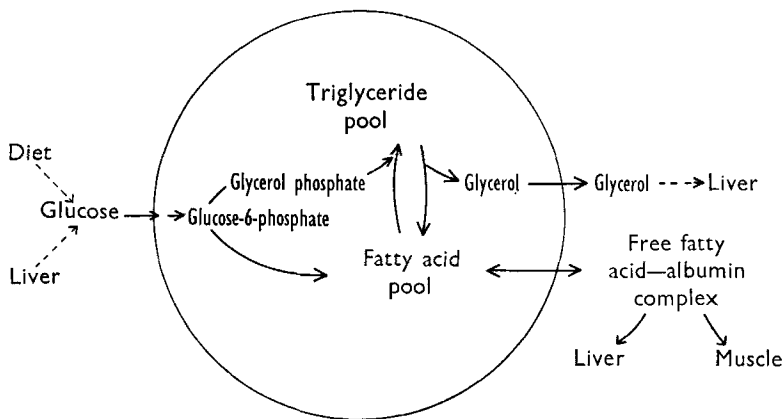

Fig. 1. Some reactions in adipose tissue. (Redrawn from Ashmore, Cahill & Hastings, 1960.)

excellent paper by Ashmore, Cahill & Hastings (1960). According to this scheme the release of fatty acids could be affected by two possible mechanisms. There might be an increase in lipase activity leading to increased breakdown of triglyceride to glycerol and fatty acids. Or the release of fatty acids might be inhibited by the production of more glycerol phosphate from glucose leading to greater re-esterification: the inhibition of fatty-acid release by insulin is believed to be brought about by this mechanism. The primary action of lipolytic hormones is thought to be on the hydrolysis of triglyceride.

The free fatty acids (FFA) released from adipose tissue circulate in plasma in a fatty-acid–albumin complex and are probably utilized directly by muscle and other tissues. The concentration of FFA in plasma relative to that of glucose is quite small, but the turnover is so much more rapid that FFA and not glucose may be the principal energy substrate (Table 1). Dr Vincent Dole, to whom I am indebted for these figures, has pointed out (personal communication) that on this basis FFA alone could provide sufficient energy for basal metabolism.

In the regulation of the metabolism of adipose tissue both nervous and humoral factors appear to be involved. The subject is well reviewed by Engel & White (1960).

Table 1. *Calorie outflow from the circulating blood of man as glucose and as free fatty acids (FFA) (values of V. Dole, personal communication)*

	Glucose	FFA
Amount circulating (kcal/kg)	0·84	0·05
Turnover (percentage/min)	0·7	28
Outflow (kcal/kg day)	8·5	22

Denervation of adipose tissue reduces its ability to mobilize its lipid in response to fasting and other stimuli. Recent studies have shown that adrenaline, and particularly noradrenaline, when infused intravenously, cause an increase in the levels of plasma fatty acids and also lead to a release of FFA from adipose tissue incubated in vitro. In dogs, administration of a ganglion-blocking agent, hexamethonium, causes a rapid fall in plasma FFA. The available evidence suggests that the sympathetic nerves, through the release of noradrenaline, exercise a tonic control over the release of fatty acids from adipose tissue. In addition, emergency mobilization of FFA by circulating adrenaline may occur: the response to adrenaline is, however, relatively brief, because it is cut short by the concomitant hyperglycaemia and consequent insulin secretion.

The administration of either insulin or glucose depresses FFA levels in the plasma of normal man and animals. As has already been noted, the action of insulin on the fatty-acid balance of adipose tissue is believed to be secondary to its influence on the uptake and utilization of carbohydrate by the tissue. Insulin increases the utilization of glucose through all available pathways, including formation of triglyceride fatty acid.

It has long been known that the anterior pituitary gland was concerned in the mobilization and metabolism of lipid and these actions have generally been attributed to the growth hormone. However, effects on lipid metabolism similar to those of growth hormone can also be produced by corticotrophin, even in the absence of the adrenal glands. Studies in hypophysectomized animals indicate that the pituitary hormones are not essential for fatty-acid mobilization and ketosis, even though they may be required for the optimal response.

Although lipolytic effects either in vivo or in vitro can be obtained with both growth hormone and corticotrophin there are certain difficulties in interpreting the experimental results, and the physiological role of these hormones is not yet clear. In man, administration of human growth hormone in small doses leads to impressive rises in the levels of plasma FFA. In vitro, when incubated with rat adipose tissue, growth hormone causes release of fatty acids only when it is added in high concentration (10–500 μg/ml). The pituitary hormone most active in inducing lipolysis in vitro is corticotrophin, the effect being detectable at a concentration of 0·01 μg/ml or even less. When assayed for its effect on the levels of plasma FFA in vivo, however, this hormone has been found to be inactive, although other evidence of fat mobilization may be obtained.

To complicate the picture still further, it has been claimed (Rudman & Seidman, 1958) that the pituitary secretes a factor, separate and distinct from the known

hormones, which influences fat metabolism. It in turn differs from the fat-mobilizing substance (FMS) which Chalmers, Kekwick, Pawan & Smith (1958) obtained from the urine of fasting normal men and which appears likely to be a hormone of pituitary origin distinct from growth hormone and corticotrophin (Chalmers, Pawan & Kekwick, 1960). This material also differs from prolactin, thyrotrophin and the neurohypophysial hormones.

Perhaps the most important fact about FMS is that it appears in the urine during fasting and disappears on refeeding. This behaviour strongly suggests that it has a physiological role in the regulation of fat metabolism. Extracts of urine are prepared by alcoholic washing of a benzoic-acid precipitate, alkaline extraction of the alcohol-insoluble residue and concentration with oxycellulose (Chalmers *et al.* 1960). In mice FMS causes increases in the levels of circulating lipids, fatty livers and ketonaemia. Repeated administration causes loss of body fat without affecting body protein and without depression of appetite. Lipolytic activity can be demonstrated in vitro by incubation with rat, mouse or human adipose tissue. The release of fatty acids from the epididymal fat of rats is regularly increased by the addition of FMS to the incubating medium at a concentration of 1 μg/ml and occasionally of 0·01 μg/ml. Like adrenaline and corticotrophin, FMS increases the oxidation by adipose tissue of carbon atom 6 of glucose to CO_2 and causes a marked increase in the incorporation of radioactive carbon into triglyceride glycerol (G. F. Cahill Jr, 1960, personal communication). At present it seems unlikely that these carbohydrate effects represent the primary action of the hormone on adipose tissue: similar effects can be produced by incubating adipose tissue in the presence of fatty acids. On the other hand, lipase activity and fatty-acid release do not appear to run parallel. For example, adipose tissue removed from fasting rats releases more fatty acid but contains less lipase activity than tissue from fed animals.

The dependence of FMS release on carbohydrate metabolism was previously demonstrated in an obese patient treated with a series of 1000 kcal diets in which carbohydrate was progressively restricted (Chalmers *et al.* 1960). As measured by the ketogenic effect in mice, FMS began to appear in the urine when less than half the calories were provided as carbohydrate, and increasing amounts of FMS were found when carbohydrate was further restricted. To meet the possible objection that the increase in FMS was simply a function of the duration of the calorie deficit these

Table 2. *Ketogenic activity of the urine of an obese patient during progressive dietary substitution of carbohydrate for fat. Each diet was given for 4 days*

| | Daily intake | | | | Results of |
Diet period	Calories (kcal)	Protein (g)	Fat (g)	Carbohydrate (g)	biological assay of urine*
1	1003	29	91	18	130
2	1004	29	70	29	62
3	1002	29	49	110	19
4	1002	28	30	154	0
5	1000	28	10	191	0

*Percentage increase in blood ketones of treated mice over controls treated with saline.

observations have recently been repeated in another obese patient who received the diets in the reverse order (Table 2). Each diet was given for 4 days and the biological assay was carried out on urine collected during the last 2 days of each dietary period. Ketogenic activity was present in the urine in the periods of low-carbohydrate diets and disappeared when the carbohydrate was increased, despite the persistent calorie deficit.

REFERENCES

Ashmore, J., Cahill, G. F. Jr. & Hastings, A. B. (1960). *Recent Progr. Hormone Res.* **16**, 547.
Chalmers, T. M., Kekwick, A., Pawan, G. L. S. & Smith, I. (1958). *Lancet*, i, 866.
Chalmers, T. M., Pawan, G. L. S. & Kekwick, A. (1960). *Lancet*, ii, 6.
Engel, F. L. & White, J. E. Jr. (1960). *Amer. J. clin. Nutr.* **8**, 691.
Rudman, D. & Seidman, F. (1958). *Proc. Soc. exp. Biol., N.Y.*, **99**, 146.

Energy expenditure and calorie intake in young men

By O. G. Edholm, *Division of Human Physiology, National Institute for Medical Research, Medical Research Council, c/o Medical Research Council Laboratories, Holly Hill, Hampstead, London, N.W.3*

The determination of calorie balances in man requires accurate measurement of energy expenditure and food intake over a period of at least a week (Widdowson, Edholm & McCance, 1954; Edholm, Fletcher, Widdowson & McCance, 1955). In this country a number of surveys have been made of young men, during a period of military training. The food intake of sixty-four men was measured for 3 weeks, and the energy expenditure of thirty-five of these subjects was recorded (Adam, Best, Edholm, Fletcher, Lewis & Wolff, 1958; Adam, Best, Edholm, Goldsmith, Gordon, Lewis & Wolff, 1959). In another experiment the food intake and energy expenditure of thirteen men were followed for a period of 14 days, but the food intake was restricted for part of the time and the results will be briefly described separately (Adam, Best, Edholm & Wolff, 1957).

It is the intention in this paper, not to give the full details of these various surveys, but to discuss the problem of arriving at an accurate measure of calorie balance, and the implications of present findings.

All who have attempted dietary surveys will agree that there are a large number of possible errors, especially when it is intended to do the study without interfering with the ordinary life of the subject. The measurement of energy expenditure may be liable to even more errors, because of the difficulty of having a continuous measurement throughout the day. An independent check on the results is obviously necessary, and the evident parameter to examine is body-weight. Daily weights were recorded in all these subjects, the weighing being done between 6.15 and 6.45 a.m. immediately after the subjects had got out of bed and had emptied their bladders.