BEHIND THE HEADLINES

Behind the Headlines reproduces selected clinical articles which have been published online in *The Bulletin* in the preceding quarter, in order to disseminate this topical clinical information to a wider audience (including those Fellows and Members without internet access).

The reproduced articles aim to educate and inform the wider College membership about specialist items that have been reported in the international medical and mainstream media: to the non-specialist it may not always be clear how accurately such stories – whether reporting results of scientific studies or issues of concern to health professionals – have been reported. To clarify such situations, expert clinical comments are commissioned on matters that are recurring in the international media, or about which different reports have caused conflicting messages for those practising in other specialties.

It is hoped that this section will, in time, become an invaluable source of independent and authoritative advice for Fellows and Members interested in updating their knowledge of new developments in other specialties.

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BACKGROUND

Over the last 6–12 months one of the main clinical areas to occupy the attention of both the medical and mainstream media has been the global epidemic of obesity. Following on from *The Journal*'s earlier publication of an overview of childhood and adolescent obesity, two parallel perspectives on obesity were commissioned – a review of current treatments and a forward-looking article which reports on the latest therapeutic targets in brain and fat. In addition to these articles, further international perspectives on obesity were commissioned from Australia and Jamaica.

INTRODUCTION: OBESITY – A WORLDWIDE MEDICAL CRISIS WITH NO SIMPLE SOLUTION

BM Frier, Consultant Physician and Honorary Professor of Diabetes, Department of Diabetes, Royal Infirmary, Edinburgh, Scotland

Individuals who are overweight have existed since the dawn of human history, but seldom has obesity affected whole populations on a global scale. Famine is one of the principal factors limiting population growth, and over millennia, human evolution has favoured genetic modification that provides metabolic adaptation to cope with malnutrition and prolonged periods of starvation. The transition from a hunter-gatherer lifestyle to an agrarian society occurred relatively recently in human history, but it is the social and cultural changes of the last century that are now exerting their impact on health. It seems incongruous that the greatest expansion in the world population with its consequential nutritional demands, is concurrent with a global increase in obesity of epidemic proportions. This has been fuelled by the ready availability of inexpensive, processed, energy dense food, with increasing urbanisation and a sedentary lifestyle also contributing. Articles on obesity and its treatment are therefore timely.

Obesity is a modern nutritional disorder, simultaneously developing throughout the world, and not confined to affluent countries. While North America is leading the way, with one in five adults in the US now considered to be obese, Europe, the Middle East, Latin America and North Africa all exhibit a similar pattern, following a progressive transition to a high fat diet, rich in refined sugars. In Caribbean countries like Jamaica, where under-nutrition used to be commonplace, this trend is also apparent, as reported by Dr Rosemarie Wright-Pascoe. The rising prevalence of obesity has been highlighted by consternation about the emergence of a global pandemic of Type 2 diabetes, with the greatest rise occurring in under-developed countries. Obesity (particularly visceral or central adiposity) is associated with medical conditions other than diabetes, of which hypertension and dyslipidaemia are prominent, and

they often occur in tandem with diabetes in the metabolic (insulin resistance) syndrome. This combination of vascular risk factors is recognised to pre-dispose to the premature development of macrovascular disease, manifested as coronary heart disease and stroke. On a global scale, this may represent as great a challenge to health-care resources as AIDS or dementia. Increasing obesity in children is particularly worrying and requires an urgent appreciation by politicians (whose objectives are usually short-term) of the serious nature of this potential public health time-bomb.

Tackling the obesity epidemic presents a major problem, whether for populations or individuals. Developed countries like Australia have introduced initiatives to try to influence the behaviour of the population with regard to diet and physical exercise, as described by Dr Ann Dunbar. However, in most countries, the political will is not yet strong enough to try to counteract the highly effective strategies used by large, multinational, food corporations to sell their products. Medical teaching has generally neglected nutrition and its disorders, and the limited dietetic knowledge of most doctors, coupled with even less interest in treating obesity, has opened the field to cranks, and allowed the proliferation of unscientifically-tested diets.

The disappointing, short-term limitations of conventional dietary therapy and current oral medications to suppress appetite or encourage weight loss by other means, are described by Professor Roland Jung and Dr Alison Avenell, who emphasise the difficulty which people experience of maintaining a low calorie diet over a prolonged period. While bariatric surgery to treat morbid obesity is effective in sustaining weight loss and preventing diabetes, this is not a realistic treatment for large numbers of people, many of whom are unaware of the medical consequences of obesity and lack motivation to pursue effective treatment. However, Professor Jonathan Seckl, in discussing potential therapeutic targets in obesity, has emphasised the importance of greater comprehension of the metabolic abnormalities in adipose tissue and the brain, which underlie excessive caloric intake. This may lead to innovatory approaches to treating obesity, through manipulation of enzymes in adipose tissue that regulate fat deposition and insulin sensitivity. The urgency of a major research effort in this field could not be more pressing to confront one of the emerging medical crises of the 21st century.

OBESITY IN THE CARIBBEAN

R Wright-Pascoe, Consultant Physician, Department of Medicine, University of the West Indies, Kingston, Jamaica

Every day the people are dying, yeah
For hunger (dread, dread) and starvation
(dread, dread, dread, dread) . . .

One Drop, Bob Marley

The Caribbean is in transition. Under-nutrition, starvation and malnutrition are now rare and obesity is now not unusual. For instance, in Jamaica, the prevalence of obesity is 30·7% in females and 6·7% in males. In less than a decade, the prevalence of obesity has doubled. Although 50% of the body mass index (BMI) is genetically determined, there has not been a major influx of new genes in the Caribbean so other factors are to blame.

In their transition from 'underdeveloped' nations to 'developing' nations, the countries of the Caribbean are no longer predominantly agricultural-based societies. With tourism as one of the main industries, the continuing rural–urban drift and improvement in gross domestic product (GDP), has come increased access to diets that are high in fat and calories.[1] Intake of green vegetables, salads and fruits are less than recommended and physical activity has decreased. For instance, most Jamaicans have sedentary jobs and most, regardless of age, lead sedentary lives. In Barbados, where one of the highest GDPs in the region exists, physical activity of the young is similar to that of US youths!

Coupled with this is Caribbean peoples' perceptions of being overweight and obese as desirable traits. In the multiracial Caribbean society this perception is peculiar to blacks who have the highest prevalence of obesity in the region. Thus, cultural factors may be important in determining obesity, in this instance particularly in women.

The expected health risks to the Caribbean will be tremendous. For instance, obesity is an independent risk factor for diabetes mellitus, hypertension, and dyslipidaemia and ischaemic heart disease. The prevalence of diabetes mellitus and hypertension in the Caribbean is high.[2] Diabetic subjects have a high prevalence of abdominal obesity

and hypertension, independent risk factors for cardiovascular disease. Already, ischaemic heart disease in this population is not rare. In addition, insulin resistance syndrome, also a risk factor for cardiovascular disease, is not uncommon in the Caribbean. It is therefore not surprising that hypertension, diabetes and cardiovascular disease are some of the commonest causes for mortality. They exert a significant impact on the region's economy.[3]

Caribbean societies must be cognisant of the impact of obesity on their population especially as obesity prevalence is increasing, even in children. More comprehensive measures, similar to those recently launched in the US, must be put in place to halt this.[4,5] However, while general factors such as diet and exercise associated with obesity may be the same worldwide, the cultural backgrounds in which they operate are different. Local solutions may have to be found for local problems.

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WEIGHING IT UP DOWN UNDER

OBESITY: AN AUSTRALIAN PERSPECTIVE

A Dunbar, Honorary Senior Lecturer and General Practitioner, Greater Green Triangle University Department of Rural Health, Flinders and Deakin Universities, Victoria, Australia

Australia is seen as a highly successful sporting nation but paradoxically it is succumbing to sedentary activities. The incidence of obesity and being overweight is following the same trends as North America and the UK.

The Australian Diabetes, Obesity and Lifestyle Study (AusDiab) surveyed lifestyle factors, socio-economic factors, obesity and the incidence of diabetes between 1999 and 2000. It was a cross sectional study of over 20,000 people from 42 sites throughout Australia, and showed that 67% of males and 52% of females aged 25 and over were overweight, with 19·1% and 21·8%, respectively, being considered obese. Perhaps even more worrying were the figures from the Sentinel Site for Obesity Prevention in Victoria which reported last year that 26·7% of children aged between 7 and 11 are overweight with 7·9% of this total considered to be obese. This compares badly with the national data from 1985 giving figures of 12·1% overweight with 1·7% obese.

A recent report from the Organisation for Economic Co-operation and Development ranked Australia fourth in the world for obesity and growing at the fastest rate. As in every other country where obesity is an increasing problem, the healthcare costs for individuals and states mount with the growing levels of associated morbidity. So what has gone wrong in Australia and what is being done about it? The Federal Government has set up a National Obesity Prevention Group and similar initiatives exist at State level. There is no doubt that obesity is much higher on the health agenda now, and increasing amounts of health funds are being directed towards research. This is, as yet, not being translated into significant improvement in the overall figures. The promise of funds by politicians lags behind their delivery, and there is a suspicion that hospital deficits take priority over funding for prevention.

There are local centres of excellence that are having some impact. For instance the Sentinel Sites for Obesity Prevention are seeking to produce effective collaboration between health professionals and the community in order to try and prevent obesity in children. Here and in other areas of Victoria an increase in nutritional advice and back up is helping schools to provide guidance on healthy lunches, and educational sessions for parents are hoping to promote healthier eating patterns at home (see Table 1). School-based programs that promote healthier lifestyles, with increased activity and healthier food choices have been shown to be effective in a controlled trial. However, changes are only sustainable where the input is multifocused. For instance, individual education is provided for both children and parents, together with population-based education, and popular myths about diet and weight gain are addressed and challenged.

TABLE 1
Australian initiatives for obesity prevention.

Exercise
- 'Walking School Bus' – local government sponsored projects encouraging children and parents to walk to school.
- Physical Activity – Active Scripts issued by local general practitioners.
- Pedometers – issued by some local work places to encourage walking, including the Department of Health and Ageing.

Improved nutrition
- School lunch box surveys.
- Increasing nutrition and health education within school curricula.
- Sale of healthy snacks in schools.

Many health professionals would say that maintaining a healthy weight must remain an individual responsibility but when the costs of healthcare provision are considered there must be an onus to help produce a less 'obesogenic' environment. To achieve it requires coordinated action involving all sectors of society in a concerted and maintained effort. The health promotion sector is a poor cousin of the global food industry, but unless a partnership can be formed to advertise and promote a healthier diet, society may be the loser. Alternatively, legislation will be needed to limit the marketing of unhealthy food similar to the limitations placed on tobacco advertising and other successful tobacco control policies.

The other side of the equation is of course physical activity. It is clearly important that physical activity be encouraged safely. Convenient public transport would help to reduce the car culture, and urban planners should perhaps give more priority to pedestrians and cyclists. We must encourage our children to be fit and active, but this needs the cooperation of local government, schools and the providers of sporting facilities. Health professionals cannot be effective in isolation. Obesity is as big an epidemic now as infectious diseases were in the past. Waterborne diseases were only eliminated when safe water supplies, sewage control and provision for satisfactory personal hygiene were made available. Similarly, the solution for obesity lies in coordinated action by many public bodies, as well as by properly informed individuals.

There are issues that are perhaps more amenable to action by our profession. The teaching of nutrition within our medical schools has not had high priority and this has allowed the unopposed proliferation of crank diets. If information given by health professionals is not consistent and accurate then people will seek advice elsewhere, and in some instances the advice given may not promote good health in the long term. For instance, many would question the benefits of the Atkins diet that encourages a low carbohydrate intake. It certainly achieves weight loss but at a cost yet to be determined. Education is not only about giving information in an understandable way it is also about correcting previously held views that are incorrect.

There is no visible quick fix in Australia. Problems are mounting but they are being addressed, at least in part. Action is now more coordinated and the problems of obesity are well publicised. Cooperation with local authorities is increasing but with competing agendas, progress is slow. In the past, Australia has sometimes moved from having the worst problems to having the best solutions. Levels of road traffic accidents and smoking providing good examples. Seatbelts and random breath testing of drivers were introduced in Australia long before they were in the UK and smoking rates are among the lowest in the world. All these major effects were brought about through firm government action. Will Australia be first to control the junk food industry?

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OBESITY – A REVIEW OF CURRENT TREATMENTS*

R Jung, Specialist in Obesity, Diabetes and Endocrinology, Ninewells Hospital and Medical School, Dundee, Scotland; A Avenell, Clinical Research Fellow, Health Services Research Unit, Foresterhill, Aberdeen University, Scotland

Leave gormandising; know, the grave doth gape for thee
thrice wider than for other men

William Shakespeare, *Henry IV Part 2;* King to Falstaff

Obesity has, at last, reached the political agenda, with the realisation that the epidemic of Type 2 diabetes, fuelled by obesity, is preventable by weight control. For some decades, Sweden has been at the forefront of the anti-obesity campaign introducing many of the national programmes now being considered as public policy solutions by other nations. Sweden has advocated and publicised healthy diet and exercise programmes, made widely available low-fat products clearly designated with nutritional information, and major food outlets such as McDonald's have offered lighter meal options. Television commercials aimed at children under 12 years are restricted, schoolchildren as young as eight years learn to cook healthy meals, sports programmes for youngsters are heavily subsidised and vending machines in schools a rarity. Yet Swedish youngsters show a relentless rise in overweight/obesity. The prevalence of overweight/obese children in Sweden is 18% (15% overweight and 3% obese) compared to 14% in Germany, 20% in UK (12% overweight and 8% obese) and 26% in the US. Although the measures put in place by Sweden may delay and limit the degree of obesity, it is still a disappointment – but why? Is it general inactivity associated with sedentary activities such as watching television, using computers and mobile telephoning? The Scottish Intercollegiate Guidelines Network (SIGN) clinical guideline on the management of obesity in children and young people[1] advises fewer than two hours of inactivity as well as at least 30 minutes (preferably 60 minutes) of physical activity per day, in addition to a healthier diet and family involvement. Does worldwide advertising overcome local initiatives? Is it a lack of developmental training of very young children (four to eight years) and their families in healthy eating especially of vegetables and fruit, now being tested in Wales?[2] Other ideas abound, including taxing high-fat-density foods, candy and high-energy drinks, introducing many more low-energy versions of popular fast foods and drinks, compulsory smaller portion and low-energy meal availability (at lower prices!) at all food outlets. The important point is that research indicating whether any of these policy issues would be effective in the long term is just not available.

Prevention is crucial but treatment of those people who are obese is essential to prevent disease progression. The popular SIGN clinical guideline on *Obesity in Scotland: integrating prevention with weight management*[3] gave practical guidance. Health Technology Assessment (UK) has commissioned two recent reports, on obesity surgery,[4] and another on the other therapies for obesity.[5] The US Preventive Service Task Force has also published their recommendations for the screening for obesity of all adults and the value of intensive behavioural interventions comprising diet and exercise to promote sustained weight loss.[6]

The Health Technology Assessment reports have systematically reviewed randomised controlled trials (RCTs) of at least one year of follow-up, essential as short episodes of weight loss are rarely sustained. Low-fat, or 600 kcal per day deficit, diets were found to be efficacious in 12 RCTs, reducing weight for at least 36 months but not sustained for 60 months. Mean weight loss was 5·3 kg at 12 months and 3·6 kg at 36 months, with significant reduction in the risk factors of blood pressure, lipids and fasting glucose at one year. The clinical outcomes of such a modest weight loss were impressive, with 30% less development of Type 2 diabetes or impaired glucose tolerance (Swinburn) at two years, and significantly less antihypertensive medication usage for up to 30 months (Hypertension Optimal Treatment (HOT) trial)[7] and an impressive 60% maintenance off hypertension medication (control 35%) in the Dietary Intervention Study of Hypertension trial.[8]

Low-calorie diets (LCDs), i.e. 1,000–1,600 kcal per day, showed no added advantage to either 600 kcal deficit or low-fat diets. Likewise very low-calorie diets (i.e. <1,000 kcal per day) showed no advantage at one year compared with LCDs, although short-term weight losses were impressive (13·4 kg). Similar was noted for the protein sparing modified fast (PSMF). The presently fashionable Atkins diet is similar to PSMF in its high-protein, low-carbohydrate components but is distinguished by a far higher fat content. Therefore, in recent trials it has been compared in total caloric content to conventional LCDs where weight loss was significantly improved on Atkins at six months (7%

*Based on a lecture at the St Andrew's Day Symposium at the Royal College of Physicians of Edinburgh, December 2003.

weight loss vs 3·2% LCDs) but not at 12 months (4·4% vs 2·5%).[9] Interestingly despite a high fat intake, high-density lipoprotein and triglycerides were improved at one year but not total cholesterol, low-density lipoprotein cholesterol or blood pressure. Long-term effects of such an unusual diet with unrestricted red meat intake, relative lack of vegetables and fruit and high saturated fat, are as yet unknown but subject to much alarm in health circles.

Exercise added to diet is certainly beneficial on weight and is possibly maintained longer than diet (8·2 kg advantage at 36 months in the longest trial). Behavioural therapy is beneficial at 12 months but the limited trial data suggest that its benefit is less well maintained than exercise at 18 and 36 months. All three modalities given together alter outcomes, with the risk of developing hypertension reduced to 0·66 at 18 months in the Trial of Hypertension Prevention 1 (TOHP 1)[10] and to 0·79 at four years in TOHP 2.[11] In the Finnish Diabetes Prevention Study there was 58% less Type 2 diabetes at three years in those on diet and exercise.[12]

Family therapy advocated in children in *SIGN 69* was beneficial in five RCTs in adults compared to individual treatment (5·6 kg loss advantage at 24 months), whereas group therapy was similar in effectiveness at 12 months to individual treatment sessions.[1]

Drug treatment with orlistat or sibutramine was effective up to 24 months (3·4 kg loss advantage) with generally improved risk factors and outcomes apart for some evidence of increased blood pressure with sibutramine. The Xenical in the Prevention of Diabetes in Obese Swedish Subjects[13] prevention study using orlistat has recently reported a 37% reduction in Type 2 diabetes. Metformin, however, used in the United Kingdom Prospective Diabetes study trial of Type 2 diabetes[14] showed weight maintenance but not weight loss for up to 15 years (the usual trend is for weight to rise with time), with the percentage of HbA1c reduced by 2·3%, reduced all-cause mortality (odds ratio 0·62) and reduced myocardial infarction mortality (odds ratio 0·51) over ten years. Metformin used in the Diabetes Prevention Programme[15] reduced development by 31%, whereas lifestyle intervention was more effective at 58%.

The research so far indicates that even modest, maintained weight loss is beneficial but larger weight loss produced by bariatric surgery (gastrointestinal surgery to produce weight loss) has a major impact especially on diabetes development and progression. Bariatric surgery produced weight loss of 23–37 kg for up to eight years with an 84% reduction in Type 2 diabetes. Although blood pressure and cholesterol were improved at two years, blood pressure reduction was not sustained at eight years indicating that, in the long term, diabetes is more influenced by weight than hypertension. The National Institute of Clinical Excellence[16] in England has reviewed bariatric surgery and has concluded that it is most cost-effective for the severely obese who have diabetes or impaired glucose tolerance (£2,329 per quality adjusted life year).

The opening quote indicates that, even in the sixteenth century, Shakespeare was well aware of the danger to health of obesity, so is it not timely four centuries later for there to be a major international effort to try to understand and overcome this epidemic? Obesity is not a vagary of fashion but a nutritional disease associated with extensive human suffering and a massive financial cost to society.

DECLARATION OF INTERESTS

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PONDERING OBESITY:
THERAPEUTIC TARGETS IN BRAIN AND FAT

JR Seckl, Moncrieff-Arnott Professor of Molecular Medicine, Endocrinology Unit, School of Molecular and Clinical Medicine, University of Edinburgh, Western General Hospital, Edinburgh, Scotland

I am resolved to grow fat and look young till forty,
and then slip out of the world with the first wrinkle.

John Dryden, *The Maiden Queen,* 1668

The archetypal seventeenth-century view of obesity as a convenient disguise for ageing reflects an era when the average life expectancy was less than half the eight decades or more enjoyed in contemporary Western society. Hundreds of millions of years of vertebrate evolution and most of human history has produced efficient metabolic adaptations to episodic starvation. Dryden's heroine not only exemplified the optimum Enlightenment complexion but also was likely to be resistant to the inevitable episodic famine and endemic contagion. Today, obesity itself has reached epidemic proportions for the world's affluent nations and, increasingly, for developing countries as well. Excess fat contributes to much early morbidity and mortality bringing a contemporary irony to Dryden's verse. Indeed, it has been suggested that the recent welcome downturn in cardiovascular mortality in developed countries will soon be countered by an upsurge in cardiovascular disorders driven by the epidemic of obesity and its attendant risks of diabetes, dyslipidaemia and hypertension.

The primary cause of obesity is a chronic imbalance between calorie intake and energy expenditure. Underlying variable vulnerabilities within individuals modulate the likelihood of the development of adiposity and its many complications, notably the Metabolic Syndrome (Reaven's Syndrome X; the Insulin Resistance Syndrome), which describes a constellation of cardiovascular risk factors, specifically insulin resistance, Type 2 diabetes, dyslipidaemia and hypertension. The relative risk of morbidity in the Metabolic Syndrome is increased by the co-occurrence of obesity, particularly visceral (abdominal) obesity. The Metabolic Syndrome is also rapidly increasing in prevalence and is a worldwide burden upon healthcare delivery. Understanding the pathogenesis and potential treatments for visceral obesity and its cardiometabolic associations is a high priority.

In terms of treatment, millennia of professional and social exhortations to 'eat less' are undermined by the primal nature of the drive to eat and the body's physiological adjustments when obesity is chronic. These mean that dieting is misperceived by the brain and periphery as 'starvation' engendering potent physiological countermeasures to

defend the status quo, however overweight the subject may be. Drug treatments for obesity have also had at best a very chequered history; from thyroxin to amphetamines, most have fallen by the wayside from toxicity or inefficacy. New thinking is desperately required.

Two recent areas of research into obesity have caused considerable scientific and popular interest; the role of the brain in controlling appetite and metabolism and the emerging biology of adipose tissue. These two fields have converged with recognition that the fat and other metabolic tissues send potent signals to the brain and vice versa.

For the brain, previous rather simplistic notions of generalised hypothalamic appetitive and satiety 'centres', largely based upon studies of crude lesions in animals and humans, have been superseded by an increasingly sophisticated knowledge of specific neuronal subnuclei, their interconnections and the many biochemical signals that underpin a series of complex control systems. Driven by the recent technologies of human genetics, molecular biology, biochemical microanatomy, functional pathway tracing and the explosion of pharmacophores, a series of novel hormonal and neuronal pathways have been identified and are increasingly understood. A fine example lies in the biology of the arcuate nucleus in the hypothalamus. Gross lesions of the arcuate nucleus had little effect upon appetite and it was largely overlooked until it was recognised to be a major central nervous system site for receptors for the adipose hormone leptin to deliver its satiety signal to the brain. Subsequent careful study revealed the complexity of the arcuate nucleus which is a major primary relay for both 'eating' (orexigenic) and 'stop eating' (anorexigenic) signals; total lesions produce a balanced effect on both paths, but each is a major physiological player.

Recent work suggests an expanding number of key signalling molecules from the periphery. These include leptin, which indicates satiety and sufficient bodily 'energy abundance' (i.e. adipose mass) for reproduction and other purposes. In contrast, the peptide ghrelin, derived predominantly from the stomach, is released prior to eating and is a potent stimulus to increased consumption of calories, acting upon a separate group of neurons in the arcuate nucleus. Indeed, ghrelin levels rise following dieting and weight loss perhaps explaining rebound weight gain, and loss of ghrelin with barostatic gastric surgery (for morbid obesity) may underpin successful weight control. Other peripheral peptides released from the gastrointestinal tract in relation to food consumption, notably peptide YY3-36, are also promising, not only reducing food intake in normal controls but also, crucially, in obese subjects. Within the arcuate nucleus neurons a series of neurotransmitters such as alpha-melanocyte stimulating hormone (α-MSH) and neuropeptide Y transduce the peripheral hormonal signals of leptin, ghrelin and others into further neuronal components of the intra- and extra-hypothalamic circuitry, altering appetite. A small, but important group of obese children have been identified who harbour mutations of the genes encoding some of the inputs, notably of leptin, of the key hypothalamic transmitters and their receptors, perhaps most commonly of the hypothalamic receptor for the anorexic agent α-MSH. However, these pathways are complex in the extreme and the transmitters and receptors involved are not restricted to appetitive pathways so other effects of drugs modifying such systems are anticipated. The efficacy of such approaches in long-term therapy is also unclear; the history of appetite modulators is not a happy one. Moreover, the bare biology does not necessarily indicate therapeutic effectiveness. A case in point is leptin which shows paradoxically increased levels in obesity, reflecting a state of leptin resistance. Whilst the potential biological value of such resistance to allow our ancestors fully to exploit episodic caloric excess may be speculated upon, this does rather obviate any therapeutic utility for the majority of obese patients. Nonetheless, drugs developed to modify appetite selectively, exploiting mimics for endogenous signals, are a substantial hope for the future. The ethical complexities of medicalising a fundamental human behaviour such as appetite remains a thorny problem for the fluoxetine and sildenafil generation.

An additional prospect is provided by our emerging understanding that adipose tissue is not as dull and inert as previously opined. Adipocytes, in addition to their recognised role in regulating energy balance directly by insulin-modulated uptake of glucose and lipids, produce a range of important hormonal signals which indirectly modulate insulin resistance (resistin and tumour necrosis factor alpha), insulin sensitisation (adiponectin), inflammation (interleukins), appetite (leptin), blood pressure control and angiogenesis (angiotensinogen) and more. Here the future therapeutic aim may be less to control appetite than to dissociate obesity from its adverse metabolic consequences. Thus recent interest has concentrated upon adiponectin, the major protein product of adipose tissue. Adiponectin levels not only correlate directly with insulin sensitivity, but low plasma levels also predict the onset of insulin resistance/Type 2 diabetes. Treatment of rodents with this peptide improves insulin sensitivity and reduces weight and triglyceride levels. Polymorphisms in the adiponectin gene segregate with weight and it clearly represents an important line for future understanding.

Another recent highlight reflects a possible solution to the longstanding endocrine conundrum of the close morphological and metabolic similarities between the rare Cushing's syndrome of glucocorticoid excess and simple obesity with or without the Metabolic Syndrome. Raised plasma cortisol levels cause the phenotypic changes in

Cushing's syndrome and enhance appetite. In contrast, cortisol levels are modestly, if at all, elevated in patients with the Metabolic Syndrome and are reduced in simple obesity. A likely resolution to this paradox has emerged recently in the guise of tissue metabolism of glucocorticoids by the hitherto arcane enzyme 11β-hydroxysteroid dehydrogenase Type 1 (11β-HSD-1). This catalyses the conversion of otherwise inert cortisone to physiologically active cortisol in specific tissues including adipose and liver. Recent evidence has shown an adipose-selective 2–3-fold increase in 11β-HSD-1 in rodent models and human populations with obesity. It has been hypothesised that, by locally increasing glucocorticoid action, this might produce a localised 'Cushing's syndrome of adipose tissue'. To address causation, transgenic mice overexpressing 11β-HSD-1 only in adipose tissue have been generated. These mice have elevated glucocorticoid levels only in fat, whilst systemic levels are unaltered. The transgenic mice show visceral obesity, hyperglycaemia, insulin resistance, dyslipidaemia and hypertension, thus fully modelling the metabolic syndrome. In contrast, 11β-HSD-1 knock-out mice, made to explore the therapeutic potential of inhibitors, show improved glucose tolerance and lower plasma triglyceride levels driven by increased insulin sensitivity. The 11β-HSD-1 knock-out mice can apparently 'have their cake and eat it', since when fed a high-fat 'cafeteria' diet the knock-out mice gain less weight despite eating more. The biology appears conserved, at least in part, since administration of the 11β-HSD inhibitor carbenoxolone to humans also increases insulin sensitivity. The pharmaceutical industry is producing inhibitors, the first of which are entering early clinical phase studies.

Thus the emerging understanding of fat and brain has illuminated novel approaches to obesity. Today's bleak news from epidemiology may be assuaged by the hope that the future will see drugs to modify appetite selectively and to reduce the severity and impact of metabolic consequences in the already stout.

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PUBLICATION REVIEW: OBESITY AND INSURANCE

The impact of obesity on personal and national health is becoming all too apparent, but the full ramifications of obesity may not yet be apparent to either the public or the profession. Swiss Reinsurance Company of Zurich, a large international insurance company, has recently published a major report on obesity *Too Big to Ignore: the impact of obesity on mortality trends* written by Ernest Eng, a member of the company's Life and Health Business Group and a graduate of the London School of Economics. This report, which can be accessed on the Internet, contains a lot of information, including useful illustrations, and while much will be familiar to readers, the following summarised points by the *Journal*'s editor should be of interest.[1]

- Increasing obesity in those who are already insured poses a threat to the profitability of the insurance industry due to obesity-related illness. This applies particularly in Western Europe and North America. Mortality trends related to obesity, particularly obesity in childhood, and the need to include the risks of insured individuals becoming obese in the future could increase the costs of life insurance to individuals. Insurance costs between best and worst risk cases could vary by a factor of 4–5 in countries where 'preferred underwriting' is common.
- The report uses the WHO definition of obesity (BMI >30 Kg/m^2), but points out that studies on Chinese populations in Hong Kong, Singapore, and Taiwan, and on Japanese people suggest the need for different BMI definitions of obesity in Asians (see Table 1).

TABLE 1
Comparison of WHO BMI with proposed Asian BMI.

Weight class	WHO BMI (Kg/m^2)	Proposed Asian BMI (Kg/m^2)
Normal	18·5–24·9	18·5–22·9
Overweight	25·0–29·9	23·0–24·9
Obese	>30·0	>25·0

- Waist circumference is advocated as a measure of obesity in addition to BMI. It correlates well with abdominal fat on CT scanning, and is an independent risk factor over and above BMI. The National Institutes of Health (NHH) have defined increased risk at above 102 cm (40 inches) in men and 88 cm (35 inches) in women.
- Mortality rates are falling while obesity rates are rising in developed countries. Falling mortality rates may be masking the adverse effects of obesity.
- Obesity is most prevalent in the developed world (about 20%) but is also affecting the developing world (5%).
- The prevalence of obesity in children has doubled over 20 years, and one-third of obese pre-school children become obese adults.
- Obesity is most prevalent in poorer and less educated people and in women. It is related to high-calorie high-fat diet, low physical activity associated with sedentary work, automated homes, cars, passive recreations, and possibly low birth weight and arrested growth in childhood.
- A 10% increase in weight leads to 30% increase in heart disease, and a BMI rise of 1 Kg/m^2 (about 3 Kg) gives a 5–7% increase in risk of heart failure. An obese 40-year-old non-smoker stands to lose 6–8 years of life.
- Prevention is better than cure. It is not yet known whether weight loss fully reverses the ill-effects of obesity.

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The course will be held on **Friday 10 September 2004** at the College in Edinburgh. Places are available at a cost of £175 per participant and those interested in attending are advised to book early. E-mail **h.elliot@rcpe.ac.uk** to reserve a place.

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