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Hurdles and hopes in the management of human obesity

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ABSTRACT

A population shift towards obesity is a major side-effect of changes in lifestyle that accompany economic prosperity, and a high risk factor for many chronic degenerative diseases including non-insulin-dependent diabetes mellitus (NIDDM), coronary heart disease and hypertension. According to current WHO population statistics, 40% of obese patients eventually develop NIDDM, 80% of individuals with NIDDM are obese and the incidence of hypertension in obesity and NIDDM could be as high as 50%. Of particular concern for developing countries is the strong epidemiological evidence indicating that the prevalence of obesity and diabetes often increase in epidemic proportions in communities emerging from lifestyles of subsistence into affluence. Even modest increase in prosperity seem to be associated with the most marked increases in the proportion of these chronic diseases. Indeed, obesity and its pathophysiological complications have become health priorities among American Indians, Australian Aborigines, Pacific Islanders, and are rapidly becoming major concerns among many other developing countries. For example, the prevalence of obesity (BMI >30) for the middle-age group is 32% in women living in Urban Trinidad, 16.4% in Nicaragua, 14% in Costa Rica, values which are higher than for the USA (12-15%) or in the UK (8-9%). Even more spectacular are the health statistics about the middle-aged Pima Indians in Arizona and inhabitants of the South Pacific Island of Nauru, showing that more than 80% are obese, and 50-70% have NIDDM. These grim figures must be weighed against the hard fact that there is at present no effective cure for obesity, and judging from the outcome of health policies in countries with a long experience in dealing with this problem, the management of obesity has a long and disappointing history. In fact, for the past decades, a wide array of treatment has been available to their public (low-calorie regimes, low-fat or high fibre foods, anorectic drugs, exercise and behavioural therapy, etc), but in the vast majority of cases, the result is a transient phase of weight loss, followed by a return to the obese condition within a few years. Despite the poor prognosis of treating obesity by reducing food intake (by dieting alone or with the help of anorectic drugs), thi approach will continue to be the most common form of treatment in the foreseeable future. However, there is growing realisation that in response to reduced food intake, the accompanying fall in energy expenditure is a major factor that limits weight loss and contributes to obesity relapse. After an analysis of the various approaches to reduce energy intake, this paper will examine the extent to which re-adjustments in the various compartments of energy expenditure contribute to this apparent adaptation to reduced food intake. It will then analyze the rationale, applicability and effectiveness of various approaches (behavioural, dietary, and pharmacological) that could conceivably stimulate the metabolic rate and thus counteract such adaptive changes in energy expenditure in order to improve the efficacy of obesity management.

TREATMENT OF OBESITY: BASIC PRINCIPLES

Obesity is a problem of energy imbalance characterized by excessive fat deposition. Consequently, excess fat cannot be lost through metabolic processes unless energy intake is lower than energy expenditure (EE). In other words, for the individual to lose weight, energy balance must be negative, and there are fundamentally three ways to interfere with energy balance regulation:

(1) reducing the amount of food energy ingested,
(2) reducing nutrient absorption/utilization, and
(3) increasing energy expenditure.

REDUCTION IN THE AMOUNT OF FOOD INGESTED

This approach is undeniably the most common form of treatment. It has a long history characterized by claims of a 'successfulí treatment in one decade becoming failures in the next. In general, the key to successful dietary treatment is to make it easier for the obese patient to reduce energy intake. It is amazingly easy to keep to a reducing diet when confined to a metabolic ward or while attending a 'Health & Slimming' camp, but quite impossible to do so at home. To quote Garrow (1992): "*The difficult thing is not to eat little, but to eat little when the option of eating more is available*".

From starvation to VLCD

In the 60's, it was common clinical practice to use therapeutic starvation in the hope that it offered a permanent reduction in weight loss. It was remarkably well tolerated by most patients (Bloom, 1959; Munro *et al.,* 1970), but many subjects rapidly regained all the weight that they had lost. Furthermore, the method was not without risk, and it fell into disrepute following a few deaths (Munro & Cantley, 1992). A parallel development has been the widespread use of very low calorie diets (VLCD). The original liquids were comparable to therapeutic starvation-rendered unsafe by inappropriate selection and lack of supervision. Subsequent formulations and regulatory recommendations (DHSS report, 1987) have resolved the problems of safety and there are several types of VLCD with various combinations of protein, carbohydrate, minerals, vitamins and with energy contents varying from 150-600 kcal (0.6 to 2.5 MJ). However the problem with any VLCD is that it fails to re-educate faulty eating habits and the normal pattern is for weight loss to be followed by weight regain. Awareness of this has encouraged the shift in emphasis to combining VLCD into a comprehensive weight maintenance programme designed to re-educate eating patterns using behavioural and cognitive therapy. There is a very large literature on these approaches, and it is common to see papers extolling one particular therapy, such as behaviour therapy over 'control' treatment by diet alone, but there is at present no good evidence to substantiate these claims. Furthermore, the therapeutic advantage of VLCD over LCD in outpatients continues to be a hotly debated issue (Wadden, 1993), with opponents to the use of VLCD pointing out clinical trials which failed to detect differences in weight loss between outpatients treated with VLCD and those with LCD (Frost *et al.,* 1991), with the conclusion that compliance to VLCD is poor.

Popular slimming regimens

Amidst such confusions, the market has been flooded with all kinds of what can be called the commercial slimming regimens. Each particular brand seem to have its "guru" advocating the efficacy of the diet that made them sucessful slimmers-whether calorie-counted diet, carbohydrate-restricted diet, fat-restricted diet, high-protein diet, and diets based upon the timing of meals or meal frequency, etc. A few have some merit, and some lack scientific foundation though not necessarily unsafe. Now and then, however, there appears what can be termed 'charlatan' diets. A good example is the Beverley Hills Diet which is based on the false propositions that obesity is due to impaired digestion of food, and that food is digested if eaten in association with certain other foods (mainly fruits) which contain enzymes. A serious criticism of such charlatan diets is that they not only have no scientific basis, but they are outright dangerous since they put people who follow them at risk for serious nutritional deficiencies.

Appetite suppressants

An appealing option for those who find it difficult to eat less food is to use appetite suppressants. The history of anorectic drugs is indeed extensive, and the number of compounds screened by pharmaceutical companies is enormous, but of those that eventually reached the marketplace relatively few are still in use. During the past 30 years, there has been a dramatic reduction of prescriptions issued for anti-obesity anorectic drugs. The first reason was the recognition that the extra weight loss attributable to drugs only lasted for as long as the drug was being given. Indeed, the study by Stunkard *et al.* (1980) provided grounds to suspect that the end result of short-term drug therapy was a degree of weight regain greater than might have occurred had the drug been withheld. The second reason was the increasing public awareness of the abuse potential of amphetamine congeners: drugs acting satiety through central catecholaminergic pathways with side effects including insomia, restlessness, palpitations. This effectively left the field open for DL-fenfluramine and later D-fenfluramine, drugs acting principally through the serotonergic system. Long-term fenfluramine administration promotes weight loss (Guy-Grand *et al.,* 1989)-but unfortunately, the hazards of treatment in general, and of pulmonary hypertension in particular (Douglas *et al.,* 1981), remain uncertain. Furthermore, a recent follow-up study of obese women treated with D-fenfluramine showed that this drug did not effectively prevent weight regain despite continued dietary effort (Andersen *et al.,* 1992). The field is considered played out by many research workers, and there is little experimental work with new anorectic compounds today. On the other hand, the 1980's saw revived interest in bulking agents, i.e. inert fillers that give satiety without calories. This is largely as a result of the acclaimed nutritional benefits of dietary fibre, not only for slimming but also as part of a 'healthful' diet for everyone. Most commercial bulking agents contain cellulose derivatives, e.g. methylcellulose, or natural gums, e.g. guar; they form hydrophilic gels, taking up relatively large volumes of water. At dose rates of 16 g per day, they reduce voluntary food intake by about 20% (Evans & Miller, 1975)-which is certainly worthwhile if it could be maintained over long periods of time. However, 16 g is not consumed with ease, and the doses recommended commercially are between 4 and 6 g, sometimes a few milligrams; also there is a danger of oesophageal or intestinal obstruction. More promising were the diabetic foods containing guar gum, e,g. guar bread, which slows down the rate of absorption of carbohydrate and induce a feeling of satiety, but these proved to be rather unpalatable.

REDUCTION IN FOOD ENERGY ABSORBED

An alternative option to lose weight without the will power to eat less is to absorb less, and this has included approaches involving:
(a) surgery,
(b) drug-induced malabsorption, and
(c) novel fats and sugars which are not either poorly absorbed or poorly utilized.

Bypass surgery

In the early 1970's, the discreditation of therapeutic starvation coincided with the development of jejunal-ileal bypass surgery, but in addition to the inevitable gastro-intestinal upsets, the procedure was inherently hazardous. The risks included acute hepatic failure, arthritis, and various nutritional deficiencies including magnesium, zinc and copper. This procedure was replaced by gastric surgery, gastric ballon, vertical banding gastroplasty and gastric exclusion. The proliferation of various procedures illustrated that none was ideal, and although some remain as therapeutic options, it might be argued that at best surgery merely replaces one problem, that of severe obesity, with another, i.e. the small stomach syndrome. To-day surgery is considered only for the massively obese patients (> 100% overweight or > 45 kg overweight), and only if non-surgical treatment has failed to reduce body weight sufficiently, and in patients exhibiting serious physical and psychological problems (VanItallie & Burton, 1979). Because the mortality risk due to the surgery is high (5%) and the risk for serious post-surgical complications is even higher (15-20%), the criteria for eligibility for surgery is continuously being evaluated. {A less drastic surgery is to eliminate body fat by lipectomy or liposuction-techniques often utilized in plastic surgery. However, only a few kilograms of the excess fat is accessible to surgical removal, and reliable data about the long term fate of the reduced fat depot remains elusive).

Drug-induced malabsorption

Agents aimed at reducing the absorption of food have been proposed, but despite world-wide sales of at least one product usually referred to as a starch blocker, they have so far proved ineffective. The ability to block specific enzymes in the gut is superficially attractive but the use of proteinaceous agents, themselves susceptible to digestive enzymes, is not productive. Currently the interest in drug-induced malabsorption has shifted to lipase inhibitors that reduce the enzymatic break down of dietary lipids and hence reduce fat absorption (Drent & van der Veen, 1993). Some of these products (e.g. Orlistat) have reached the stage of clinical trials, amidst contraindication of potential gastrointestinal disturbances and reduced bioavailability of micro-nutrients and fat-soluble vitamins. If an energy-yielding substrate (carbohydrate, fat or protein) is not digested and absorbed in the small bowel, it will become a substrate for colonic bacteria. The result, at best will be increased flatulence, and at worst, increased liability to large bowel cancer. It is difficult to see how it would be possible to guarantee the safety of such preparations for long-term use.

Novel 'low energy' sugars and fats

These are increasingly flooding the market, and started more than a decade ago with sweeteners

without calories (saccharin, aspartame) in sweets, candies, deserts. Perhaps the most spectacular development in this area is the discovery of synthetic edible oils, like olestra, which are simply not absorbed (Jandacek, 1991), and they have been coined as fat-free fat by the popular press. The scientific committee of the United States FDA (food and drug administration) has recently approved the sales of chips fried in Olestra. This decision will probably be re-evaluated in the next few years, before proceeding to allow it to be incorporated in other snacks and deserts. Opponents of fat-free fats claim that the general public has become the guinea-pigs to test the long-term safety of these novel fats. They argue that they are unlikely to be of any efficacy in obesity management, and draw comparison with the widespread use of energy-free sugars which have not proven to be effective in losing weight, nor have their use prevented an increase in the prevalence of obesity in the USA. So far, however, the pressure from industry and from a gullible public in search for hedonism have prevailed such that government bodies are likely to allow their use-at least as long as they are not proven unsafe.

METABOLIC READJUSMENTS COUNTERACTING THE EFFICACY OF THE DIET THERAPY

Independently of the method utilized to lose weight by reducing food intake/absorption, however, the fact remains that the most difficult battle for the obese dieter is to prevent weight regain after all the efforts of losing the weight. Indeed, follow-up studies indicate that more than 95% of the patients treated have returned close to their starting weight within 1 to 5 years, (Sohar & Sneh, 1973; Wadden, 1993; Wadden *et al.*, 1989).

Why is it so difficult to maintain weight after slimming? The answer is no doubt multifactorial, but much has to do with the fact that a highly complex inter-relationship exists between energy intake and energy expenditure (EE). Indeed, a reduction in food intake will have repercussions on all the components of EE. These purely energetic aspects of dieting are illustrated in Figure 1 which depicts schematically the extent to which the various compartments of EE in an average obese person may be readjusted following a weight loss of say 20 kg. First of all, the loss in body mass will entail *obligatory* reductions in (i) the energy cost for basal metabolism, since the basal metabolic rate (BMR) is related to metabolic mass, (ii) in the amount of energy spent in performing work since from a consideration of simple mechanics, the energy cost of physical activity (i.e. work done on the environment) is related directly to body weight, and (iii) in the absolute level of energy dissipated as a result of specific dynamic action of food (i.e. in diet-induced thermogenesis, DIT), given that less food is now required to maintain the lower body weight. Based upon estimates that the composition of weight loss in the obese is~75% fat and 25% lean body mass (Garrow, 1978), and that body weight in non-athletic individuals is maintained at an energy cost in the range of 15-25 kcal per kg per day, it can be calculated that a weight loss of 20 kg body weight will result in an obligatory reduction of 300-500 kcal in daily EE.

These values represent the minimum deficits in EE because there may also be *behavioural* changes (e.g. reductions in the intensity and duration of physical activities) as well as specific *regulatory* or *adaptive* mechanisms operating to spare energy (Figure 1). Early evidence in support for the latter contention that metabolic efficiency may increase in response to therapeutic

dieting, at least in certain individuals, derives from the study of Miller and Parsonage (1975). They showed that among a group of 29 obese women isolated in a country house and kept on a 1500 kcal dietary regime for 3 weeks, nearly a-third of the women failed to lose weight, and that the resistance to slimming was associated with a low BMR and low daily EE. More recent studies indicate that after substantial weight loss, some post-obese women tend to have a lower 24h-EE than weight-matched controls (Geissler *et al.,* 1986, McNeill *et al.,* 1990) and others a reduced energy requirement (per unit of metabolic mass) for weight maintenance (Leibel & Hirsh, 1984). In our own studies, post-obese subjects had a normal BMR but they showed only a-third to a-half of the thermogenic response to food observed in lean controls (Dulloo & Miller, 1986; Dulloo *et al.,* 1989). Taken together, it is clear that in response to dieting and weight loss, there is a lack of homogeneity concerning the compartments of EE exhibiting regulatory readjustments in favour of energy economy, but the final outcome seems to point in the same direction-i.e. the post-obese subjects tend to be metabolically more efficient in energy utilization as evidenced by a lower daily 24h EE of 5-15% than weight-matched lean individuals. It can be argued that a between-group difference of 5% in daily EE is small and probably undetectable statistically with small numbers of subjects, but if the increase in metabolic efficiency persists in a dynamic phase of weight regain, it can contribute to the rapid restoration of body fat (Dulloo *et al.,* 1994). Nonetheless, in the face of both genetic and dietary variability, coupled with limitations in methodological and experimental approaches, the accurate analysis of human data on obesity remains difficult. This has resulted in controversies concerning the existence and quantitative importance of an increase in whole-body metabolic efficiency following weight loss in obese humans (Luke & Schoeller, 1992). However, long-term energy balance measurements and precise body composition analysis in animal models support the existence of a physiological regulatory adaptation to low calorie intake corresponding to 10-15% of normal EE, and that it is "carried on" to accelerate the replenishment of fat stores whenever the level food intake exceeds that the energy requirements for maintaining the lower body weight (Dulloo & Girardier, 1990; Dulloo & Calokatisa, 1991). Furthermore, the results of a very recent reanalysis of the classical Minnesota study of Keys *et al.* (1950), in which normal-weight men were subjected to experimental semi-starvation and refeeding, strongly support the contention for the existence of an increase in metabolic efficiency geared at recovering specifically body fat in human (Dulloo, Jacquet & Girardier, 1996).

Taken together, it is clear from Figure 1 that as a result of weight loss, the accompanying reductions in the various compartments of EE result in an energy requirement for weight maintenance that is substantially lower than pre-dieting values-e.g. at least some 300-500 kcal daily after a weight loss of 20 kg. Reductions in EE of this magnitude are not only counterproductive to the efficacy of the dietary regime in achieving the target weight, but they also contribute importantly to the relapse of the obese condition. Hence, approaches that can effectively and safely raise the rate of EE would be an invaluable help in the management of obesity.

STRATEGIES TO COUNTERACT DIMINISHED ENERGY EXPENDITURE

The idea of stimulating metabolic rate in order to facilitate weight loss is not new, but the physiological basis upon which various approaches were developed has undergone considerable

changes over the past decades. The remaining of this paper analyses the potentials and limitations of these various strategies which include behavioural, dietary, hormonal and pharmacological interventions.

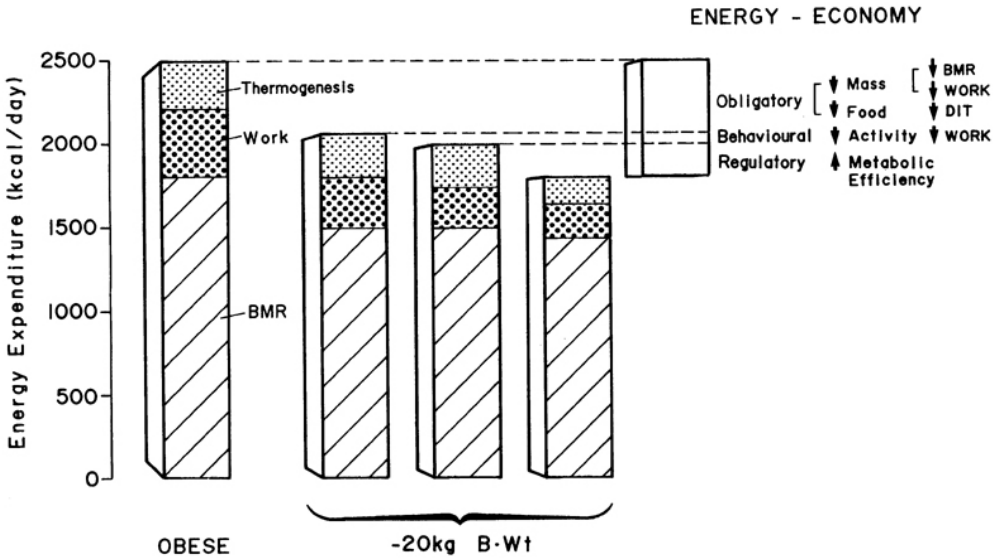

Figure 1: Schematic representation of re-adjustments in the compartments of energy expenditure and the types of energy economy as a result of weight loss (say 20 kg). Energy expenditure (often referred to as metabolic rate or heat production) can be divided into 3 compartments: (i) the basal metabolic rate, BMR-which corresponds to energy spent in maintaining metabolism under conditions of rest, thermoneutrality and mental relaxation, (ii) Work-the amount of energy spent in physical activity, i.e. muscular contraction, and (iii) Thermogenesis-which is defined as the heat production which is not due to basal metabolism nor to physical work per se; this includes (a) diet-induced thermogenesis (DIT)-i.e. the heat production following a meal, (b) isometric and dynamic thermogenesis-related to muscle tension and stretched muscle respectively, (c) cold-induced thermogenesis-related to body temperature regulation, (d) psychological thermogenesis-related to stress, and (e) drug-induced thermogenesis-e.g. stimulation of resting metabolic rate by nicotine from cigarette smoking or by caffeine-containing beverages. (Taken from Dulloo, 1993a)

Exercise

In theory, an increase in the amount and intensity of physical activity would seem to be an effective way to compensate for the drop in EE in response to low calorie intake. Exercise could enhance EE both directly by expending more calories for the performance of an increased work load, as well as indirectly by protecting musculature during dieting, thereby lessening the reduction in lean body mass and minimising the obligatory fall in EE. In addition, advocates for exercise therapy in weight control often point to certain evidence, albeit controversial, that regular exercise may elevate the resting metabolic rate well after the cessation of the physical activity per se. This notion is based upon the possibility that neurohormonal changes (e.g increased sympathetic activity and plasma catecholamines) which occur during the exercise may persist and stimulate thermogenic processes well beyond the period of exercise, and for long enough duration to make a substantial difference to daily EE. In practice, most clinics and slimming groups try to combine both types of treatment (i.e. dieting and exercise), but even those who claim to be successful admit that very few of their slimmers of the year can maintain their ideal body weight for longer than a few years. In fact, the compliance is poor and the drop out

rate is high probably because the amount and intensity of exercise required to produce a substantial increase in daily EE often involving daily aerobic exercise exceeding 60% of maximal aerobic capacity for 1-2 hours-is simply beyond the physical ability of most individuals (Garrow, 1995). To illustrate further the limitations of exercise therapy in body weight control, it is perhaps worth considering that to compensate for the obligatory reduction in EE after a 20 kg loss, i.e. a minimum of 300-500 kcal daily, it would be necessary to increase physical activity to levels corresponding to some 2 hours of jogging daily-or equivalent to some 14 hours of jogging over the week-ends. Given the amount of time that the person will have to spend on such recreational activities, it not surprising therefore that exercise therapy results in a high drop-out rate and poor compliance.

Diet Composition

Over the decades there have been frequent claims, albeit equivocal, that one food is more thermogenic than others. The explanation for such differences has generally been attributed to (a) the energy costs of their metabolic fates and rates of oxidations, (b) to the central actions of their metabolites or related signals, or (c) to their effects in directly altering cell membrane fluidity and hence tissue responsiveness to neuro-hormonal control of energy metabolism. Table 1 summarises the current state of knowledge concerning the effects of nutrients and dietary composition on postprandial thermogenesis (DIT) assessed over a few hours, on 24h EE measured in room calorimeters, as well as the effect of diet composition on weight loss during slimming hypocaloric trials. In general, diets high in protein are often (Nair *et al.,* 1983; Dauncey & Bingham, 1983; Zed & James, 1986), though not always (Belko *et al.,* 1986), reported to be more thermogenic than those lower in protein. Similarly, diets rich in carbohydrates are reported to increase DIT to a greater extent than isocaloric diets rich in fat (Schwartz *et al.,* 1985; Welle *et al.,* 1981), although a lack of difference has also been reported (Kinabo & Durnin, 1990a). Differences in postprandial thermogenesis have also been shown among various carbohydrates, with sucrose or fructose being more thermogenic than glucose both in lean and obese human volunteers (Sharief & Macdonald, 1982) More recently, interests have also focused on the differential effects of fatty acid composition on DIT, and there are reports that diets rich in medium-chain triglycerides (MCT) are more thermogenic than those rich in long-chain triglycerides (LCT), or that diets high in polyunsaturated fats (PUF) are more thermogenic than those high in saturated fats (SF) (Seaton *et al.,* 1986; Jones & Schoeller, 1988).

Table 1. Diet composition, thermogenesis and weight loss in human

Diet-induced Thermogenesis	24h-calorimetry Metabolic Rate	Wt loss during Hypocaloric Trials
HP > LP (l,o)	HP > LP (l)	HP = NP (o)
HC > HF (l,o)	HC = HF (l,o)	HC = HF (o)
Suc > Glu (l)	?	?
Fruc > Glu (l,o)	?	?
PUF > SF (l)	PUF = SF (o)	PUF = SF (o)
MCT > LCT (l)	MCT > LCT (l)	MCT = LCT (o)

H, High; L, Low; N, Normal; P, Protein; C, Carbohydrate; F, Fat
(l) in Lean subjects; (o) in Obese subjects (see text for details and references)

However, it is often argued that such differences apply only to artificial meals (single nutrients rather than food), relate to incomplete measurements of the thermic effect of the meal, or that they are so trivial in quantitative terms that they have no impact on long-term EE particularly during weight loss. In fact, recent studies found no differences in 24h EE in response to isocaloric exchange between high-fat and high-carbohydrate diets (Abbott *et al.,* 1990; Lean & James, 1988) nor between diets high in PUF compared to SF (Hill *et al.,* 1991) in both lean and obese humans, although 24h EE in young men was found to be greater with low-to-moderate amounts of MCT substituting LCT (Dulloo *et al.,* 1996). However, clinical trials have failed to show differences in weight loss when obese patients were put on hypocaloric diets differing in the ratios of fat to carbohydrate, MCT to LCT, or in the ratio of PUF to SF (Hill *et al.*, 1991; Bogardus *et al.,* 1981; Haslett *et al.,* 1983; Yost & Eckel, 1989). Nonetheless, considerable optimism persists in that even though alterations in dietary composition have no impact on EE once the obese condition is already morbid or during weight loss, they may have a role in the dynamic phase leading to the obese condition. This contention is to some extent supported by the demonstration (Lean & James, 1988) that after weight loss, the 24h EE of post-obese subjects were greater by 5% (~100 kcal) when fed a diet high in carbohydrates and very low in fat (3%) than an isocaloric diet high in fat (55%). Whether such differences in EE also occur with less extreme differences in diet composition, and whether they persist during a more dynamic phase of weight gain is not known. For ethical, practical and methodological reasons, such investigations are difficult to conduct in humans, but studies in laboratory animal models have provided insights into the potential role of manipulating dietary composition on the elevated efficiency favouring fat deposition during obesity relapse (Dulloo & Girardier, 1992). The general conclusions are that high fat diets (>35% of energy intake) may exacerbate the efficiency of fat deposition during body weight recovery, an effect that largely depends upon their fatty acid composition (Dulloo *et al.,* 1995). However, within the recommended range of nutrient intake for general good health (adequate protein and <35% fat), neither differences in fat levels (6-30%), fatty-acid chain length and degree of unsaturation, nor differences in carbohydrate types were found to influence the energetics of fat deposition during weight recovery.

Meal frequency

Since the work of Fabry (1964) in man showing an inverse relationship between meal frequency and adiposity, several studies have investigated the notion that an isoenergetic low calorie diet taken as a large number of small meals (nibbling) may be more energy-costing and hence induce greater weight loss than the same diet taken as a small number of large meals (gorging). However, although a recent study (Tai *et al.,* 1990) indicated a greater thermogenic effect when the same caloric load was provided in 6 small portions compared to one large portion, other studies report that meal frequency has no effect on DIT (Belko & Barbieri, 1987; Kinabo & Durnin, 1990*b*). Similarly, 24h calorimetry measurements have been unabled to detect differences in daily EE during nibbling versus gorging (Dalloso *et al.,* 1982), and seem to support the majority of chronic studies (Bortz *et al.,* 1966; Finkeistein & Fryer, 1971; Garrow *et al.,* 1981) that have failed to find any significant relationship between meal frequency and weight loss during dieting.

Hormones

Thyroid hormones are well known to be thermogenic. Crude thyroid extracts were used in obesity therapy at the turn of this century, and thyroid hormones are still used nowadays to treat the hypothyroid obese. The vast majority of obese however are euthyroid, and treatment with thyroid hormones has proven to be either ineffective or too dangerous, since an increase in metabolic rate can only be achieved with doses of the hormones which are high enough to expose them to risks of thyrotoxicosis and other complications. It is often suggested that T3 replacement may play a role in enhancing weight loss during dieting (when both the metabolic rate and T3 levels fall), but much of the additional weight loss is due to reductions in body protein rather than fat (Bray & Teague, 1983). The reports that other hormones e.g. glucagon, growth hormone, human chorionic gonadotropin (HCG) and some of the oestrogens were thermogenic in man have never been confirmed (Bray & Teague, 1983). Glucagon seemed particularly interesting in view of its antagonism to the energy storage function of insulin, but the exogenous doses of glucagon required to elicit a thermogenic response are far outside the physiological range. Because of its influence on body energy partitioning in favour of protein at the expense of fat mass, growth hormone therapy has often been suggested for obesity treatment. Indeed, the administration of growth hormone for 6 months has recently been shown to increase lean body mass and to decrease adipose tissue in elderly men (Rudman *et al.,* 1990). However, its administration for 3 months failed to alter the body weight and body fat in diet-restricted obese patients (Snyder *et al.,* 1988). In general, there is little interest to-day in testing these hormones as thermogenic anti-obesity agents mainly because of the lack of physiological basis for their use.

Synthetics

2,4 Dinitrophenol was the first synthetic drug put to use in the treatment of obesity. By uncoupling oxidative phosphorylation and hence allowing energy to be dissipated as heat, it was effective in reducing body weight among many obese humans treated in between the two world wars. It was discontinued because of serious side effects and even some deaths. Derivatives of dinitrophenol (e.g. dinitrocresol) were also tested (Dodds & Robertson, 1933), but no one was able to separate the uncoupling effects from the serious side effects such as cataracts. Anti-inflammatory drugs such as salicylates and indomethacin (Miller, 1975; Curtis-Prior, 1975) also raise metabolic rate acutely, but the effect is too mild at acceptable dosages to have practical value.

Thermogenic drugs of everyday life

Coined as the “Drugs of Everyday-life”, caffeine, nicotine and alcohol, which have become part of our food, are well known to possess thermogenic properties (Miller 1975). Smoking a packet of cigarettes a day raises the daily metabolic rate by 10% (Hofstetter *et al.,* 1986). This thermogenic effect is considerable and could, in its own rights, account for the often reported tendency to gain 5-8 kg of weight within a year after cessation of smoking. However, the high risks of cardiovascular diseases, cancer and other complications associated with cigarette smoking and alcohol consumption clearly outweigh any beneficial effect that they may have on body weight. In contrast, caffeine is relatively safe in moderate amounts and is usually found in

beverages (e.g. tea, coffee, cola drinks), and in numerous over-the-counter pharmaceutical preparations (e.g. for coughs and asthma). Its thermogenic effect in both lean and obese humans is well established (Miller, 1975; Acheson *et al.,* 1980). In commonly consumed doses, caffeine has recently been shown to enhance diet-induced thermogenesis in post-obese human subjects and to increase their daily energy expenditure by 5% (Dulloo *et al.,* 1989). Since this study was conducted in habitual coffee/tea drinkers, these data are relevant to chronic conditions of caffeine intake, and suggest that even if a certain degree of tolerance to its thermogenic effect may develop, the stimulatory effect of moderate caffeine intake on daily EE remain significant. However, a stimulatory effect caffeine on EE after weight loss does not necessarily imply that it may also have a similar thermogenic effect under conditions of more severe caloric restriction. In fact a recent double-blind study (Toubro *et al.,* 1993) indicate a mild and insignificant effect of caffeine compared to placebo on weight loss when administered in conjunction with a low 1000-kcal diet. Taken together, the available evidence suggests that although caffeine *per se* probably has little or no role in facilitating weight loss on a hypocaloric diet, the possibility remains that such normal caffeine consumption by enhancing thermogenesis may be preventing certain individuals from gaining a few more kilos of fat over a year.

Sympathomimetics

The thermogenic effects of nicotine and caffeine have long been suspected to be mediated through interference with the activity of the sympathetic nervous system (SNS): that of nicotine may be attributed to its cholinomimetic effects in stimulating postganglionic sympathetic neural transmission, whereas that of caffeine due to its ability to increase intracellular cAMP-but the thermogenic properties of both drugs can be explained on the grounds that they both exert their influence along the line of sympathetic control. It is only over the past twelve years however that interest in thermogenic drugs has shifted towards a systematic search for stimulants which mimic the activity of the SNS (i.e. sympathomimetics). This new approach follows several lines of evidence suggesting an important role of the SNS activity (via its heat-producing neurotransmitter norepinephrine, NE) in energy balance regulation, and that diminished SNS activity contribute to the diminished EE leading to obesity (Landsberg *et al.* 1984; Dulloo & Miller, 1987a). Specifically in the context of dietary treatment of obesity, the suppression of sympathetic activity by fasting or caloric restriction appears to play an important role in the regulatory (or adaptive) component of the decreased EE associated with low calorie intakes (Dulloo & Miller, 1987a, Landsberg & Young, 1993). Hence, drugs that mimic the activity of the SNS and increase the metabolic rate therefore offer considerable therapeutic potential, and provide a rational pharmacological approach in obesity treatment. This had led to the testing of a wide variety of sympathetic stimulants already in clinical use for other treatments, as well as some β-agonists used experimentally for the production of leaner livestock. In addition, several pharmaceutical companies, largely motivated by evidence suggesting that the adrenergic control of thermogenesis involves mechanisms other than conventional α-and β-adrenoceptors (Arch *et al.,* 1984), have been successful in putting forward a new generation of atypical β-agonists-often termed β-agonists. The aim is to target specifically the β3 adrenoceptors and hence minimising side-effects associated with β_1-and β_2-adrenoceptor activation. This topic concerning the search for old and novel sympathomimetics with potential thermogenic anti-obesity properties has previously been reviewed (Dulloo, Seydoux & Girardier, 1990). Those sympathomimetics of interest include ephedrine (an enhancer of NE release), clenbuterol and cimaterol (β_2-agonists)

and several of those novel β_3-agonists. In animals, they have all been shown to possess potent anti-obesity properties and to reduce specifically fat and not body protein. At the current state of knowledge, however, information about their safety and efficacy in obese human subjects is limited to only one of these novel β_3-agonists (BRL 26830A) and the "old" sympathomimetic ephedrine. When administered in conjunction with low calorie diets, both types of sympathomimetics have been shown to induce greater weight loss than with placebo, and to be reasonably well tolerated (Astrup *et al.,* 1985; Pasquali *et al.,* 1987; Connacher *et al.,* 1988). In fact, it should not be a surprise that with ephedrine, a compound apparently mediating its thermogenic effects by inducing the release of NE from sympathetic nerve terminals (Dulloo, Seydoux & Girardier, 1991; 1992), the side effects were mild and mostly transient. This is because (i) when administered in conjunction with a low calorie diet, ephedrine may merely reduce the fall in NE turnover rates rather than augmenting it above predieting levels, and also (ii) because of the well-known rapid development of tolerance vis-a-vis its effect on cardiovascular functions. In contrast, tolerance does not develop to its thermogenic effects (Astrup *et al.,* 1985)-thereby raising the possibility that ephedrine, by exerting its effects via sympathetically released NE, may be activating the same population of atypical β-adrenoceptors shown to possess high affinity for the novel β_3-agonists (Dulloo, Seydoux & Girardier, 1990). A recent study in humans in fact support this contention (Liu *et al.,* 1995).

It should be borne in mind that so far, these drugs represent only the first generation of sympathomimetics tested primarily for their thermogenic anti-obesity properties. There is no doubt that more selective and more efficacious future generations of atypical β_3-agonists will be found. At the same time, one can also look ahead to the possibilities of enhancing the effects of ephedrine on thermogenesis and fat losses, particularly by blocking the inhibitory modulators of NE release and actions. For example, methyl-xanthines and aspirin have mild thermogenic effects in their own rights when administered in therapeutic doses, but they can markedly potentiate the acute thermogenic effects of ephedrine in obese and post-obese humans subjects (Dulloo & Miller, 1986; 1987b; 1989; Horton & Geissler, 1991). Mechanisms that invoke increased and sustained levels of norepinephrine at the sympathetic neuro-effector junctions, and elevation of cAMP levels at the cellular level, are probably involved in these interactions (Figure 2): namely when NE release is enhanced by ephedrine, the inhibitory effects of adenosine, phosphodiesterase activities as well as certain prostaglandins could be antagonised by caffeine and aspirin respectively (Dulloo & Miller, 1989; Dulloo, 1993b). A controlled clinical trial in obese patients has in fact already demonstrated the weight reducing effect of another preparation containing ephedrine and caffeine (Malchow-Moller *et al.,* 1981). This effect was attributed to a central action of ephedrine in reducing appetite, but in retrospect, it seems likely that the combination of ephedrine and caffeine in that preparation stimulated thermogenesis to the extent that a rise in EE also made an important contribution to the reduction in body weight. In fact, more recent double-blind placebo-controlled studies have confirmed the synergistic interaction between ephedrine and caffeine (Astrup *et al.,* 1991) and have shown that while low doses of ephedrine or caffeine had no effect in facilitating weight loss of obese patients on a 1000 kcal regimen, the combined ephedrine + caffeine mixture induced an additional weight loss of 3-5 kg over a 6 month period (Toubro *et al,* 1993). Interestingly, side-effects with these mixtures were mild and transient: neither blood pressure nor heart rate were affected during long-term treatment. Similarly, no adverse effects were reported during treatment with a combination of ephedrine, aspirin and caffeine which, unlike placebo, induced weight loss in obese patients

without caloric restriction (Daly *et al.*, 1993). The efficacy of mixtures of ephedrine, methylxanthines and aspirin in the treatment of obesity deserves further investigations. They have been part of our traditional medicine (albeit for other clinical purposes) for several decades and have proven to be relatively safe drugs. More interesting, however, is the fact that this approach provides a rational basis to extend the search for safer and more effective xanthines and prostaglandin-inhibitors as potentiators of sympathomimetic activation of thermogenesis (Dulloo, 1993b).

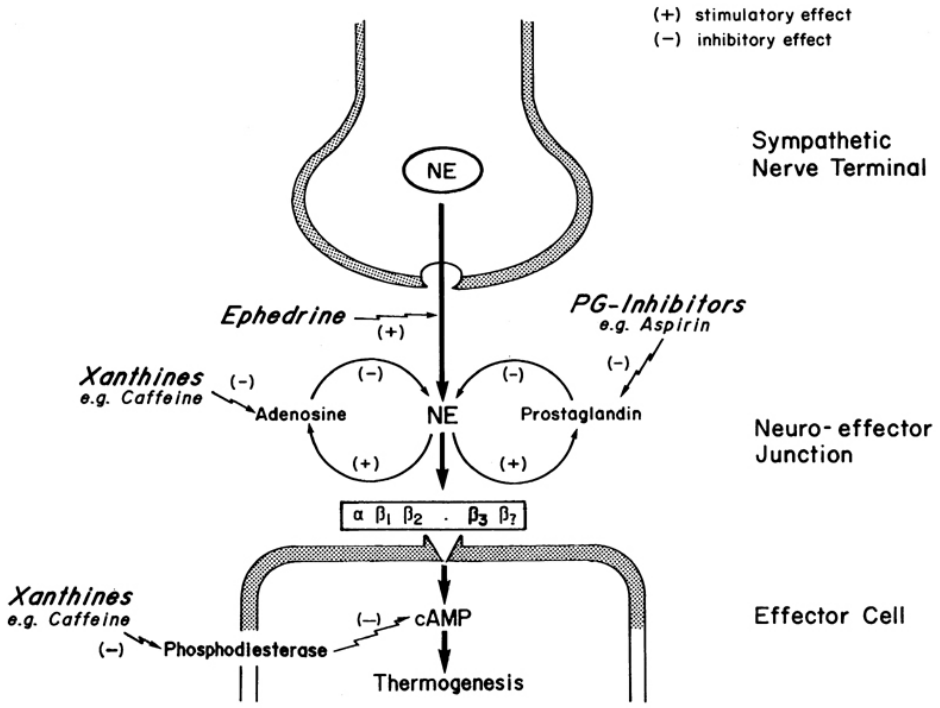

Figure 2: Peripheral mechanisms underlying the interaction between ephedrine, xanthines and prostaglandin (PG)-inhibitors in the stimulation of thermogenesis.
Norepinephrine (NE) release and action is believed to be under negative feedback modulation by (i) adenosine and prostaglandins (e.g. PG-E_2 and PG-F2α) in the synaptic neuro-effector junction, as well as (ii) at the cellular level, by the phosphodiesterase enzyme activity which breaks down NE-induced cAMP. Thus when NE release is enhanced by ephedrine, the inhibitory effects of adenosine, prostaglandins, and phosphodiesterase on further NE release and actions could be blocked by xanthines (e.g. caffeine) and/or PG-inhibitors (e.g. aspirin). In this way, the stimulatory effect of ephedrine on thermogenesis could be increased and sustained. (Taken from Dulloo, 1993b)

CONCLUSIVE REMARKS

The management of obesity is notoriously difficult because of the prolonged nature of the treatment, the need to readjust dietary energy intakes and/or physical activity permanently to maintain a reduced weight, and the changes in metabolism and in appetite that tend to minimize weight loss. In the vast majority of patients, the result is a transient phase of weight loss followed by a return to the obese condition within a few years. The hard fact therefore is that there is no cure, and a preventive policy seems to be the only solution at the present time. However, in

developed countries, the process of changing unsatisfactory dietary practices (i.e. to forestall or arrest a population shift towards a high intake of fat and sugar) and promoting health and exercise has proven to be socially, economically and politically difficult, -particularly in face of well-anchored agriculture and food businesses which effectively oppose any attempt to lessen their market horizons and financial interests. The result is that the enormous cost of the high technology, tertiary health care needed for the diagnosis and management of these high-incidence obesity-related complications is currently apparent in Western countries. Similar demands in developing countries will impose a huge burden on the human and economic resources of the country and are liable to disturb priorities in the health care or other sectors. In this context, rapidly developing countries like Malaysia and Singapore have interest to intervene before the typical dietary pattern associated with western affluence become widespread and established within their populations. The urgency for preventive measures is reinforced by reliable data indicating that the surge towards an exponential increase in the prevalence of obesity has already started in these countries (Ismail *et al.,* 1995; Hughes *et al.,* 1990).

Without being too pessimistic, the 'success rate' in the prevention of obesity will most probably be measured in terms of the ability to slow down or stabilise its prevalence-i.e. in limiting the chaos rather than its eradication-since in a world of plenty, the causes of obesity are complex, and dietary factors (high fat, high sucrose consumption) and/or reduced physical activities are only part of the explanation. Indeed certain individuals are more genetically more susceptible to fatness than others. This notion has been strengthened by adoption studies showing that identical twins have similar body mass index and fat distribution even when reared apart (World Health Organization, 1966), while adopted children tend to have body mass index and fat distribution which are better correlated with those of their biological parents than those of their adopted parents (Stunkard *et al.,* 1986). A genetic basis for obesity is therefore real, but the problem is to pin-point the metabolic basis for such predisposition for fatness, and to provide a rational approach to prevent its onset in the first place, and its relapse after therapeutic dieting.

There will therefore always be a need to treat obesity since there will always be a demand for treatment. The approach of reducing food intake either alone or combined with exercise/ behavioural therapy will continue to be the most common form of treatment in the foreseeable future, but the efficacy is very poor: < 2% success rate (Wadden *et al.,* 1989). This is in part because in response weight losses, the re-adjustments towards lower energy expenditure (EE), and hence energy economy, can be considerable and amounts to several hundreds of calories depending upon the amount and composition of weight loss (obligatory economy), whether physical activity is also reduced (behavioural economy), and also whether metabolic efficiency is enhanced (regulatory economy). Unless the post-obese or reduced-obese alters his/her pre-dieting level of food intake accordingly to maintain the new body weight, such economy in EE will precipitate the return to the obese condition. In this review, we have examined the various approaches that could lessen these economies in EE. The behavioural approaches of moderate exercising daily and the consumption of a diet favouring thermogenesis (i.e. essentially <35% of energy intake as fat) may or may not be quantitatively important for weight control, but they should be encouraged if only because they are compatible with a lifestyle generally recommended to reduce risks for cardiovascular diseases, type II diabetes, and the other complications of obesity. The pharmacological approach with sympathomimetics will certainly provide the most potent stimulus for thermogenesis. In patients showing persistent refractoriness

to weight loss or recurring obesity relapse, such pharmacotherapy aimed at enhancing thermogenesis may be an essential adjuvant to dietary control in long-term management of obesity.

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