CURRENT SURVEY

Obesity: some current views regarding its aetiology

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Summary

Obesity results from an imbalance between calorie intake and calorie output. Although an excessive calorie intake is the most obvious and usual explanation for the development of obesity, a variety of factors influencing calorie expenditure may also be involved. Some of these factors may even be inborn.

Recent work on controls of energy utilization, and on the relation between obesity and changes in the size and number of adipocytes in the body, is reviewed.

'Simple' obesity is a term often euphemistically applied to obesity which is not associated with any evident endocrine abnormality. This state is generally accepted as the consequence of overeating, but there may be a variety of other factors involved.

It is true that the development of obesity requires an imbalance, usually over a prolonged period, between calorie intake and calorie expenditure, since the first law of thermodynamics applies to man as to inanimate objects. Simply stated this law is that energy can neither be created nor destroyed, but only transformed. But the statement that body weight is simply a balance between calorie intake and output is a superficial description of a very complex situation; nevertheless, it clearly indicates two possible controls for the regulation of calorie balance—those affecting *food intake* on the one hand, and those affecting *energy utilization* on the other.

The chief factor influencing food intake is body weight. Clearly, adults consume more food than do young children, but the variation in food intake between individuals of any given weight, age or sex is remarkable. Food intake also varies, inversely, with environmental temperature, as has been exploited by the breeders of laboratory animals, who find that it is cheaper to raise the temperature of the animal house than to buy more food. It is known that there are areas in the hypothalamus influencing feeding behaviour, selective destruction

of different areas being capable of producing either hyperphagia or aphagia. The association of gastric contractions with hunger is well known, although gastric distension and motility are probably minor factors controlling food intake in man. Major factors in Western society are the availability and palatability of food; indeed, so skilful are the modern food technologists that it is not surprising that the incidence of obesity is steadily increasing, not only in adults, but also in children (Mortimer, 1968), in spite of all the attention focussed upon it in the popular press. In addition there is no doubt that psychological factors influence appetite, anxiety or depression frequently being accompanied by overeating, and the development of obesity not uncommonly starts after some emotional crisis (Angel, 1949).

Much less is known about the controls of energy utilization, though it is probable that a variety of abnormalities here may underlie or contribute to obesity. Exercise has generally been considered to play a relatively minor role in weight reduction, as such a large amount of exercise appears to be required to produce even a small weight loss. Thus, if one walked from London to Brighton, a distance of 60 miles, it has been calculated that only 1 lb of body fat would be lost! (Passmore & Durnin, 1955). Fortunately this discouraging calculation is not quite true as it does not take into account the fact that after strenuous exercise the basal metabolic rate may remain elevated for several hours. Thus the BMR may be distinctly increased for as long as 15 hr after a game of football (Edwards, Thorndike & Dill, 1935). It is known that obese children and adults are less active than their lean counterparts (Bullen, Reed & Mayer, 1964; Corbin & Fletcher, 1968; Chirico & Stunkard, 1960), and farmers are of course aware that they can fatten their livestock more rapidly by restricting their activity, so that exercise may be rather more important in weight reduction than has been thought.

But, despite the obvious gluttony and relative inactivity to which many fat people are, or have been, prone, it does seem that there are those who, for the same calorie intake and activity gain weight more rapidly, or lose it less easily. In states of famine, when everyone loses weight, the *rates* of weight loss, and the rates of weight gain when food is restored, vary (Gordon, 1968). In addition there are those people who constantly try, by overeating, to gain weight, and yet are unable to do so. Others can lose weight only with extreme calorie restriction, but regain it with the least dietary relaxation; and many people will regain their original weight after reduction, and yet not exceed this original weight. It is clear that the weights of many individuals remain remarkably stable over long periods, in spite of enormous differences between them in calorie intake. For example, among young men whose individual weights were constant for several weeks, and who had approximately the same level of activity, calorie intake varied from 1600 to 7400 calories per day (Rose & Williams, 1961).

It would seem therefore that there is some feedback mechanism, perhaps genetically determined, setting this 'natural' weight at a certain level, and that the control of this feedback may not be merely through the appetite. In short, it seems reasonable to admit that there may be some truth in the protestations of moderation in eating habits so common among fat people.

Is it possible that there is a *genetically* determined abnormality in energy utilization in the obese, such as to allow more energy to be stored as fat, and less to be used in heat expenditure than in the lean? Most of the evidence for genetic factors in obesity is indirect. There have been many large family studies establishing a familial predisposition to obesity (Angel, 1949; Dunlop & Murray Lyon, 1931; Gurney, 1936; Fellows, 1931), and this may not always be due merely to common environmental factors. If environmental factors were of predominant importance it has been argued that there should be *more* fat offspring of fat parents than there are (Angel, 1949). With two obese parents about two-thirds of the offspring are obese (Angel, 1949); in a study of seventy-five obese women, 82% had either one or two obese parents, whereas in only 38% of a non-obese group were one or both parents obese. Astwood (1962) cites an interesting family of eight siblings, living together, four of whom weighed between 275 and 457 pounds, but the other four were of normal proportions, which again suggests a genetic influence. Furthermore, twin studies have shown that the similarity between the weights of identical twins, reared and living in identical environments, extends also to those reared and living in dissimilar environments (Von

Verschuer, 1927). An interesting study reported by Withers (1964) suggests that, although about two-thirds of the children born to two obese parents are also obese, the weights of *adopted* children do not appear to bear any relation to the weights of the adopting parents, even when adoption is early.

Nevertheless, even assuming that the individual genetic make-up influences the development of obesity, it is by no means clear how this influence operates. It is possible that hereditary factors affect energy utilization—and in view of the thousands of ways in which individuals differ from one another an inflexible constancy of energy utilization would be remarkable—but it is equally possible that they affect appetite controls.

We do know that there are factors other than food intake influencing both lipogenesis and lipid mobilization in strains of certain hereditarily obese rodents. It is known for example that lipogenesis from pyruvate is greater in fat cells obtained from hereditarily obese rats than it is in fat cells obtained from rats made obese by hypothalamic lesions (Bray, 1968). In addition the cells from the genetically obese animals channelled relatively more pyruvate and glucose into glycerol than into CO_2 . In certain strains of hereditarily obese animals, though not in all, the increased lipogenesis persists after fasting has caused weight reduction (Mayer, 1960); under these circumstances enhanced fat synthesis cannot be merely a consequence of obesity, and it has been suggested that it may be a cause of the obesity of these animals. Mayer (1960) observed that in certain hereditarily obese mice weight reduction also failed to restore body composition to normal; there still remained an abnormally high fat content in the carcass. Also, at an early age, *before* such animals become obese, there is an excess of carcass fat (Mayer, 1960). This all suggests that in some animals genetic factors do in some way cause more glucose to be converted into fat, and less into oxidative pathways than normally. There is evidence that hyperinsulinism (Renold, 1968), reduced fat mobilization resulting from reduced adipose tissue lipase activity (Lochaya, Hamilton & Mayer, 1963), and the abnormal presence of glycerokinase in adipose tissue (Treble & Mayer, 1963)—which promotes triglyceride synthesis—may all be concerned in the development of obesity in these animals.

Hard facts regarding energy metabolism in man are however relatively scanty, and we lack much vital information, including for example the fundamental question of how much of a 1000 calorie meal is dissipated as heat. Much of the information we have relates to blood samples, which in terms of energy metabolism is like looking at a pipeline between two large reservoirs in the hope of understanding what is going on at each end. For example,

high levels of serum fatty acids could indicate increased mobilization of fat, or reduced removal of fat from the circulation. Much of the data on lipolysis in obesity has been based upon such measurements, and conflicting results have been obtained. Thus Dole (1956) and Solomons, Ensink & Williams (1968) demonstrated elevated fasting levels of free fatty acids and glycerol in obese subjects. Klein *et al.* (1965) however, found reduced levels of free fatty acids in their fasting obese subjects. The discrepancies between the results of different workers probably relate to differences between the subjects studied—with respect to the degree and duration of obesity, and with respect to carbohydrate tolerance. It is evidently of considerable importance to know the state of carbohydrate tolerance in such studies, as it has recently been demonstrated that basal levels of free fatty acids and glycerol increase with increasing weight in the presence of impaired carbohydrate tolerance, but diminish with increasing weight when carbohydrate tolerance is normal (Bagdade, Porte & Bierman, 1968). Defective mobilization, or increased utilization of fat does seem to occur with *prolonged* fasting and also after exercise in the obese, as suggested by smaller increments in plasma glycerol, acetoacetate (Solomon *et al.*, 1968), and free fatty acids (Klein *et al.*, 1965; Corvilain *et al.*, 1961; Opie & Walfish, 1963), under these circumstances, in obese compared with lean subjects. Defective mobilization would tend to maintain the obesity.

Among other metabolic abnormalities associated with obesity is a state of insulin resistance, which in some cases is accompanied by impaired carbohydrate tolerance (Karam, Grodsky & Forsham, 1963). Insulin resistance is present not only in muscle, as shown by Butterfield's (1968) studies of glucose uptake in the forearm muscle, but also in fat. The effect of insulin on glucose uptake by the subcutaneous adipose tissue of the forearm is attenuated in the obese (Rabinowitz, 1968), and the enlarged adipocytes obtained from obese subjects are relatively insensitive to insulin in terms of glucose uptake and utilization (Salans, Knittle & Hirsch, 1967).

Butterfield (1968) has proposed that as obesity progresses less and less insulin finds its way into muscle, because of a reduced clearance of insulin from the circulation into muscle in obesity. Hence more and more insulin is synthesized in order to dispose of glucose into the relatively insulin-insensitive adipose tissue. Lipogenesis thus proceeds under the influence of insulin, as long as sufficient insulin is available.

A recent observation of considerable interest is that insulin-like activity, determined by the fat-pad assay, increases with increasing obesity, whereas

another type of insulin-like activity, determined by the diaphragm muscle assay, declines (Shreeve *et al.*, 1968). This suggests, in obesity, either the presence of a substance which is like insulin in its lipogenic action on fat tissue, but which is opposed to its action on muscle, or the presence of a specific antagonist to the effect of insulin on muscle. An alternative possibility is a dissociation between the effects of insulin on muscle and fat in the obese. Young & Benson (1966) demonstrated an inhibitor of insulin, which is active on muscle, but not on fat, and which occurs in liver extracts and serum of rats, and man. Such an inhibitor would favour lipogenesis. Its concentration is highest in fed rats, and it disappears on fasting. It might represent a mechanism for fat storage after feeding, and it could be relevant to the aetiology of human obesity, since utilization of glucose by muscle appears to be progressively reduced in obesity, whereas utilization of glucose by fat is *relatively* facilitated. It is not known whether such a circulating inhibitor is present in subjects with spontaneous and experimental obesity.

Another factor which would tend to maintain obesity is the impaired release of growth hormone in this state (Lessoff, McHardy, Young & Greenwood, 1966), since growth hormone appears to enhance lipolysis and to increase oxygen consumption (Bray, 1969a).

If, however, any of these metabolic abnormalities were responsible for initiating obesity, one would expect that they would still be evident after weight reduction. But in general this is not so. Sensitivity to insulin (Jackson, McKiddie & Buchanan, 1969), clearance of insulin from the circulation (Butterfield, 1968) and release of growth hormone in response to hypoglycaemia (Lessoff *et al.*, 1966) all return to normal after weight reduction. In addition these abnormalities can be produced by overfeeding normal individuals (Sims & Horton, 1968), all of which suggests that they result from rather than cause the obesity.

What of the fat mobilizing substance (FMS) described by Kekwick? (Chalmers, Kekwick, Pawan & Smith, 1958). Can this have anything to do with the aetiology of obesity? This substance, which seems to be of pituitary origin (Chalmers, Pawan & Kekwick, 1960), appears in the urine during fasting—and may indeed be a cause of the lipolysis normally occurring during fasting (Cahill, Pawan & Chalmers, 1961). In addition, its injection into animals increases energy loss in stools and urine (Kekwick & Pawan, 1967), and when injected into man it can induce weight loss, ketosis, and an increase in circulating free fatty acids (Kekwick & Pawan, 1968). Obese subjects tend to have lower concentrations of FMS in the urine after fasting than lean subjects (Pawan,

1969), and it is possible that defective lipolysis, due to a deficiency of FMS might be a factor in the initiation of obesity. It may be however that the action of FMS is inhibited in the obese merely by the high levels of circulating insulin, as the rise of serum lipid levels produced in animals by injection of FMS has been shown to be inhibited by insulin (Goth & Hegedüs, 1965). Further study of FMS in experimental obesity and after weight reduction is required.

Another abnormality which might possibly cause obesity was suggested by Kreisberg (1968), who showed that glucose recycling is increased *early* in the development of obesity—that is, breakdown products of glucose metabolism are returned to the glucose pool more rapidly. This, together with the observation that glucose oxidation to CO₂ may be reduced in obese subjects, suggests a difference in the disposal of glucose between fat and thin subjects, the obese oxidizing less glucose and returning more to the glucose pool than the lean. This would result in a prolonged stimulus to insulin secretion in the obese, with hyperinsulinaemia and increased fat deposition. Studies of glucose recycling before and after weight loss in a large series of patients do not appear to have been done.

Another interesting idea is concerned with the ability to increase heat production after a meal. In the obese oxidation of glycerophosphate is reduced, which reduces heat production (Galton & Bray, 1967). Furthermore, the activity of enzymes in the glycerophosphate pathway which enhances heat production, declines with calorie restriction (Bray, 1969b). Thus, with calorie restriction heat production falls off, which would tend to maintain the obesity, and might explain the difficulty which some obese people experience in losing weight on a reducing diet. Herein lies an exciting possibility—that a thermogenic agent might be found for the treatment of obesity.

In any study of overweight people we are faced with the fact that we may be dealing with the end-stage of a dynamic process which has ceased, and such studies do not necessarily provide information about why people become obese in the first place. In this connection recent work on adipocytes is of interest. It appears that the number of fat cells in the body is largely determined by eating habits in early life. Later in life, although fasting is associated with a disappearance of the *large* adipocytes characteristic of obesity, the *number* of fat cells remains relatively unchanged in spite of weight changes (Hirsch, Knittle & Salans, 1966; Knittle & Hirsch, 1967). It may be the persistence of large numbers of relatively empty fat cells which explains the ease with which the obese regain their lost weight. As regards prevention it may be particularly important

therefore to prevent the excessive cell-multiplication which results from overfeeding in infancy and early childhood.

In summary, it is clear that there are many unanswered questions about the causes of obesity. Much more information is required in terms of measurement of energy expenditure over prolonged periods, both in the fasting state and after feeding, and during rest and activity. There are many other avenues which invite further exploration, including the nature of the increased insulin-like activity in obesity, the part played by inhibitors of insulin action in muscle, and the role of the fat mobilizing substance, of glucose recycling, and of heat production after feeding. It would certainly seem that the whole problem of obesity can no longer be ascribed simply to gluttony, but may, in part, be contributed to by a variety of metabolic errors, some of which may even be inborn.

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