REVIEW ARTICLE

Observations on obesity

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OBESITY is a tremendous threat to the health of the affluent population. The volume of morbidity associated with it is enormous; it produces more pathology than cancer or cardiac disease. We have progressed little beyond the stage where its aetiology was equated with gluttony. Perhaps this simplification is so acceptable because it enables the physician to blame his patient for what is, in effect, medical ignorance. There is much evidence that obesity is not simply the result of a calorie intake which is in excess of normal body requirements.

The syndrome is difficult to define. Marks (1960) has shown that a degree of overweight as low as 10 to 20 per cent is associated with a significant increase in mortality risk. The risk rises with the degree of overweight. The amount of morbidity must be considerably greater. Known clinical syndromes, such as those resulting from disease of the thyroid or pituitary, have been excluded from present consideration.

'Simple' obesity is not just an excess of fat. In a 12-stone man there are about 6 stones of water. Fluid control is at least as important as consideration of the metabolism of the primary foods—fats, carbohydrates and protein.

Genetic factors

There are inherited tendencies. Obese strains occur among mice, rats, dogs and pigs and hereditable factors are utilised in the farming industry. There are numerous examples of obesity present as a family characteristic in humans (Mayer 1965). Family diet may well be a factor here but it is certainly not the whole story. Identical twins brought up in different environments often closely approximate in weight. Adopted children brought up in a family vary more widely in weight than siblings who are genetically related. The factors which are inherited are probably multiple. They may include body configuration, minor degrees of glandular imbalance and defects in various enzyme systems.

Biochemical and hormonal variations

The obese may exhibit certain biochemical differences from the normal. Some might be aetiological and some the result of the disease process. In the post-absorptive state, the obese have raised plasma levels of valine, leucine, isoleucine, tyrosine and phenylalanine; glycine concentrations are reduced (Felig *et al.* 1969). Under conditions of starvation there is a similar elevation of plasma amino-acid levels, but glycine-concentration in the plasma is also raised. Glucose infusions stimulate immunoreactive insulin and this will lower the amino-acid concentrations in both the normal and the obese. Nevertheless, the proportional differences between the amino-acid levels in obese and normal are retained under the influence of the immunoreactive insulin. If the obese lose weight, these differences return to normal. Felig suggests that the raised amino-acid levels may be an indication of insulin resistance.

Insulin increases the synthesis of both fatty acids and triglycerides. Pancreatic adenoma is often associated with obesity and congenitally obese mice have hypertrophic, insulin-producing islets of Langerhans. Yudkin, *et al.*, (1969) have shown that, in certain predisposed subjects, high sucrose intakes were associated with high serum insulin

levels; weight gain and increased platelet adhesiveness. The obese exhibit an increase in the fasting and 'post-glucose' plasma insulin levels (Karam *et al.* 1963). In obesity there is a reduced uptake of glucose in muscle. More glucose is stored in adipose tissue which is less sensitive to insulin and therefore requires an increased insulin production (Butterfield and Whichelow, 1968). In the light of these reports of raised insulin levels, the association between diabetes and obesity has some incongruity.

Adrenaline stimulates the release of fatty acids; it also causes the breakdown of glycogen to glucose. This latter process is mediated via the enzyme phosphorylase. The phosphorylase concentrations in the adipose tissue of the obese is several times that of normal; it is also in raised concentration in the liver. The fasting obese appear to show a reduced response to the adrenal medulla and this might contribute to increased levels of amino-acids and immunoreactive insulin in the blood (Januszewicz *et al.* 1967). It might also be associated with the raised phosphorylase concentrations. Both glucagon and growth hormone play a part in the complex hormone balance. Glucagon stimulates glycogenolysis by activating liver phosphorylase and growth hormone causes hyperglycaemia and lipolysis in abnormal states.

Kekwick *et al.* (1959) have shown that the urine of normal and obese subjects, during fasting, contains a 'fat mobilizing substance'. The substance is a polypeptide and can cause hypoglycaemia, ketonaemia and depletion of body fat when injected into human volunteers. The pituitary is necessary for its production and it disappears from the urine if the level of carbohydrate intake rises above 80gm/day.

Some control mechanisms

Experimental work is of interest here. Bilateral destruction of the ventromedial nuclei of the hypothalamus produces obesity. This has been demonstrated in the rat (Hetherington and Ranson 1940); in the mouse (Mayer *et al.* 1955) and by other workers in cats, dogs, monkeys and ruminants. Brobeck (1946) showed that the obesity could be accounted for almost entirely by increased food intake and called the condition 'hypothalamic hyperphagia'. Anand and Brobeck (1951) showed that bilateral destruction of the lateral hypothalamic area caused aphagia. There is, therefore, a hypothalamic feeding centre. The ventrolateral area controls the initiation of feeding and the ventromedial nucleus exerts an inhibitory action.

Mayer has demonstrated that the cells of the ventromedial area have a special affinity for glucose. Injections of gold-thioglucose will produce obesity in the experimental animal. This is because the cells of the satiety centre exhibit their affinity for glucose and selectively take up the toxic gold salt. It is postulated that there is a glucostatic mechanism controlling food intake which is dependent on the special response of these cells to blood glucose levels. Krauss and Mayer (1965) have demonstrated that there are similar mechanisms for shutting off food intake in response to high blood protein levels or amino-acid imbalance. This appears to operate under exceptional circumstances. There is evidence of other limiting factors to food intake such as pyrexia, dehydration and gastric distension, all of which exert an effect via the hypothalamic centre.

Peripheral receptors play a part in the control of feeding. There is experimental evidence that receptors in the gastric mucosa exert a controlling influence. The receptors are sensitive to the intakes of food and probably respond to blood glucose levels.

In the rat, these receptors appear to be sensitive to the caloric constituent of feeds.

Some disadvantages of calorie restriction

The mainstay of the treatment of obesity has always been the reduction of food intake. The theoretical basis for this is the simple correlation between an excessive food intake and obesity. There are flaws to this concept.

Each person must utilize a certain number of calories each day. If the calorie intake is reduced then there should be a weight loss corresponding to the calorie deficit. To some extent the calorie theory implies that fats, carbohydrates and protein can be regarded as mutually interchangeable, calorie for calorie, for the purpose of dieting. William Banting (1863), a nineteenth century London undertaker, pointed out that carbohydrate-restricted diets produced the greatest weight reduction. Innumerable diets since then have tended to support this observation. The three primary food substances are not metabolized to their fullest extent immediately on intake and each exerts a complex effect on the body metabolism. Their reaction under hormone control has already been touched upon; furthermore, carbohydrates stimulate and fats depress lipogenesis.

Starvation tends to produce an increased efficiency in the utilization of food and the normal and obese react differently. Normal people on a 1,000 calorie diet, containing 90 per cent fat, showed marked hyperketonaemia, hyperketonuria, hypoglycaemia and a negative nitrogen balance. The obese, under similar conditions, responded with little ketosis, unchanged blood sugars and little nitrogen loss (Kaunitz 1966).

If rats are given less than half the quantity of their freely chosen food intakes, they lose weight initially; the body then appears to adjust and the weight becomes constant; finally they may regain some weight. Similar results have been obtained in experiments on humans. The obese, on a calorie-restricted diet, lose weight initially and then appear to make some adjustment toward the lower food intake. Furthermore, the obese tend to adjust more rapidly to calorie restriction than the normal and their calorie expenditure drops more rapidly than that of the controls. Bray (1969) has shown that patients partially offset the effects of calorie restriction by a reduction in their basal calorie expenditure. Kekwick *et al.* (1959) postulated that the amount of energy made available to the organism could be varied constantly. Stirling and Stock (1968) have suggested that this might be achieved by reducing the activity of the glycerophosphate cycle. This is, in fact, reduced in obesity. Similar adaptive processes have been shown to take place in malnutrition with regard to reduced protein intakes (Waterlow 1968).

The starvation treatment of obesity is, therefore, considerably handicapped by the ability of the body to adjust. To some extent this might be expected. The human being has evolved, like any other animal, to live in the natural state. There is little evidence that he has evolved physiologically to adapt to a civilized environment. In the wild state, man's food must have come irregularly and it would be a survival characteristic if he were able to cope with wide variations in the quantity and regularity of food intakes.

Calorie-restricted diets are remarkably unsuccessful in the long term. In a nine-year prospective study of 98 children, only 25 per cent were within 20 per cent of normal weight. Among the girls in the study the proportion of grossly overweight patients at the final examination was greater than at the first examination (Lloyd *et al.*, 1961). In adults the results are no better and about 80 per cent of patients tend to regain, in the long term, the weight lost on calorie-restricted diets. Jackson *et al.* (1969) point out that 'starvation does not cure the underlying disturbance in obesity and that, in most cases, it only temporarily halts further weight increase'.

Discussion

The successful treatment of any disease must be directed against its causation. The obese do not necessarily eat more than the normal. Obese children in an English orphanage ate less than their non-obese counterparts (Kaunitz 1966). In studies on obese high school girls and also on boys, it was found that the obese ate less than the controls (Johnson *et al.* 1957). In their review of 8,513 patients treated for weight reduction, Godfrey, Newton and Rosen (unpublished data) noted that many obese

patients had calorie intakes below normal. This was common amongst obese, middle-aged women.

Obesity may not be primarily synonymous with an excess of fat. Some 40 to 50 per cent of the obese patient consists of water. This must have some considerable significance on the grounds of quantity alone. It has no calorific value and this factor may explain the perplexing discrepancies between calorie intakes and obesity.

The body contains 16 litres of extracellular fluid. This must contribute considerably to the shape and contour of the patient and influence the clinician when he estimates whether his patient is obese or not. The cosmetic effect of changes in this relatively large quantity of water must be considerable, and it is the cosmetic defects which bring far more obese patients to the physician than fears prompted by assurance company statistics. The water content of the body has been regarded as relatively constant in weight in relation to the height and lean tissue mass. In the average male this would represent 60 per cent by weight of the total body weight and the figure falls to 40 per cent in the obese. This implies that the greatest variation in obesity is in increases in the fat content. There is much evidence that this is not entirely true. Godfrey, Newton and Rosen have shown that the average loss in weight in the first week of dieting was 5.53lbs. In many cases over 7lbs were lost in the first three days. This rapid weight loss, often with an associated diuresis and without constitutional upset, must largely represent a loss of water rather than fat. There is much supporting evidence which suggests that fluid variations are important in the obese. Fluctuations of from 2 to 5 lbs in association with the menses are very common and a gain and loss of 9½lbs was noted in an 11-stone, nineteen-year-old girl, in association with menstruation. The contraceptive pill frequently results in gains in weight independently of increased food intake. These increases in body fluid are probably produced by hormonal imbalance and the defect is more likely to be in the pituitary than in the sex glands. In all but the minor degrees of overweight, the problem of obesity must be both that of fluid retention as well as excessive fat deposition.

In the affluent society increased food intake plays a major rôle in a percentage of cases of obesity. The environment is full of constantly improving culinary techniques; and all the pressures of the advertising world exhort the susceptible to greater intakes of more and more varied foods. Small wonder that the uncivilised physiology of our make-up is so often unable to cope with these sophisticated stresses. The timing of food intakes may be important. Fabry (1967) has shown that in people taking three or fewer meals per day there was a greater tendency to overweight than in controls taking five or more smaller meals. In this country, in 1968, some 40 per cent of the population was found to take a substantial breakfast, but less than 8 per cent of those who have a weight problem do so. The vast majority of patients with a weight problem do not eat breakfast, take a small lunch and a large evening meal.

It has been noted that the obese tend to move less than normal. This was demonstrated by Johnson *et al.* (1957) in 'time and motion' studies on obese schoolchildren. It is not always clear whether the obese move less because of their obesity or whether inactivity causes gain in weight. Obesity may develop in a person who has reduced his physical activity. The motor car and the office desk frequently bear the blame for this. The defect, however, does not lie with these modern whipping boys but with the inability of the body to adjust to the reduction in energy output.

Stress is an important factor in the aetiology of this disease. There is the connection between compulsive eating and gain in weight. The psychological mechanisms have been well documented. There remains a small group in whom psychological stress appears to result in a gain in weight which is apparently unrelated to any increase in food intake. The type of stress is that which appears to set up emotions of rage and frustration in a

susceptible individual and are maintained over a relatively prolonged period of time. Presumably the effects are mediated via the pituitary.

The genetic factors have already been touched upon. It is interesting to speculate that a very minor enzyme defect could be a major aetiological factor. It is only recently that the significance of the inheritance of glucose-6-dehydrogenase deficiency has been appreciated. The WHO (1967) report estimated that some 100 million people have this defect, which under certain environmental conditions conferred some survival advantages. An inherited enzyme abnormality, producing obesity in the civilised society, could well be of survival value in a primitive society, if it conferred the ability to cope better with starvation and irregular feeding.

Conclusion

Obesity is a disease which presents a considerable threat to health, and much of its aetiology is unknown. There are innumerable dietary treatments and their number and variety is some indication of their lack of effectiveness. The most successful diets are those which restrict the carbohydrate or fat intakes, allow a relatively high daily calorie ration and in which the food is divided into four or more meals spread, in timing, throughout the day. Treatment should include measures aimed at reducing fluid retention by restricting the fluid intake and the judicious use of diuretics. It is unlikely that the risks of toxicity from drugs prescribed by a competent physician could ever compare to the risks of the disease. The future of treatment must eventually lie with a better knowledge of the hormonal control, and the possible mutual interaction between the metabolites of the various dietary constituents and their effect on lipogenesis.

Summary

Obesity is one of the major health hazards in the civilized society. Its cause is largely unknown but it is clearly not due, primarily, to excessive food intake. The various genetic factors and known metabolic and hormonal abnormalities are outlined. The neurological control of dietary intakes and the ineffectiveness of 'starvation' diets are underlined. The aetiology of the disease is discussed. The problem must be viewed in the light of the fact that the basic physiology of the human animal is adapted to live in a 'natural' habitat and not under the sheltered conditions of the welfare society. More than 50 per cent of the average, adult body weight is made up by water. Variations in this must play a considerable rôle in the production of obesity. The normal stimuli to feeding and the material factors governing food intakes in an affluent society must provide problems for our unsophisticated physiologies. Psychological stress may be aetiological in two ways. In most cases, where it is operative, it produces the syndrome of compulsive eating but in some it may operate directly via the hypothalamus and the pituitary. The most effective treatment at present is based on principles which involve the use of high protein diets and fluid control in combination with drugs. The future control of the disease must lie in a better understanding of the hormonal factors and the mutual interaction of the dietary metabolites.

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FROM A LETTER TO A FRIEND

In the Years of his Childhood he had languish'd under the Disease of his Country, the Rickets; after which notwithstanding many have been become strong and active Men; but whether any have attain'd unto very great Years, the Disease is scarce so old as to afford good Observation. Whether the Children of the English Plantations be subject unto the same Infirmity, may be worth the Observing . . . . . but too certain it is, that the Rickets encreaseth among us; the Small-Pox grows more pernicious than the Great; the King's Purse knows that the King's Evil grows more common. Quartan Agues are become no Strangers in Ireland; more common and mortal in England: and tho' the Ancients gave that Disease very good Words, yet now that Bell makes no strange sound which rings out for the Effects thereof.

Some think there were few Consumptions in the Old World, when Men lived much upon Milk; and that the ancient Inhabitants of this Island were less troubled with Coughs when they went naked, and slept in Caves and Woods, than Men now in Chambers and Feather-beds.

SIR THOMAS BROWNE. *The works of Sir Thomas Browne*. Vol. III. 1907. Edinburgh. John Grant. p. 377.

A LETTER TO A FRIEND

Tho' we could not have his Life, yet we missed not our desires in his soft Departure, which was scarce an Expiration; and his End not unlike his Beginning, when the salient Point scarce affords a sensible Motion, and his Departure so like unto Sleep, that he scarce needed the civil Ceremony of closing his Eyes; contrary unto the common way wherein Death draws up, Sleep let fall the Eye-lids. With what Strift and Pains we came into the World we know not; but 'tis commonly no easie matter to get out of it: yet if it could be made out, that such who have easie Nativities have commonly hard Deaths, and contrarily; his Departure was so easie, that we might justly suspect his Birth was of another nature, and that some *Juno* sat cross-legg'd at his Nativity.

SIR THOMAS BROWNE. The works of Sir Thomas Browne, Volume III. 1907. Edinburgh. John Grant. P. 371.