Proceedings of the Nutrition Society (1995), **54**, 267–274

Feeding, fasting and starvation: factors affecting fuel utilization

BY I. A. MACDONALD AND J. WEBBER
Department of Physiology and Pharmacology, University of Nottingham Medical School, Queen's Medical Centre, Nottingham NG7 2UH

Alimentation, jeûne et privation de nourriture: les facteurs qui affectent l'utilisation des substrats énergétiques

RÉSUMÉ

Cet article porte sur le métabolisme de l'énergie et l'utilisation des substrats dans la sous-alimentation. Il s'intéresse particulièrement aux études sur l'homme, bien que des études sur l'animal soient également prises en compte, avec des distinctions entre le jeûne aigu (jusqu'à 4 jours), des périodes plus longues de sous-alimentation et la déficience chronique en énergie (comme dans la sous-alimentation grave et prolongée). Il y a des augmentations significatives de la lipolyse du tissu adipeux et la gluconéogenèse hépatique dans les tout premiers jours du jeûne. Ceci s'accompagne d'une légère augmentation du taux métabolique du repos (TMR), avec un pic après 36–48 heures de jeûne, puis une chute qui atteint des valeurs inférieures à la normale. Il y a également une réduction de la sensibilité à l'insuline dans le jeûne, essentiellement parce que l'insuline ne peut stimuler l'oxydation du glucose, sans que soit affecté son effet de stimuler la synthèse du glycogène de tout le corps. Outre l'effet sur la lipolyse et le TRM, le jeûne augmente également la réponse thermogénique aux perfusions de catécholamines. Dans la sous-alimentation plus longue et moins grave, il y a une chute du TRM (après 4–7 jours) et une résistance à l'insuline similaire à celle observée dans le jeûne aigu. Cette chute du TRM semble être dûe en partie à une diminution de l'activité métabolique de la masse maigre (MM), mais l'existence de modifications similaires chez l'animal est un sujet de controverse. Il semble que toute réduction du TRM par unité de MM se fait, en partie au moins, par l'intermédiaire de réductions des concentrations de l'insuline plasmatique et du triiodothyronine libre. Chez les sujets qui ont une déficience chronique en énergie le TRM par unité de MM n'est pas abaissé, probablement parce que la composition de leur MM est modifiée. Il est nécessaire de poursuivre cette étude pour définir les mécanismes sous-jacents à ces modifications du TRM, à la réponse thermogénique et à la sensibilité à l'insuline dans la sous-alimentation.

The ability of an organism to withstand periods of inadequate nutrition depends on the presence of appropriate nutrient stores together with the necessary adaptive responses. This is particularly true when considering energy metabolism during underfeeding and starvation, where the adaptations to undernutrition are vital for ensuring that the nutrient stores are utilized optimally. Professor Jéquier's (1995) paper in the present symposium considers the utilization of substrates during the postprandial period; the

present paper considers energy metabolism and substrate use in undernutrition, and the responses to food ingestion in the undernourished state. The major focus will be on studies in humans, mainly in experimental undernutrition. The terminology used in describing undernutrition is a significant source of confusion. For example, the most important single contribution in this area, *The Biology of Human Starvation* by Keys *et al.* (1950), did not investigate starvation but rather studied prolonged underfeeding (approximately 6 MJ/d for 6 months). In the human studies described in the present paper, a distinction will be made between fasting for up to 24 h, starvation for several (2–4) days and undernutrition–underfeeding for 7 d or more. In addition, chronic severe undernutrition will be referred to as chronic energy deficiency.

METABOLIC FUEL SUPPLY IN UNDERNUTRITION

In the average, non-obese, 70 kg adult the body energy stores comprise approximately 500 000 kJ lipid, 100 000 kJ protein and 4200 kJ carbohydrate (glycogen). Under normal circumstances, approximately 50% of daily energy expenditure is derived from carbohydrate, thus for a daily expenditure of 8 MJ, the carbohydrate store will only last for 1–2 d of fasting–starvation before carbohydrate supply becomes dependent on gluconeogenesis. In reality, it is probable that the glycogen store is only depleted after several days of starvation, because even after an overnight fast, gluconeogenesis makes a significant contribution to hepatic glucose production (for review, see Shulman & Landau, 1992). In addition, as starvation proceeds there is less dependence on glucose as a metabolic fuel and a major focus of the first part of the present paper will be the control of substrate supply and utilization in fasting and starvation.

Adipose tissue lipolysis increases substantially in the first few days of starvation. Using stable-isotope-tracer methods, Wolfe *et al.* (1987) showed 2–3-fold increases in the rates of appearance of glycerol and palmitate in plasma. Interestingly, the lipolytic response to starvation was much less marked in the obese, although in both groups of subjects there was a similar starvation-induced enhancement of the lipolytic response to an adrenaline infusion. In the non-obese, the increased rate of lipolysis in starvation releases non-esterified fatty acids (NEFA) at a much greater rate than that needed for energy metabolism. Thus, there is a substantial amount of re-esterification, and the energy costs of this fatty acid–triacylglycerol recycling can account for 2–3% of resting energy expenditure in the starving individual (Klein *et al.* 1989). Although the lower rate of lipolysis in the obese releases fatty acids in excess of the rate of fat oxidation, the surplus is smaller than that in the non-obese and so the energy cost of fatty acid–triacylglycerol recycling will be substantially lower in the obese.

The increase in lipolysis in the early stages of fasting seems most likely to be due to a variety of factors, including an increase in β-adrenoceptor sensitivity and a reduction in plasma insulin concentration. The elevated rate of lipolysis seen after 84 h of starvation is abolished by the intravenous infusion of propranolol (a non-selective β-adrenoceptor antagonist) at that time-point (Klein *et al.* 1989). However, oral ingestion of propranolol throughout an 84 h fast has much less of an effect on the elevated rate of lipolysis (Klein *et al.* 1989), suggesting the recruitment of alternative mechanisms or that the dose of propranolol was ineffective at preventing the rise in adrenoceptor sensitivity normally occurring in starvation.

The hypoinsulinaemia occurring during fasting contributes to the rise in basal lipolysis,

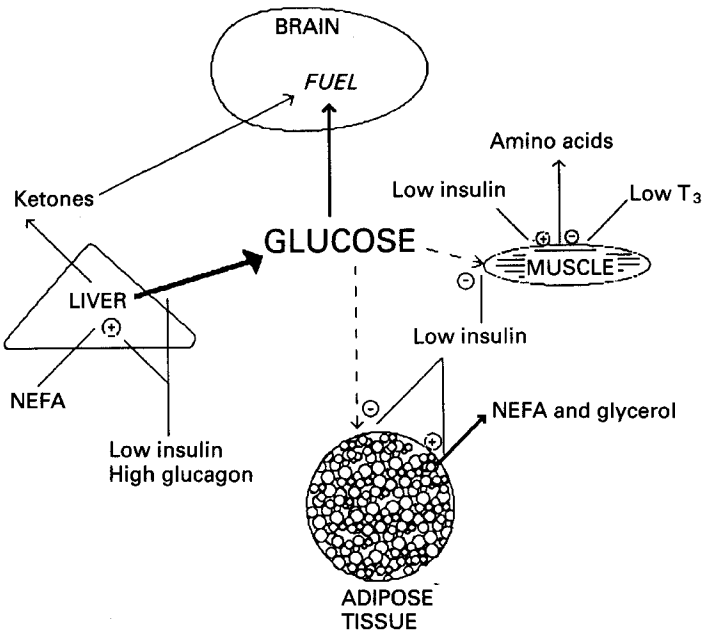

Fig. 1. Metabolic and hormonal responses to starvation. →, ⟶, ⇢, directions of uptake or release; ⊕, indicates stimulation; ⊖, indicates inhibition; NEFA, non-esterified fatty acids; T_3, triiodothyronine.

but is not critical for the enhanced lipolytic responses to infused adrenaline seen after 4 d of starvation (Jensen *et al.* 1987). Further evidence of the importance of hypo-insulinaemia comes from a study by Klein *et al.* (1990), where infusion of glucose to maintain euglycaemia during fasting reduces the fall in plasma insulin and the magnitude of the enhanced lipolytic response to adrenaline.

The time-courses of the changes in glucose and fatty acid metabolism during the early stages of fasting–starvation provide some insight into the possible controlling mechanism. Klein *et al.* (1993) showed a 35% fall in plasma insulin during the first 24 h of fasting with 50–80% increases in the rates of lipolysis. By contrast, there was no change in the rate of glucose production. Thus, a rise in fat mobilization precedes any fall in glucose release. However, this takes no account of the likelihood that the mechanisms of glucose production alter during the fast, such that gluconeogenesis is the principal source of glucose at 24 h of fasting. Further evidence supporting this comes from the observations by Romijn *et al.* (1990) and Klein *et al.* (1993) that net glucose oxidation approaches zero within the first 24 h of starvation. This apparent paradox has a simple explanation, in that oxidation of glucose produced via gluconeogenesis from amino acids would not appear through whole-body indirect calorimetry as net glucose oxidation, but rather as protein oxidation. The subsequent reductions in glucose production and oxidation in later starvation are probably a result of increased fat oxidation, leading to inhibition of pyruvate dehydrogenase complex activity (see Denton & McCormack, 1995).

The primary metabolic responses to fasting–starvation are summarized in Fig. 1, and comprise a fall in peripheral (i.e. non-neuronal tissue) glucose utilization, an increase in fatty acid and ketone body utilization and decrease in proteolysis. These changes are

https://doi.org/10.1079/PNS19950053 Published online by Cambridge University Press

mediated in part by reductions in plasma insulin and free triiodothyronine (T_3) concentrations and by increases in plasma glucagon and adrenaline. There is a major debate as to the role of altered sympathetic nervous system activity during starvation in humans, the detail of which is beyond the scope of the present review. These initial responses to starvation and undernutrition maintain glucose supply to the central nervous system (CNS), although with more prolonged starvation this becomes less critical as the CNS can derive a substantial proportion of its metabolic fuel from the oxidation of ketone bodies (Owen *et al.* 1967).

ENERGY METABOLISM IN STARVATION AND UNDERFEEDING

It is generally believed that resting and total energy expenditure fall in starvation and underfeeding. Whilst this is undoubtedly true after a few days of undernutrition, it may not be the case initially. The classical studies of Benedict *et al.* (1919) revealed a modest rise in resting energy expenditure in the first 12 d of a prolonged period of underfeeding. This was followed by the expected fall over the next 30 d. Similarly, the first 2 d of total starvation are accompanied by increased resting energy expenditure (Mansell *et al.* 1990; Webber & Macdonald, 1994), which is likely to be due in part to the energy costs of gluconeogenesis, ketogenesis and fatty acid–triacylglycerol recycling. The rates of gluconeogenesis and fatty acid–triacylglycerol recycling seen after 2–3 d of starvation could easily account for 5% of resting energy expenditure. As starvation proceeds there is a fall in resting energy expenditure, such that it is normally below initial values after 4 d of starvation (for review, see Elia, 1992).

With underfeeding there is also a fall in resting energy expenditure which is manifest in previously healthy women within 7 d of reducing their energy intake to 2 MJ/d (Mansell & Macdonald, 1988). This fall in resting energy expenditure during prolonged underfeeding and starvation is due in part to a reduction in the longer-term aspects of food-induced thermogenesis, to a reduction in the amount of metabolically-active tissue (due to mobilization of body protein stores) and a decrease in the metabolic activity of the remaining tissue. This latter effect was originally described by Keys *et al.* (1950), who showed a 16% fall in resting energy expenditure per unit body cell mass, and later confirmed by Grande *et al.* (1958). There is some disagreement as to whether there are similar reductions in resting energy expenditure per unit metabolically-active tissue occurring in experimental animals; for example, Even & Nicolaidis (1993) failed to see any reduction in basal energy expenditure of rats severely underfed for 10 d.

The mechanisms of the reduction in resting energy expenditure during prolonged experimental undernutrition are not understood, but seem likely to be related to decreases in plasma insulin and free T_3 concentrations. It is important to distinguish between this experimental undernutrition and the chronic energy deficiency seen in underdeveloped countries. The studies of Shetty and colleagues (Shetty, 1993) have shown clearly that such individuals may have increased energy expenditure per unit fat-free mass (i.e. active body tissues), possibly due to an alteration in the composition of the fat-free mass.

RESPONSES TO THERMOGENIC STIMULI IN UNDERNUTRITION

It is now widely believed that the thermogenic response to nutrient ingestion, or infusion, includes a regulated (or facultative) component which contributes to the overall

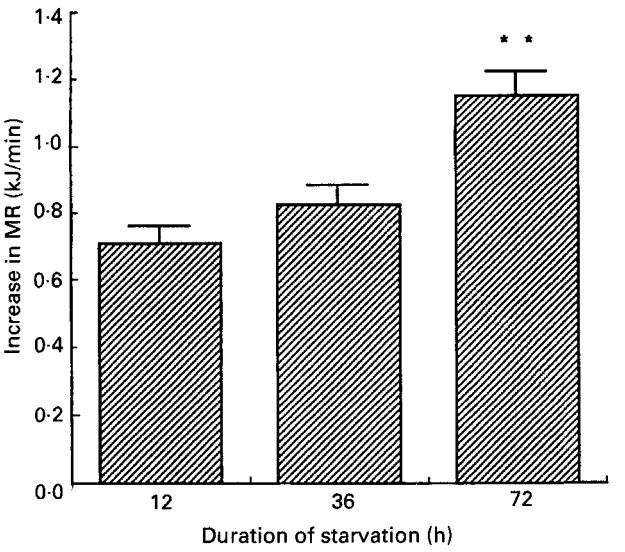

Fig. 2. Effect of starvation on thermogenic responses to infused adrenaline. Values are means with their standard errors represented by vertical bars for twenty-nine subjects. Mean values were significantly greater at 72 h than either of the responses at 12 or 36 h: $^{**}P<0{\cdot}01$. Adapted from Webber (1993). MR, metabolic rate.

regulation of energy expenditure. This facultative thermogenesis is thought to be mediated at least partly through activation of the sympathetic nervous system (SNS), and reduction in this may be a means of decreasing energy expenditure in undernutrition. Such reduced facultative thermogenesis could be due to altered sensitivity to the thermogenic effects of catecholamines, or to a decrease in activation of the SNS.

Catecholamine-induced thermogenesis

In experimental undernutrition, there is no reduction in the thermogenic response to adrenaline during either starvation or 7 d underfeeding. In fact, starvation for up to 72 h is accompanied by an increase in the thermogenic response to adrenaline (Fig. 2; Mansell *et al.* 1990; Webber, 1993), whilst after 7 d of underfeeding there is no alteration in the thermogenic response to adrenaline (Mansell & Macdonald, 1989). This contrasts with the responses to infused noradrenaline in chronic energy deficiency, where there appears to be reduced sensitivity but a similar maximum response (Fig. 3; Kurpad *et al.* 1989).

Nutrient-induced thermogenesis

In both acute starvation (Gallen *et al.* 1990) and 7 d underfeeding (Mansell & Macdonald, 1988) there is no alteration in the thermogenic response to a test meal, at least in the first 90 min after ingestion of the drink. However, the test meal in the underfed state is substantially larger than the normal meal and it may not be possible for the body to deal efficiently with it. Similarly, in chronic energy deficiency the thermogenic response to a test meal is greater than that seen in normal-weight or moderately-underweight subjects (Piers *et al.* 1992*b*). This may also be due to the relative

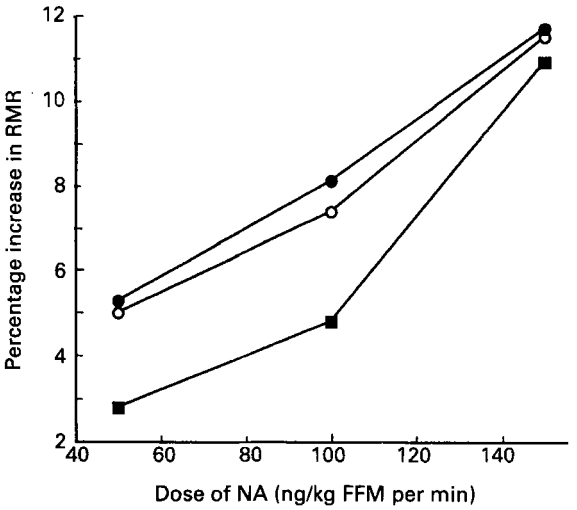

Fig. 3. Thermogenic responses to infused noradrenaline (NA) in normal weight (○), underweight (●) and chronically energy-deficient subjects (■). RMR, resting metabolic rate; FFM, fat-free mass.

size of the test meal and further studies are needed to assess the thermogenic responses to smaller meals in control and undernourished subjects.

An alternative means of investigating responses to nutrients is to determine the thermogenic responses to glucose infusion. This is best done in the 'glucose clamp', where insulin is infused to produce a stable plasma concentration at the upper end of the physiological range and glucose is infused to maintain a stable blood glucose concentration. The rate of glucose infusion is a measure of insulin sensitivity, and combination with indirect calorimetry allows glucose utilization to be partitioned into storage and oxidation and the assessment of the glucose-induced thermogenic response. Using this technique, it has been shown that the insulin resistance seen in starvation and underfeeding is predominantly due to a decrease in insulin stimulation of glucose oxidation, with glucose storage being relatively unaffected (Gallen & Macdonald, 1990; Mansell & Macdonald, 1990; Webber *et al.* 1994). Furthermore, in both starvation and underfeeding there is a marked reduction in glucose-induced thermogenesis during the glucose clamp. Whilst these latter observations are the only demonstrations of reduced nutrient-induced thermogenesis in experimental undernutrition, they provide some evidence of a possible improvement in metabolic efficiency as an adaptation to undernutrition.

Refeeding the undernourished

Dulloo & Girardier (1992) showed that refeeding of rats after 2 weeks of underfeeding was accompanied by a marked increase in energetic efficiency which was relatively unaffected by the fat content of the diet. Furthermore, Piers *et al.* (1992*a*) showed that supplementary feeding of subjects with chronic energy deficiency produced an increase in resting fasting energy expenditure, but actually decreased the thermogenic response to a test meal. However, this reduction was from an elevated baseline response and so it may not be appropriate to interpret it as evidence of improved energetic efficiency.

CONCLUSION

In the early stages of starvation an increase in adipose tissue lipolysis (possibly due to a decrease in plasma insulin) and fat oxidation are key steps which probably then lead to a reduction in glucose oxidation. However, gluconeogenesis continues to provide glucose for utilization by neural and other tissues, which does not appear as net whole-body glucose oxidation. In association with this increase in lipolysis in the early stages of starvation there is a small rise in resting energy expenditure, but this reverts to a decreased energy expenditure after 72 h without food.

With more prolonged undernutrition, total energy expenditure falls but the mechanisms of this are not fully understood. Although one would expect a reduction in food-induced thermogenesis in prolonged undernutrition, there is a lack of convincing evidence that this occurs. It is clear, however, that in more controlled experimental conditions glucose-induced thermogenesis is diminished in undernutrition. The mechanisms underlying this effect and the improved metabolic efficiency during refeeding remain to be elucidated.

The authors are grateful to Alison Kitchen for typing the manuscript and to the Wellcome Trust for grant support for the studies described from their laboratory.

REFERENCES

Benedict, F. G., Miles, W. R., Roth, P. & Smith, M. (1919). *Human Vitality and Efficiency Under Prolonged Restricted Diet. Carnegie Institution of Washington Publication* no. 280. Washington, DC: Carnegie Institution of Washington.

Denton, R. M. & McCormack, J. G. (1995). Fuel selection at the level of the mitochondria in mammalian tissues. *Proceedings of the Nutrition Society* **54,** 11–22.

Dulloo, A. G. & Girardier, L. (1992). Influence of dietary composition on energy expenditure during recovery of body weight in the rat: implications for catch-up growth and obesity relapse. *Metabolism* **41,** 1336–1342.

Elia, M. (1992). Effects of starvation and very low calorie diets on protein–energy interrelationships in lean and obese subjects. In *Protein–Energy Interaction*, pp. 249–284 [N. S. Scrimshaw and B. Schürch, editors]. Lausanne, Switzerland: IDECG.

Even, P. C. & Nicolaidis, S. (1993). Adaptive changes in energy expenditure during mild and severe feed restriction in the rat. *British Journal of Nutrition* **70,** 421–431.

Gallen, I. W. & Macdonald, I. A. (1990). The effects of underfeeding for 7 d on the thermogenic and physiological response to glucose and insulin infusion (hyperinsulinaemic euglycaemic clamp). *British Journal of Nutrition* **64,** 427–437.

Gallen, I. W., Macdonald, I. A. & Mansell, P. I. (1990). The effects of a 48 h fast on the physiological responses to food ingestion in normal weight women. *British Journal of Nutrition* **63,** 53–64.

Grande, F., Anderson, J. T. & Keys, A. (1958). Changes of basal metabolic rate in man in semistarvation and refeeding. *Journal of Applied Physiology* **12,** 230–238.

Jensen, M. D., Haymond, M. W., Gerich, J. E., Cryer, P. E. & Miles, J. M. (1987). Lipolysis during fasting: Decreased suppression by insulin and increased stimulation by epinephrine. *Journal of Clinical Investigation* **79,** 207–213.

Jéquier, E. (1995). Nutrient effects: postabsorptive interactions. *Proceedings of the Nutrition Society* **54,** 253–265.

Keys, A., Brozek, J., Henschel, A., Mickelsen, O. & Taylor, H. L. (1950). *The Biology of Human Starvation.* Minnesota: University of Minnesota Press.

Klein, S., Holland, O. B. & Wolfe, R. R. (1990). Importance of blood glucose concentration in regulating lipolysis during fasting in humans. *American Journal of Physiology* **258,** E32–E39.

Klein, S., Peters, E. J., Holland, O. B. & Wolfe, R. R. (1989). Effect of short- and long-term β-adrenergic blockade on lipolysis during fasting in humans. *American Journal of Physiology* **257,** E65–E73.

Klein, S., Sakurai, Y., Romijn, J. A. & Carroll, R. M. (1993). Progressive alterations in lipid and glucose metabolism during short-term fasting in young adult men. *American Journal of Physiology* **265,** E801–E806.

Kurpad, A. V., Kulkarni, R. N., Sheela, M. L. & Shetty, P. S. (1989). Thermogenic responses to graded doses of noradrenaline in undernourished Indian male subjects. *British Journal of Nutrition* **61,** 201–208.

Mansell, P. I., Fellows, I. W. & Macdonald, I. A. (1990). Enhanced thermogenic response to epinephrine after 48 h starvation in humans. *American Journal of Physiology* **258,** R87–R93.

Mansell, P. I. & Macdonald, I. A. (1988). The effect of underfeeding on the physiological response to food ingestion in normal weight women. *British Journal of Nutrition* **60,** 39–48.

Mansell, P. I. & Macdonald, I. A. (1989). Underfeeding and the physiological responses to infused epinephrine in lean women. *American Journal of Physiology* **256,** R583–R589.

Mansell, P. I. & Macdonald, I. A. (1990). The effect of starvation on insulin-induced glucose disposal and thermogenesis in humans. *Metabolism* **39,** 502–510.

Owen, O. E., Morgan, A. P., Kemp, H. G., Sullivan, J. M., Herrera, M. G. & Cahill, G. F. (1967). Brain metabolism during fasting. *Journal of Clinical Investigation* **46,** 1589–1595.

Piers, L. S., Soares, M. J., Kulkarni, R. N. & Shetty, P. S. (1992*a*). Thermic effect of a meal. 3. Effect of dietary supplementation in chronically undernourished human subjects. *British Journal of Nutrition* **67,** 187–194.

Piers, L. S., Soares, M. J. & Shetty, P. S. (1992*b*). Thermic effect of a meal. 2. Role in chronic undernutrition. *British Journal of Nutrition* **67,** 177–185.

Romijn, J. A., Godfried, M. H., Hommes, M. J. T., Endert, E. & Sauerwein, H. P. (1990). Decreased glucose oxidation during short-term starvation. *Metabolism* **39,** 525–530.

Shetty, P. S. (1993). Chronic undernutrition and metabolic adaptation. *Proceedings of the Nutrition Society* **52,** 267–284.

Shulman, G. I. & Landau, B. R. (1992). Pathways of glycogen repletion. *Physiological Reviews* **72,** 1019–1035.

Webber, J. (1993). The effects of acute starvation and of obesity on thermogenesis and substrate utilization in man. DM Thesis, University of Nottingham.

Webber, J. & Macdonald, I. A. (1994). The cardiovascular, metabolic and hormonal changes accompanying acute starvation in men and women. *British Journal of Nutrition* **71,** 437–447.

Webber, J., Taylor, J., Greathead, H., Dawson, J., Buttery, P. J. & Macdonald, I. A. (1994). Effects of fasting on fatty acid kinetics and on cardiovascular, thermogenic and metabolic responses to the glucose clamp. *Clinical Science* **87,** 697–706.

Wolfe, R. R., Peter, E. J., Klein, S., Holland, O. B., Rosenblatt, J. & Gary, H. Jr (1987). Effect of short-term fasting on lipolytic responsiveness in normal and obese humans. *American Journal of Physiology* **252,** E189–E196.

Printed in Great Britain