Review Article

Obesity in perspective

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Summary

Attitudes to obesity are changing. It is currently regarded as a common, multifactorial disorder with serious medical and psychological consequences. It is also resistant to treatment. Recent research with experimental animals has given new insights into the molecular pathology of this condition and gives some hope of novel therapeutic intervention.

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Obesity is a symptom frequently described[1,2] as the presence of more than 20 - 30% of body weight as fat (mainly triglycerides). It should not be confused with overweight (composed of organ, bone, muscle and fat mass), oedema or mild fatness. The prevalence of obesity in Western society is increasing.[3] It is frequently associated with an increased risk for renal disease, cirrhosis of the liver, heart disease (i.e. sudden death, angina pectoris, congestive heart failure but not coronary thrombosis), gallbladder and endocrine disease, osteo-arthritis, hypertension, diabetes mellitus, gout, suboptimal pulmonary function and impaired life expectancy.[1,4] Mortality is not a linear function of body weight, but increases dramatically above a certain figure.[5,6]

Obesity is frequently associated with increased blood levels of free fatty acids, triglycerides, uric acid, glucose and insulin, and with decreased levels and response of growth hormone (increased synthesis of cholesterol has also been reported, although blood levels may be normal). (These parameters are of course influenced by diet and whether the person is in a dynamic or static phase of weight gain.[2]) The socio-economic cost to society is considerable, and it must be emphasized that obesity as defined is a public health problem and not one merely cosmetic in nature. To the individual the cosmetic aspect may, however, represent a severe social and psychological handicap which can dramatically alter his quality of life.[4,7,8]

The aetiology of this condition is multifactorial and may involve hypothalamic, neural and neurotransmitter mechanisms and/or genetic, hormonal, metabolic and/or nutritional factors.[1,9,10] The primary derangement is an increased caloric intake (metabolizable energy) in relation to caloric expenditure. This may not imply hyperphagia, but may be related to increased caloric density due to eating pattern or diet,[1] reduced caloric expenditure due to physical or mental inertia,[11] increased fat anabolism due to differential tissue utilization of glucose,[11,12] or to a more efficient catabolism,[13] i.e. reduced thermogenic capacity.

Obesity therefore represents a syndrome rather than a specific disease. It is not a self-inflicted condition any more than is heart disease or depression, but represents a disturbance in whole-body energy metabolism which may have various aetiological factors.[1,10]

The syndromes of obesity are: (*i*) genetic (e.g. Prader-Willi syndrome); (*ii*) nutritional (diet, eating pattern); (*iii*) hypothalamic (e.g. tumour); (*iv*) endocrine (e.g. Cushing's syndrome, adult-onset diabetes mellitus); (*v*) metabolic (distribution and activation of enzymes in various tissues); (*vi*) hormonal (distribution of receptors in various tissues); and (*vii*) psychological (reactive obesity). (Genetic and endocrine factors are not dealt with in this review. For excellent recent summaries see Bray and York[10] and Bray[14] (autonomic and adrenal hypothesis) respectively. Genetically selected animal models have contributed enormously to the study of obesity.)

These syndromes are not mutually exclusive; several of them may interact to produce the resultant obesity.

Nutritional status and physical exercise are the primary contributing factors to obesity which are recognized by the man in the street (i.e. gluttony and sloth) and indeed by many medical practitioners.[6] Although these factors are present in the majority of cases of obesity encountered, they are possibly overlaid on (for example) a hypothalamic-mediated hyperphagia or on a genetic predisposition which results in an altered metabolic profile and in a person more susceptible to obesity. Established obesity may be maintained in the presence of a 'normal' nutritional intake,[15] and in experimental animals obesity can develop in the absence of hyperphagia.[16]

Areas of the hypothalamus are thought to control hunger (ventrolateral area (VLH))[17,18] and satiety (ventromedial area (VMH)).[19] The noradrenergic neurons passing through the VMH area (ventromedial bundle) may be involved in these neuro-endocrine control mechanisms (VMH = α-adrenoceptors; VLH = β-adrenoceptors) and they may interact with the nigrostriatal dopaminergic (VLH) and serotonergic (VMH) neurons.[20] Certain anorexiant drugs have been shown to interact with these neurons, e.g. amphetamines (dopamine, noradrenaline) and fenfluramine (dopamine, serotonin).[20] Gastric distension acting through neural pathways (vagus nerve) represents a crude physiological signal of satiety, although there may be feedback from the gut to the hypothalamus through certain gut hormones, e.g. bombesin, cholecystokinin.[20] Other metabolic products have also been proposed to be involved in metabolic feedback on hypothalamic control of appetite, e.g. short-chain fatty acids,[21] tryptophan.[22] It has also been suggested[20] that glucose or insulin may act on the VMH area (satiety) and increase noradrenergic output while free fatty acids may act on the VLH area (hunger). Opioid receptors in the reward areas of the brain may also be involved in appetite control.[21]

Classification

The obesities have been classified morphologically into two types:[23] (*i*) hypertrophic (± 80%) — increased size of fat cells (also known as alimentary, social, exogenous, mobile, acquired or late-onset); and (*ii*) hyperplastic (± 20%) — increased number of fat cells (also known as endogenous, essential, metabolic, hypercellular, pathological, refractory or early-onset).

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Hypertrophic obesity is generally of maturity-onset (> 30 years of age) and mild. It responds to diet and exercise and is frequently found in lower socio-economic groups. It should be noted that the division into the two types is not clear-cut and not universally accepted. An increase in adipose cell size is present in all forms of obesity, and the overall incidence of obesity increases with age (up to ± 50 years).

Hyperplastic obesity has generally an early age of onset and is more refractory to treatment. The increase in adipocyte cell number is generally not reversible (although this can be achieved transiently by surgical lipectomy and may occur with 'prolonged' weight loss) even in the face of weight loss, which represents a reduction in fat cell size but not in number.[24] This adipocyte hyperplasia represents a significant factor in obesity refractory to long-term treatment. Adipocyte proliferation mainly takes place early in life (< 2 years) and at puberty (females), but when adipocytes reach a certain size, adipocyte proliferation occurs at any age,[24-26] and thereafter adipocyte number correlates with the extent of obesity.[1] Therefore while fat infants frequently become fat adults, this is not always the case, although neonatal or infant adipocyte hyperplasia represents an increased risk factor for future adult obesity. Conversely, hyperplastic obesity has on occasions been shown to be adult-onset in nature, i.e. reactive obesity.

It is a matter of common experience that each adult has the capacity to maintain a fairly constant body weight over prolonged periods. This requires physiological regulation of some precision.[27,28] Certain perturbations may alter this weight (dynamic phase) and possibly establish a new steady state (static phase). In respect of the development of obesity, the new steady state may be one where adipocyte hyperplasia during the dynamic phase has led to an increase in weight. This new steady state can be maintained without increased nutritional intake and becomes the new norm for that individual.[24,26,27] (Certain people, however, continually put on weight, particularly if obesity is already well-established.) Various factors have been suggested to account for the body's ability to maintain relatively constant weight.[29] These have given rise to the terms lipostat (long-term control),[26,30] thermostat[31] and glucostat[32] (short-term control) and aminostat[33] (age-related control). They represent attempts to explain weight homeostasis on the basis of biochemical feedback of dietary metabolites on hypothalamic regulation of appetite and metabolism (possibly all these mechanisms operate and this makes weight control on the basis of dietary content difficult as each dietary component may trigger its own satiety signal). It has also been suggested that insulin is involved in the short- (VMH area) and long-term (other brain areas) control of weight homeostasis, and in stimulation of sympathetic noradrenaline release.[34] None of these hypotheses has been validated, but what is apparent is that during the dynamic phase of obesity the body weight homeostatic mechanisms fail to operate or are overridden.

In practical terms it means that established obesity (static phase) is more refractory to treatment, and that prolonged weight loss is difficult to maintain.[24] This may also be attributed, in part, to the difference in insulin response in adipocytes of varying size (small > large) and to a reduction in thermogenesis on hypocaloric intake.[2]

A further complication is the possibility that the nature of adipocytes (omental or subcutaneous) may not be uniform.[1] This may explain the characteristic distribution of fat found in certain endocrine obesities.

Treatment

Obesity (particularly hyperplastic) represents an extremely demanding therapeutic challenge.[6] Most physicians, while not completely in agreement with many widely publicized diets, recommend caloric restriction on a balanced or supplemented diet, mild aerobic exercise, and behavioural therapy for mild obesity.[2,35] Specific dietary restriction (i.e. popular diets) can increase individual motivation and give an easy method for individual determination and control of caloric intake, and the reduction in food variety reduces palatability and appetite but can lead to dietary deficiency states. The importance of mild exercise should also be stressed. The increased prevalence of obesity in handicapped children suggests that lack of exercise may not only be a symptom characteristic of obesity, but also contribute to its development. While exercise as a treatment of obesity may have little impact on overall energy expenditure (basal metabolism, i.e. maintenance of vital cell functions, accounts for the major part (60 - 70%) of energy utilization[13]), it may alter hormonal or metabolic factors and relieve secondary changes of obesity, e.g. insulin resistance, or cause prolonged (± 24 hours) post-exercise changes in metabolic rate which may contribute to continuing weight loss.

Psychological or environmental factors may also play a role in the development of obesity. While normal people tend to start (hunger signal) and stop (satiety signal) eating in response to internal physiological stimuli, indications[36] are that obese people tend to respond more readily to external appetite stimuli, i.e. smell, taste and presentation of food. Such factors may override internal hunger and satiety signals.

These internal signals may be manipulated with anorexiant drugs, and their use (when recommended) is as a supplement to hypocaloric diets, but behavioural therapy is important in long-term weight loss, particularly as repeated unsuccessful attempts at weight loss can alter metabolic response with the increased likelihood of the development of more severe obesity in the future,[37] i.e. 'rebound effect' or 'adaptive hyperlipogenesis'. Such episodes are also disheartening for the individual. Behavioural therapy aims to reinforce altered activity patterns and lifestyle (it is difficult to contemplate eating only pineapples for the rest of your life!), to change priorities and gratification signals, and to build a better self-image and develop self-confidence and a sense of personal responsibility.[35]

Therapy with anorexiant drugs, thyroid hormones or biguanides is controversial and should be carried out under close medical supervision, or after firm diagnosis of (for example) hypothyroidism. Surgical intervention by intestinal bypass, gastric banding or jaw wiring is recommended only for grossly obese patients and these procedures are normally carried out in specialist clinics and preceded by procedures to reduce oedema, improve respiratory function and establish metabolic homeostasis. While intestinal bypass has a good record in terms of prolonged weight loss, it has many serious long-term side-effects.[5] Suction lipectomy should be performed by an experienced plastic surgeon and it is intended more as a cosmetic procedure than as a treatment of gross obesity.[38]

At the present time it must be stated that the results obtained in the treatment of obesity are disheartening for both therapist and subject. Nevertheless, more recent experiments with animal models have given rise to new insights into the molecular pathology of obesity which may find application in humans, and gives some hope for novel therapeutic intervention in the near future.

While the first half of this presentation dealt mainly with caloric intake, the second part will deal mainly with caloric expenditure.

New horizons

Thermogenesis

The role of thermogenesis in body-weight homeostasis was first suggested by Rubner[39] and Neumann[40] in 1902. Temperature homeostasis in man is controlled by areas of the hypothalamus, and production of thermal energy is linked to oxygen consumption and to the efficiency of generation or utilization of adenosine triphosphate (ATP). After a meal there is an increase in body temperature due to the processes of digestion and absorption. This has been called the specific dynamic action of food. It has often been equated with dietary-induced thermogenesis (DIT), although this latter effect is more prolonged and depends on the nature of the food and the metabolic fate of the absorbed nutrient.[13] The DIT of food will be treated here as heat generation distinct from what is known as adaptive or regulatory thermogenesis (AT) (this has also been suggested to be a component of DIT), although the DIT and AT effects may interact. AT (also known as non-shivering thermogenesis: NST) is a metabolic response to cold stress which is distinct from shivering thermogenesis (ST), which is a neuromuscular response to sudden cold exposure. AT (NST) has features in common with the action of noradrenaline at thermoneutrality.[41] It has been shown that genetically obese mice have a reduced capacity for NST and are more sensitive to prolonged exposure to reduced temperature.[20] In the presence of cold exposure or increased noradrenergic output at thermo-

neutrality there is an increase in metabolic rate and cardiac output which is inversely related to animal body weight (i.e. mice > rats > man in thermogenic response).[42] The site of AT (NST) in man is thought to be skeletal muscle, liver and brown adipose tissue (BAT).[43,44] Although BAT constitutes only 2% of body weight in humans, 30% of the increase in total cardiac output is diverted to this tissue (in rats) under the influence of noradrenaline, and more than 60% of the excess oxygen consumed (increased metabolic rate) is taken up by BAT.[45] Cold acclimatization has been shown to increase the number of BAT cells in areas of mice normally associated with white adipocytes,[46] and Rothwell and Stock[47] have demonstrated an increased thermogenic response to noradrenaline in cafeteria-fed obese rats during the period of subsequent weight loss (22 days). BAT is highly vascularized and innervated, and stimulation by noradrenaline is via sympathetic nerves and BAT β-receptors. It may also be regulated by the VMH area of the brain.[20] It has been proposed that altered blood flow gives rise to tissue-specific (BAT) metabolism and oxygen consumption. Blood flow to the heart, diaphragm (respiratory muscles), skin and white adipose tissue of mice is increased after administration of noradrenaline.[20]

BAT thermoregulation is derived from β-oxidation of fatty acids by BAT mitochondria and the uncoupling of subsequent respiratory chain ATP synthesis from electron transport.[48] This occurs through a leak in membrane proton conductance which is mediated by a 32 000 MW polypeptide (thermogenin), acetyl CoA or fatty acids and guanosine diphosphate.[48,49] The result is an increase in oxygen consumption and increased heat dissipation due to thermal leak from a relatively inefficient synthesis of ATP. The obese person would in this respect appear to be more efficient than the lean individual. (Such processes are used by the BAT of hibernating animals on revival in spring,[50] and these animals have frequently been used as experimental models, e.g. hamsters.) (A review of thermogenesis in BAT and its implications in obesity has recently been published by Himms-Hagen.[51])

In other respects also obese people use energy more efficiently than lean people. The activity of the Na/K-ATPase ion pump is reduced in certain tissues of the obese mouse[52] and man.[53] This pump maintains intracellular ion gradients necessary for secretory processes, enzyme action and neurotransmission. It requires ATP and may be influenced by thyroid hormones (increased) and insulin (decreased),[53] but its role in obesity is not yet firmly established.

Newsholme[54] and Newsholme *et al.*[55] have proposed a further component of thermoregulation which they suggest will give increased sensitivity in metabolic regulation, and may produce heat as a side-effect of ATP consumption. The term 'futile cycles' has been used to describe these metabolic pathways. The concept applies to independent (non-equilibrium) forward and reverse reactions where ATP is consumed and heat is generated in an exothermic (reverse) reaction. (It is through such reactions that heat is generated for the flight of the bee.) These cycles have two components necessary for cycling activity and the relative rate of each reaction (i.e. forward and reverse) controls the flux through or across the cycle, and the rate of cycling. The rate of cycling controls the heat generated, e.g. simultaneous high levels of insulin (forward reaction) and noradrenaline (reverse reaction) could give a low cycle flux, a high cycling rate and substantial heat production (Fig. 1).

Newsholme[56] has reported that the rates of the triacylglycerol/fatty acid, glucose/glucose-6-phosphate, fructose-6-phosphate/fructose bisphosphate and glycogen/glucose-1-phosphate cycles are increased in BAT and/or white adipose tissue by cold stress, noradrenergic stimulation and/or feeding. He has suggested that a reduced capacity for cycling may contribute to the development of obesity.

Finally, it should be stated that increased thermogenesis must involve increased heat loss to maintain thermoneutrality. Heat loss may be reduced in the obese and this may limit thermogenesis.[2] Conversely, it has also been suggested that thermogenesis itself may act as a satiety signal.

The AT (NST) in BAT, activity of the Na/K-ATPase pump and futile energy cycles may all be activated by noradrenaline, which also increases cardiac output to specific tissues and increases metabolic rate. Noradrenaline has specific adrenoceptors on both white adipose tissue and BAT.

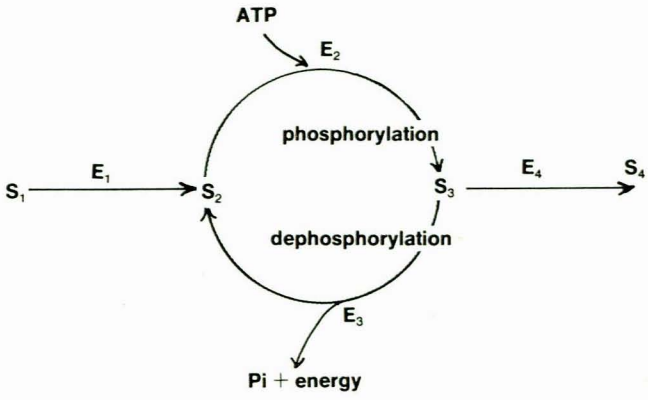

Fig. 1. Diagram of a futile cycle. The two enzymes involved in the cycle are E_2 and E_3 which control the conversion of substrates S_2 and S_3. If both E_2 (insulin) and E_3 (noradrenaline) enzymes are activated, a rapid cycle will be established with consumption of ATP and thermogenesis. The flux across the cycle ($S_1 \rightarrow S_4$) will under these circumstances be reduced.

Adipocyte receptors

Adipocyte homeostasis has often been discussed in terms of the lipogenic effect of insulin and the lipolytic effect of noradrenaline/adrenaline (adrenocorticotrophic hormone, thyrotrophin and glucagon are also lipolytic). It is now known that there are four different types of adrenoceptors in human white adipose tissue — β_1, β_2, α_1 and α_2. (This topic has recently been reviewed in depth by Kather[57] and by Fain and Garciá-Sainz[58] and will be discussed only briefly.) (Adrenaline originates mainly in the adrenal medulla, and noradrenaline is released from sympathetic nerve endings.[58] The role of this 'sympatho-adrenal system' in obesity has recently been reviewed by Landsberg and Young.[59])

The β_1-receptors (adrenaline = noradrenaline) are linked to the adenylate cyclase system and to the stimulation of lipolysis, and this effect is inhibited by insulin. The β_2-receptors (adrenaline > noradrenaline) may be linked to the methylation of certain phospholipids, and possibly to eicosanoid biosynthesis, although this is not conclusive.[58] The ratio of $\beta_1 : \beta_2$ receptors may vary with adipocyte cell maturity, but both types are present on mature adipocytes.[57] The α_1-receptors (noradrenaline) are coupled to the phosphatidylinositol cycle[57] and to alterations in intracellular levels of eicosanoids and calcium.[60–62] They are the predominant catecholamine receptors found on hepatocytes and they regulate glycogen metabolism, i.e. inhibit glycogen synthetase, but they have no established role in adipocyte lipolysis.[57] They are absent in subcutaneous adipose tissue but are present in omental adipocytes.[63] The α_2-receptors (adrenaline) are also coupled to the adenylate cyclase system. While β_1-stimulation increases cyclic adenosine monophosphate (cAMP) levels and lipolysis, α_2-stimulation lowers intracellular cAMP and inhibits lipolysis. In man, α_2-adipocyte responsiveness has been shown[57] to be increased in areas of preferred fat deposition, e.g. hip and gluteal regions. The ratio of $\beta_1 : \alpha_2$ receptors and their individual responsiveness may be influenced by thyroid hormones, i.e. hypothyroidism decreases β_1-receptor response, hyperthyroidism decreases α_2-receptor response.[57] Hypothyroid rats have also been shown to have increased levels of cAMP phosphodiesterase, increased transport of hexoses into adipocytes and decreased levels of serum growth hormone.[58] The α_2-receptor responsiveness is (paradoxically) increased in fasting subjects.

While β_2- and α_1-receptor stimulation may influence intracellular eicosanoid levels, the eicosanoids also have their own adipocyte cell surface receptors. At nanomolar concentrations (in the presence of guanosine triphosphate) prostaglandin (PG) E_2 is a potent inhibitor of catecholamine-induced lipolysis,[57] while PGD_2, PGI_2 and micromolar concentrations of PGE_2 stimulate lipolysis.

Scaramuzzi *et al.*[64] and Curtis-Prior[65] have proposed that PG metabolism may play a role in obesity, and may offer an area for therapeutic intervention.

Adipose tissue metabolism is obviously complex, and despite apparent morphological homogeneity, at the molecular level white

adipocytes are heterogeneous. To complicate the picture further, insulin (in the absence of calcium) has been shown to increase intracellular levels of the breakdown products of the phosphatidylinositol cycle,[66] and non-hormonal factors can affect catecholamine actions on lipolysis, e.g. cholera and pertussis toxin, forskolin.[58]

The four types of adrenoceptors are probably present in BAT, although the presence of α_2-receptors is not conclusive. Stimulation of hamster BAT α_1-receptors stimulates respiration, and the β_1-receptors on BAT of rats stimulate lipolysis, respiration, cAMP formation and thermogenesis and may be influenced by thyroid hormones.[58]

Insulin and the respiratory control of metabolic fate

The preceding sections suggested that a more efficient catabolism (i.e. defect in thermogenesis) or change in the catecholamine/eicosanoid control of lipolysis may be present in obesity. A further possibility is that there is a more efficient or increased fat anabolism (i.e. lipogenesis). That is a shift in tissue (muscle → adipocyte)[11,67,68] and metabolic priorities. Hyperinsulinaemia and peripheral insulin resistance are often found in obesity. This resistance is not easy to define (generally as decreased clearance of glucose from the circulation), and it may apply to specific tissues. Whole-body measurements of metabolic rate or reduced clearance of glucose from plasma are difficult to interpret in this respect, and the ultimate metabolic fate of glucose used as a measure of post-insulin-receptor metabolism will influence conclusions drawn. Insulin has been shown to increase glucose utilization for esterification of fatty acids in large adipocytes.[69]

It has been demonstrated in the fetus that hyperinsulinism gives rise to hypoxia,[70–73] and it has been suggested that this hypoxia may modify glucose metabolism and increase glycerol-3-phosphate synthesis in white adipose tissue by shunting glucose through the hexose monophosphate shunt pathway.[12] (This may be an attempt to clear circulating glucose in a manner conservative with respect to oxygen consumption. The contribution of the hexose monophosphate shunt pathway to glucose metabolism in isolated rat adipocytes has been shown to be increased by insulin and decreased by noradrenaline[74] and growth hormone.[75]) Increased export of very-low-density lipoprotein (VLDL) from the liver has been observed in obese rats[76] and increased transport of this VLDL to adipocytes would result in increased levels of adipocyte fatty acids, and in the presence of increased glycerol-3-phosphate, increased triglycerides, i.e. adipocyte hypertrophy. Insulin has been shown to increase adipocyte lipoprotein lipase activity,[77] and lipoprotein lipase activity[77] and fasting insulin levels[78] have been correlated with fat cell size. Respiratory embarrassment is also present in gross obesity, and it has been suggested that this may be related (exponentially) to the degree of obesity.[79]

Thermogenesis (BAT, NA/K-ATPase and futile cycles) also requires oxygen. Therefore oxygen utilization and the ultimate tissue and metabolic fate of glucose may depend upon the availability of oxygen and on the ratio of insulin : catecholamines, although many other factors may act as fine controls, e.g. thyroid hormones. Oxygen itself may exert a respiratory control on the action of hormones,[80] and it is interesting to speculate on the effect of oxygenation on eicosanoid metabolism in the microcirculation,[81] as these compounds have potent vasoactive properties and are an important part of the cell second messenger system.[60–62] Hypoxia is frequently found in grossly obese patients (e.g. pickwickian syndrome), and a mechanism along the lines suggested may contribute to a vicious cycle of hyperinsulinism, respiratory compromise, reduced thermogenesis, increased triglyceride synthesis, continuing weight increase and obesity refractory to treatment.

Treatment

Experiments are continuing with centrally acting (noradrenergic neurons), non-amphetamine appetite suppressants, e.g. mazindol (Teronac; Wander), and sustained weight loss (± 12 months) on a hypocaloric diet has been demonstrated.[82] In man fenfluramine, besides its effects on the central nervous system, has been shown to increase uptake of glucose into muscle in preference to adipose tissue (an action which mimics the effect of mild exercise).[83]

Attempts have been made at dietary manipulation of thermogenesis (high-carbohydrate/low-protein diet)[84] or eicosanoid levels (evening primrose oil),[85] but without obvious therapeutic potential at this stage.

The complexity of adrenoreceptors in adipose tissue and the fact that they are not exactly similar to those in other tissues[57,58] has led to the development of specific adrenergic agonists. Yen *et al.*[86,87] have recently used a β-receptor agonist (LY 79771) to reduce body weight and increase metabolic rate, thermogenesis and lipolysis in obese mice. The drug did not inhibit appetite. Arch *et al.*[88] and Arch and Ainsworth[89] have used a β-adrenergic agonist (BRL 26830A) which is specific for BAT of rats. It has been shown to stimulate thermogenesis and reduce body weight in genetic, gold thioglucose- and cafeteria-fed obese rats. The drug had no effect on their lean counterparts.

Recent studies by Triscari and Sullivan[90] in rats have focused on a novel inhibitor of hepatic fatty acid synthesis (R022-0654). Weight gain was decreased in lean and obese rats and could be accounted for by a decrease in total body lipid. Appetite was only transiently affected.

Knoll[91] of Budapest has described a naturally occurring glycoprotein (satietin) which is non-addictive, does not affect body temperature and has anorexic properties.

A further angle of approach is through the *in vitro* culture work with pre-adipocytes which is being done in many laboratories.[24,92] The results may shed some light on the process of adipocyte proliferation. Some preliminary work suggests that a serum-derived factor may initiate the process.[93] This has obvious therapeutic potential.

Hyperinsulinaemia is frequently present in obesity, and in some cases may contribute to the condition. Attempts are being made[94,95] to synthesize somatostatin analogues (e.g WY-18166, Wyeth Laboratories) which specifically inhibit insulin release and do not affect release of growth hormone or glucagon. Some preliminary work has also been done by Yen *et al.*[96] (Eli Lilly Research Laboratories) using dehydroepiandrosterone, which inhibits glucose-6-phosphate dehydrogenase activity (rate-limiting enzyme in hexose monophosphate shunt pathway), and it has been shown to reduce body fat in growing obese mice.

Conclusion

It is now realized that obesity is enormously more complex than was previously thought. Homeostatic body weight mechanisms make it difficult to treat, although recent research gives some hope for therapeutic intervention in the near future. The study of obesity and adipocytes is continuing to shed light on physiological, hormonal and metabolic mechanisms which may have application not only to adipocytes and obesity, but to many other cell types and to many diseases. These studies are concerned with such basic problems as the control of cellular proliferation, the tissue-specific utilization of substrates, alterations in blood flow to and oxygen status of specific tissues *in vivo*, and alterations at the second messenger level which will ultimately control cellular behaviour and intracellular metabolic fate. The unravelling of the molecular pathology of obesity will undoubtedly give answers with far-reaching consequences.

REFERENCES

1. Salans LB. The obesities. In: Felig P, Baxter JD, Broadus AE, Frohman LA, eds. *Endocrinology and Metabolism.* New York: McGraw-Hill, 1981: 891-916.
2. Pizak VK. Medical management of obesity. *Postgrad Med* 1983; **74:** 158-172.
3. Walker ARP. Does sugar cause or promote obesity? *S Afr J Sci* 1983; **79:** 43-46.
4. Allon N. The stigma of overweight in everyday life. In: Bray GA, ed. *Obesity in Perspective* (DHEW Publication No. (NIH) 75-708). Washington, DC: US Government Printing Office, 1973: 83-102.
5. Bray GA. Syndromes of obesity: pathogenesis and treatment. *Med Int* 1978; **2:** 503-509.
6. Rössner S. Risks of overweight and benefits of weight reduction. *Acta Med Scand* 1984; **215:** 1-3.

7. Hirsch J. The psychological consequences of obesity. In: Bray GA, ed. *Obesity in Perspective* (DHEW Publication No. (NIH) 75-708). Washington, DC: US Government Printing Office, 1973: 81-82.
8. Dwyer J, Mayer J. The dismal condition: problems faced by obese adolescent girls in American society. In: Bray GA, ed. *Obesity in Perspective* (DHEW Publication No. (NIH) 75-708). Washington, DC: US Government Printing Office, 1973: 103-110.
9. Assimacopoulos-Jeannet F, Jeanrenaud B. The hormonal and metabolic basis of experimental obesity. *Clin Endocrinol Metab* 1976; **5:** 337-365.
10. Bray GA, York DA. Hypothalamic and genetic obesity in experimental animals: an autoimmune and endocrine hypothesis. *Physiol Rev* 1979; **59:** 719-809.
11. Butterfield WJH. Introduction. In: Baird IM, Howard AN, eds. *Obesity — Medical and Scientific Aspects.* Edinburgh: E & S Livingstone, 1969: 3-9.
12. Macfarlane CM, Tsakalakos N. Relative fetal hypoxia as a contributing factor to fetal macrosomia in diabetic pregnancy. *Med Hypotheses* 1983; **11:** 365-374.
13. Stock M, Rothwell N. *Obesity and Leanness - Basic Aspects.* London: John Wiley, 1982: 39-58, 82.
14. Bray GA. Integration of energy intake and expenditure in animals and man: the autonomic and adrenal hypothesis. *Clin Endocrinol Metab* 1984; **13:** 521-546.
15. McCarthy MC. Dietary and activity patterns of obese women in Trinidad. *J Am Diet Assoc* 1966; **48:** 33-37.
16. Cox JE, Powley TL. Development of obesity in diabetic mice pair fed with lean siblings. *J Comp Physiol Psychol* 1977; **91:** 347-358.
17. Anand BK, Brobeck JR. Hypothalamic control of food intake in rats and cats. *Yale J Biol Med* 1951; **24:** 123-140.
18. Brobeck JR. Regulation of energy exchange. In: Ruch TC, Patton HD, eds. *Physiology and Biophysics.* Philadelphia: WB Saunders, 1966: 1022-1029.
19. Hetherington AW, Ranson SW. Hypothalamic lesions and adiposity in rats. *Anat Rec* 1940; **78:** 149-172.
20. Cawthorne MA. Metabolic aspects of obesity. *Mol Aspects Med* 1982; **5:** 293-400.
21. Bray GA. Regulation of energy balance: studies on genetic, hypothalamic and dietary obesity. *Proc Nutr Soc* 1982; **41:** 95-108.
22. Fernstrom JD, Wurtman RJ. Brain serotonin content: increase following ingestion of carbohydrate diet. *Science* 1971; **174:** 1023-1025.
23. Hirsch J, Knittle JL. Cellularity of obese and nonobese human adipose tissue. *Fed Proc* 1970; **29:** 1516-1521.
24. Vasselli JR, Cleary MP, Van Itallie TB. Modern concepts of obesity. *Nutr Rev* 1983; **41:** 361-373.
25. Greenwood MRC, Hirsch J. Postnatal development of adipocyte cellularity in the normal rat. *J Lipid Res* 1974; **15:** 474-483.
26. Faust IM, Johnson PR, Stern JS, Hirsch J. Diet-induced adipocyte number increase in adult rats: a new model of obesity. *Am J Physiol* 1978; **235:** E 279-286.
27. Hervey GR. Regulation of energy balance. *Nature* 1969; **222:** 629-631.
28. Miller DS. Energy metabolism. In: Baird IM, Howard AN, eds. *Obesity — Medical and Scientific Aspects.* Edinburgh: E & S Livingstone, 1969: 56-74.
29. Smith GP. Humoral hypothesis for the control of food intake. In: Bray GA, ed. *Obesity in Perspective* (DHEW Publication No. (NIH) 75-708). Washington, DC: US Government Printing Office, 1973: 19-29.
30. Kennedy GC. Role of depot fat in hypothalamic control of food intake in rat. *Proc R Soc Lond [Biol]* 1953; **140:** 578-592.
31. Brobeck JR. Food intake as a mechanism of temperature regulation. *Yale J Biol Med* 1948; **20:** 545-552.
32. Mayer J. Regulation of energy intake and body weight: glucostatic theory and lipostatic hypothesis. *Ann NY Acad Sci* 1955; **63:** 15-43.
33. Frazier LE, Wissler RW, Stefler CH, Woolridge FL, Cannon PR. Studies in amino acid utilisation: I. The dietary utilisation of mixtures of purified amino acids in protein-depleted adult albino rats. *J Nutr* 1947; **33:** 65-83.
34. Landsberg L, Young JB. The role of the sympathetic nervous systems and catecholamines in the regulation of energy metabolism. *Am J Clin Nutr* 1983; **38:** 1018-1024.
35. Rodin J. *Controlling Your Weight.* London: Century Publishing, 1983: 99-107, 115-149.
36. Schacter S, Goldman R, Gordon A. Effects of fear, food deprivation and obesity on eating. *J Pers Soc Psychol* 1968; **10:** 91-97.
37. Di Girolamo M, Smith V, Bjorntorp P. In: Bjornthrop P, Cairella M, Howard AN, eds. *Recent Advances in Obesity Research.* London: John Wiley, 1981: 99-105.
38. Fuerst ML. Suction assisted lipectomy attracting interest. *JAMA* 1983; **249:** 3004-3005.
39. Rubner M. *Die Gesetze des Energieverbrauchs bei der Ernährung.* Leipzig: F Denticke, 1902.
40. Neumann RO. *Arch Hyg (Berl)* 1902; **45:** 1-87.
41. Hsieh ACL, Carlson LD, Gray G. Role of the sympathetic nervous system in control of chemical regulation of heat production. *Am J Physiol* 1957; **190:** 247-251.
42. Heldmaier G. Nonshivering thermogenesis and body size in mammals. *Z Vergl Physiol* 1971; **73:** 222-248.
43. Himms-Hagen J. Obesity may be due to a malfunctioning of brown fat. *Can Med Assoc J* 1979; **121:** 1361-1364.
44. Rothwell NJ, Stock MJ. A role for brown adipose tissue in diet-induced thermogenesis. *Nature* 1979; **281:** 31-35.
45. Foster DO, Frydman ML. Non-shivering thermogenesis in the rat: II. Measurements of blood flow with microspheres point to brown adipose tissue as the dominant site of the calorigenesis induced by noradrenaline. *Can J Physiol Pharmacol* 1978; **56:** 110-122.
46. Young P, Arch JRS, Ashwell M. Brown adipose tissue in the parametrial fat pad of the mouse. *FEBS Lett* 1984; **167:** 10-14.
47. Rothwell NJ, Stock MJ. Effects of continuous and discontinuous periods of cafeteria feeding on bodyweight, resting oxygen consumption and noradrenaline sensitivity in the rat. *J Physiol (Lond)* 1979; **291:** 59.
48. Nicholls DG. Brown adipose tissue mitochondria. *Biochim Biophys Acta* 1979; **549:** 1-29.
49. Heaton GM, Wagenvoord RJ, Kemp A, Nicholls PG. Brown adipose tissue mitochondria: photoaffinity labelling. *Eur J Biochem* 1978; **82:** 515-521.
50. Smith RE. Metabolism and cellular function in cold acclimatisation. *Physiol Rev* 1962; **42:** 60-142.
51. Himms-Hagen J. Thermogenesis in brown adipose tissue as an energy buffer: implications for obesity. *N Engl J Med* 1984; **311:** 1549-1558.
52. York DA, Bray GA, Yukimura Y. An enzymatic defect in the obese (ob/ob) mouse: loss of thyroid induced sodium- and potassium-dependent adenosine-triphosphatase. *Proc Natl Acad Sci USA* 1978; **75:** 477-481.
53. Belfiore F, Iannello S, Rabuazzo AM, Borzi V. The activity of sodium and potassium-activated adenosine-triphosphatase (Na K-ATP'ase) in the adipose tissue of obese patients. In: Enzi G, Crepaldi G, Pozza G, Renold AE, eds. *Obesity: Pathogenesis and Treatment.* London: Academic Press, 1981: 129-134.
54. Newsholme EA. The interrelationship between metabolic regulation, weight control and obesity. *Proc Nutr Soc* 1982; **41:** 183-191.
55. Newsholme EA, Arch JRS, Brooks B, Surholt B. The role of substrate cycles in metabolic regulation. *Biochem Soc Trans* 1983; **11:** 52-56.
56. Newsholme EA. Evidence for the role of substrate cycles in improving sensitivity in metabolic control. Paper presented at the 8th Congress of the South African Biochemical Society, 3-5 July 1984, University of Port Elizabeth.
57. Kather H. Hormonal regulation of adipose tissue lipolysis in man: implications for the pathogenesis of obesity. *Triangle (Engl)* 1981; **20:** 131-143.
58. Fain JN, Garciá-Sainz JA. Adrenergic regulation of adipocyte metabolism. *J Lipid Res* 1983; **24:** 945-966.
59. Landsberg L, Young JB. The role of the sympathoadrenal system in modulating energy expenditure. *Clin Endocrinol Metab* 1984; **13:** 475-499.
60. Wolfe LS. Prostaglandins, thromboxanes, leukotrienes and other derivatives of carbon-20 unsaturated fatty acids. *J Neurochem* 1982; **38:** 1-14.
61. Michell RH. Inositol phospholipids and cell surface receptor function. *Biochim Biophys Acta* 1975; **415:** 81-147.
62. Berridge MJ. Phosphatidylinositol hydrolysis: a multifunctional transducing mechanism. *Mol Cell Endocrinol* 1981; **24:** 115-140.
63. Burns TW, Langley PE, Terry BE *et al.* Pharmacological characterisations of adrenergic receptors in human adipocytes. *J Clin Invest* 1981; **67:** 467-475.
64. Scaramuzzi OE, Baile CA, Mayer J. Prostaglandins and food intake in rats. *Experientia* 1971; **27:** 256-257.
65. Curtis-Prior PB. Prostaglandins and obesity. *Lancet* 1975; **i:** 897-899.
66. Farese RV, Larson RE, Sabir MA. Insulin acutely increases phospholipids in the phosphatidate-inositol cycle in rat adipose tissue. *J Biol Chem* 1982; **257:** 4042-4045.
67. Shreeve WW, Hoslin M, Oji N, Shigeta Y, Abe H. Insulin and the utilisation of carbohydrates in obesity. *Am J Clin Nutr* 1968; **21:** 1404-1418.
68. Albrink MJ. Dietary fiber, plasma insulin, and obesity. *Am J Clin Nutr* 1978; **31:** S277-S279.
69. Nestel P, Goldrick B. Obesity: changes in lipid metabolism and the role of insulin. *Clin Endocrinol Metab* 1976; **5:** 313-318.
70. Carson BS, Phillips AF, Simmons MA, Battaglia FC, Meshia G. Effects of sustained insulin infusion upon glucose uptake and oxygenation of the ovine fetus. *Pediatr Res* 1980; **14:** 147-152.
71. Quissell BJ, Bonds DR, Krell LS, Carson BS, Battaglia FC, Meschia G. The effects of chronic insulin infusions upon fetal oxygenation. *Clin Res* 1980; **28:** 125A.
72. Widness JA, Susa JB, Garcia JF *et al.* Increased erythropoiesis and elevated erythropoietin in infants born to diabetic mothers and in hyperinsulinemic fetuses. *J Clin Invest* 1981; **67:** 637-642.
73. Macfarlane CM, Tsakalakos N. Hyperinsulinaemia and hypoxaemia in cord blood of neonates born to mothers with gestational diabetes. *S Afr Med J* 1985; **67:** 81-84.
74. Katz J, Landau BR, Bartsch GE. The pentose cycle, triose phosphate isomerisation, and lipogenesis in rat adipose tissue. *J Biol Chem* 1966; **241:** 727-740.
75. Landau BR, Bartsch GE, Williams HR. Estimation of the glucuronic acid pathway contribution to glucose metabolism in adipose tissue and the effect of growth hormone. *J Biol Chem* 1966; **241:** 750-760.
76. Robertson RP, Gavereski DI, Hendersen JV, Porte D, Bierman EL. Accelerated triglyceride secretion — a metabolic consequence of obesity. *J Clin Invest* 1973; **52:** 1620-1626.
77. Pykälistö OJ, Smith PH, Brunzell JD. Determinants of human adipose tissue lipoprotein lipase: effects of diabetes and obesity on basal- and diet-induced activity. *J Clin Invest* 1975; **56:** 1108-1117.
78. Stern JS, Batchelor BR, Hollander N, Cohen CK, Hirsh J. Adipose-cell size and immunoreactive insulin levels in obese and normal weight adults. *Lancet* 1972; **ii:** 948-951.
79. Buskirk ER, Barlett HL. Obesity and pulmonary function. In: Bray GA, ed. *Obesity in Perspective* (DHEW Publication No. (NIH) 75-708). Washington, DC: US Government Printing Office, 1973: 225-231.
80. Randle PJ. Fuel and power in the control of carbohydrate metabolism in mammalian muscle. *Soc Exp Biol Symposia* 1964; **18:** 129-155.
81. Markelonis G, Garbus J. Alterations of intracellular oxidative metabolism as stimuli evoking prostaglandin biosynthesis: a review of prostaglandins in cell injury and an hypothesis. *Prostaglandins* 1975; **10:** 1087-1106.
82. Enzi G, Baritussio A, Marchiori E, Crepaldi G. Short-term and long-term clinical evaluation of a non-amphetamine anorexiant (Mazindol) in the treatment of obesity. *J Int Med Res* 1976; **4:** 305-318.
83. Butterfield WJH, Whichelow MJ. Fenfluramine and muscle glucose uptake in man. *Lancet* 1968; **ii:** 109.
84. Young JB, Saville E, Rothwell NJ. Effect of diet and cold exposure on norepinephrine turnover in brown adipose tissue of the rat. *J Clin Invest* 1982; **69:** 1061-1071.
85. Haslett C, Douglas JG, Chalmers SR, Weighhill A, Munro JF. A double blind evaluation of evening primrose oil as an antiobesity agent. *Int J Obes* 1983; **7:** 549-553.
86. Yen TT, McKee MM, Stamm NB, Bernis KG. Stimulation of cyclic AMP and lipolysis in adipose tissue of normal and obese A^{vy}/a mice by LY79771, a phenethanolamine, and steroisomers. *Life Sci* 1983; **32:** 1515-1522.
87. Yen TT. The antiobesity and metabolic activities of LY 79771 in obese and normal mice. *Int J Obes* 1984; **8:** 69-78.
88. Arch JRS, Ainsworth AT, Cawthorne MA *et al.* Atypical β-adrenoceptor on brown adipocytes as target for anti-obesity drugs. *Nature* 1984; **309:** 163-165.

89. Arch JRS, Ainsworth AT. Thermogenic and antiobesity activity of a novel β-adrenoceptor agonist (BRL 26830A) in mice and rats. *Am J Clin Nutr* 1983; **38:** 549-558.
90. Triscari J, Sullivan AC. Antiobesity effects of a novel lipid synthesis inhibitor (RO — 22 — 0654). *Life Sci* 1984; **34:** 2433-2442.
91. Knoll J. Satietin: endogenous regulation of food intake. *Adv Biochem Psychopharmacol* 1982; **33:** 501-509.
92. Cryer A. Adipocyte histogenesis. *Trends Biochem Sci* 1980; **5:** 196-198.
93. Pairault J, Green H. A study of the adipose conversion of suspended 3T3 cells by using glycerophosphate dehydrogenase as a differentiation marker. *Proc Natl Acad Sci USA* 1979; **76:** 5138-5142.
94. Brown M, Vale W, Rivier J. Insulin selective somatostatin analogue. *Diabetes* 1977; **26:** suppl. 1, 360.
95. Efendic S, Luft R, Sievertsson H. Relative effects of somatostatin and two somatostatin analogues on the release of insulin, glucagon and growth hormone. *FEBS Lett* 1975; **58:** 302-305.
96. Yen TT, Allan JA, Pearson DV, Acton JM, Greenberg MM. Prevention of obesity in A ^{vy}/a mice by dehydroepiandrosterone. *Lipids* 1977; **12:** 409-413.

Neurobehavioural effects in rats fed low doses of cadmium and lead to induce hypertension

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Summary

Rats given diets supplemented with low doses of cadmium or lead or both elements together showed an increase in cadmium levels within the brain in all supplemented groups. Hypo-activity was noted after 16 months of dietary supplementation with lead or with cadmium and lead. Activity was unaffected by feeding with cadmium alone.

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Reports on the neurophysiological and behavioural effects of lead, both in animals and in humans, are numerous and complex. Investigators who have measured activity in rats given lead in accordance with various protocols and at different stages of development have found that it can promote hyperactivity or hypo-activity, or even produce no apparent change in activity. Most of the literature makes it clear that the developing brain is at greatest risk, possibly because the permeability of the immature blood/brain barrier to lead is greater than that in adult or post-weanling rats.

It has also been established[1-11] that lead and cadmium ingested in small amounts may cause hypertension in experimental animals. Since hypertension can be induced by stress in an animal model,[12] and hyperactivity and aggression are established symptoms of lead toxicity,[13] the question arises whether hyperactivity or other changes in neurobehavioural patterns correlate with the hypertension produced by the ingestion of trace metals.

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The neurochemical explanation for neurobehavioural effects

At low doses lead inhibits the following enzymes in the brain: tetrahydrobiopterin synthetase, dihydrobiopterin reductase, adenyl cyclase, aminolaevulinic acid (ALA)-dehydrase, ($Na^+ + K^+$)-adenosine triphosphatase (ATPase), K-nucleophosphatase (NPPase), gamma-aminobutyric acid (GABA)-transaminase, glutaminase, aldolase, acetylcholinesterase and butyrylcholinesterase. The biopterins are enzyme co-factors involved in the biosynthesis of the neurotransmitters dopamine and noradrenaline.[13] Some of the effects of lead on GABA metabolism may result from the ability of ALA, levels of which are characteristically elevated by exposure to lead, to act as a 'false neurotransmitter' mimicking the structurally related GABA. However, a recent study indicates that lead does not alter presynaptic actions of brain choline or GABA when calcium levels are normal.[14] In summary, the effects of lead appear to be impairment of inhibitory neurochemical functions and sensitization to stress. In the latter effect, the overall inhibition of GABA may play an important role.

Effects of cadmium on the central nervous system

The administration of cadmium results in decreased activity of the Na,K,Mg_2-dependent ATPase of brain, both *in vitro* and *in vivo*. In increasing doses cadmium abolishes reflexes, then the sensation of pain, and finally causes death by asphyxia due to pulmonary oedema. It has been suggested that the marked prostration, flaccidity of muscles and respiratory paralysis observed in rats after intravenous injections of toxic doses of cadmium may be due to displacement of calcium ions from their action sites.[13]

Aims

The objective of the present experiment was to examine the relationship between brain trace element levels and neurobehavioural activity, using an animal activity monitor, in