EATING DISORDERS AND OBESITY: HOW DRUGS CAN HELP

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Eating Disorders and Obesity: How Drugs Can Help

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T. Silverstone
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Preface

The eating disorders (such as anorexia nervosa and bulimia) and obesity, have become major public health problems throughout the developed world. And, they are beginning to cause concern in the developing world. It was not always thus. Anorexia nervosa was something of a clinical curiosity until the 20th century and was relatively uncommon until after World War II. Bulimia nervosa was not formally described before 1979. Obesity, which at one time was considered the mark of the successful man, is now recognized to be a serious health hazard. It has reached epidemic proportions, consuming an ever larger proportion of the health resources of many countries.

It is customary in current medical practice, as well as in formal nosological systems, [such as the Diagnostic and Statistical Manual of the American Psychiatric Association, 4th edition (DSM-IV) and the International Classification of Disease (ICD 10)], to distinguish between 'eating disorders' (which are viewed primarily as disorders of behavior), and disorders of body weight, such as obesity. The eating disorders are categorized as mental illnesses, and as such, are the province of psychiatrists and allied mental health workers. Obesity, on the other hand, which is seen primarily as a physical condition, is more the concern of specialists in internal medicine. However, a moment's reflection will reveal that such a separation is both arbitrary and unjustified. Obesity arises from *behaviors* which are physiologically inappropriate (such as consuming food when there is no metabolic need); conversely eating disorders can cause profound alterations in *physiology and body composition*. Furthermore, many of the drugs used in the treatment of eating disorders, such as the newer 'atypical antipsychotics', frequently cause obesity, and some appetite suppressants prescribed for obesity, can cause marked changes in mood and behavior. Thus, the distinction between the two groups of conditions is not as clear-cut as DSM-IV and ICD-10 make it appear. Most patients who develop one of the eating disorders are extremely frightened of gaining weight. The disordered eating can be viewed as a pathological reaction to this fear and a distorted attempt to establish control of body weight.

This book, as its title implies, focuses on the place of drugs in the treatment of both sets of illnesses – the eating disorders and obesity. It is arranged in two parts: Part I addresses the science of eating behavior. It examines the physiology, psychology and pharmacology of normal eating, addressing two fundamental questions: 'why do we eat?' and 'why, having started eating, what makes us stop?' Part II is clinically oriented. It covers each of the recognized eating disorders, and obesity. Each of its constituent chapters reviews the clinical features, the epidemiology and pathophysiology of the particular disorder being covered, before going on to discuss the available treatment options with particular reference to drugs. The last two chapters deal with disorders of eating and body weight at the two ends of the life cycle: childhood and adolescence at one end; old age at the other.

In our society, the homily that "Cleanliness is next to godliness" has given way, as Hilde Bruch so pithily expressed it, to: "*Slenderness* is next to godliness". That this is indeed the case, is exemplified by icons of American beauty such as beauty pageant contestants and *Playboy* centerfolds, who have become progressively thinner and thinner over the past 50 years. Similar standards of what constitutes the desirable female figure have now spread throughout the developed world and are percolating through the developing world as well. This concern with being too fat is what typically lies behind the onset and continuance of the specific eating disorders such as anorexia nervosa and bulimia nervosa.

The eating disorders are serious maladies which can give rise to a host of debilitating physical and psychological consequences. It is estimated that the global burden of disease for which these illnesses are responsible in women, is higher than that due to schizophrenia or bipolar affective disorder. Obesity is of even greater concern. It is associated with a whole range of serious, life-threatening medical conditions such as diabetes, hypertension and coronary heart disease, and significantly prejudices longevity. Obesity-related conditions contribute to several hundred thousand deaths a year in the United States alone.

This book was written to help all the many health professionals, and their patients, who are wrestling with the myriad physical and psychological problems caused by eating disorders and obesity. I trust that it will also inform policy makers and public health planners.

I wish to express my thanks to Dr. Janet Polivy, Dr. Peter Herman and Dr. Patty Pliner of the feeding research group in the Department of Psychology in the University of Toronto for including me in their weekly seminars. These provided a stimulating collegial environment which helped

me greatly during the course of writing this book. I would also like to thank Peter Brown, of IOS Press for his continuing commitment to this project, and for his stalwart support throughout. Finally, I wish to express gratitude to my wife, Sarah Romans, a fellow health professional, for the unstinting assistance she has given me throughout this book's gestation.

Trevor Silverstone
Toronto, May 2005

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Contents

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Part I

Regulation of Energy Balance in Humans

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Eating Disorders and Obesity: How Drugs Can Help
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Chapter 1

How the Body Regulates Eating and Body Weight

In most people, body weight is maintained within a relatively narrow range during most of their adult lives. Such stability of weight clearly requires a close match, over long periods, between energy intake, in the form of ingested food, and energy output expended in work and exercise and in maintaining basal metabolism. This process is referred to as *energy homeostasis*. It is achieved within the remarkably small error of 1%, remarkable when we consider that, in the developed world, each person consumes on average over one million kilocalories a year (Cummings and Shannon 2003). Yet, for those with eating disorders or obesity, the regulating mechanism underlying this close balance between energy input and output has been overridden or has broken down. In order to address such clinical problems effectively, we clearly need to understand how this balance is achieved in healthy individuals of normal weight.

Energy balance is regulated by a complex set of processes which involve the gastrointestinal tract, adipose tissue and control centres in the brain. These are all interconnected through the nervous system and an array of peptide signalling mechanisms. In addition, a host of psychological and social factors play a major part in determining feeding behaviour (see Chapter 2). There are significant genetic influences on all of these mechanisms (de Castro 2004).

Most of our energy intake takes place in the form of meal eating. Thus, knowing what determines the frequency and size of meals would lead to a greater understanding of the mechanisms regulating food intake and body weight (Smith 2000). In this context, we need to know what factors initiate a meal, what signals bring a meal to a close, what changes take place in the period after a meal ends and before the start of the next meal. The events which occur during this complex series of events will be described under three headings: (1) the sequence of behaviours which occur before, during and after a meal; (2) the anatomical framework supporting the various elements of this sequence; (3) the physiological determinants of the sequence (neurochemical, metabolic and endocrine).

1. The Behavioural Sequence Involved in Meal Eating

1.1. Starting a Meal

The initiation of a meal is often triggered by the subjective sensation of hunger. The physiological processes which generate the sensations that we associate with feeling hungry are not known with certainty. Most people, when asked what bodily sensations they are aware of when they feel hungry, describe a feeling of 'emptiness' in their abdomen. Many associate feeling hungry with waves of what feel like intra-abdominal contractions – so-called 'hunger pangs'. This localisation of hunger as reflecting intra-abdominal events gave direction to the first systematic experiments on human hunger. These were conducted by the celebrated American physiologist, Walter Cannon (Cannon and Washburn 1912). He and his collaborator induced fasting subjects to swallow an empty balloon, which was inflated with air when it was in the stomach. By attaching the other end of the tube to a manometer they could monitor the motor activity of the otherwise empty stomach by recording changes in intra-gastric pressure. Recording over several hours they observed periods, each lasting 20–30 minutes, during which the stomach contracted rhythmically at a rate of about 3 times per minute. Such periods of gastric motility were associated with a reported increase in hunger. Similar observations were subsequently made by others using a variety of pressure recording techniques (Silverstone et al. 1968). It is clear, however, that such activity is neither sufficient nor necessary for the experience of hunger. People who have had a total gastrectomy for underlying disease continue to experience hunger. Furthermore, even when gastrointestinal tract is intact, the linkage between such motor activity and feeling hungry is only relatively loose.

Other bodily changes which have been observed in experimental animals to occur just before a meal include a fall in blood glucose, a lowering of metabolism, and an increase in liver temperature. When insulin is administered to healthy, normal weight subjects it increases hunger ratings, but that occurs only after blood sugar levels have started to rise following an initial fall (Silverstone and Besser 1971). This finding suggests it is the change in the rate of glucose utilisation, which accompanies lowered blood sugar levels, rather than the absolute level of blood sugar, that is related to hunger. None of these physiological events are essential to the initiating of eating, which can occur independently of them. Of greater relevance to humans are psychological and social cues such as time of day, emotional state and cultural patterns (see Chapter 2).

Before we put any food in our mouth we normally can see it, and often smell it. These pre-ingestive stimuli, when positive, stimulate changes within the gastrointestinal tract preparatory to digestion – the 'cephalic phase' – first described by Pavlov in 1895. After putting food into our mouth (ingesting it) we chew, then swallow it. When food is placed in the mouth it stimulates oral and olfactory receptors. We know from our own experience that the more delicious a food tastes, the more of it we tend to eat. The converse also applies. In more general terms we might say that such 'pre-orosensory' stimulation is an important determinant of the size of the meal consumed. The orosensory stimuli, when pleasurable, provide 'positive feedback' in that they promote the continuation of eating. Taste operates through several neuroanatomical levels in the brain (Scott 2001), with signals passing from taste receptors in the tongue and palate to the medulla, pons, thalamus, cortex, amygdala and hypothalamus. Optimal control of appetite occurs when orosensory signals are coupled with signals arising from the stomach and intestine (French and Cecil 2001).

1.2. Ending a Meal

Provided the food is palatable and there are no social or psychological constraints being applied (see Chapter 2) we tend to carry on eating until we feel sated ('full up'). Then we stop. The size of meal is determined by how much we like it ('positive feedback') and the "postingestive stimulation produced by the food being eaten" (Smith 2000). The latter tends to limit the amount consumed ('negative feedback'). It has been said, with some reason, that meal termination, in contrast to the initiation of eating, "tends to be a more biologically controlled process" (Schwartz et al. 2000) (see below).

1.3. The Between-Meal Interval before the Next Meal Starts

Experimental animals display a characteristic set of behaviours after they stop eating and before they start eating again: referred to as the 'satiety cascade' (Blundell 1992). Humans are much more variable. In some cultures it is customary to sleep for an hour or so ('siesta'), particularly after a large lunch. In other cultures the mid-day meal is a much briefer affair and work resumes shortly after the meal ends. However, even in these societies it is not uncommon to feel somewhat lethargic after eating.

The length of time before the next meal starts depends largely on how much was consumed at the previous meal. The more that had been eaten, the longer before the next meal starts. That relationship between the

amount eaten at one meal and the time before the next meal starts is one of the few consistent behavioural relationships observed in human eating. The *amount* eaten at the next meal, or indeed at any given meal, is much less predictable. As Smith remarks, "The controls of meal size are different from the controls of meal number. Thus the duration of eating and the amount eaten during a meal is determined by mechanisms that maintain eating once eating has begun" (Smith 2000).

2. The Anatomical Framework of Eating

Two organs in the body play a paramount role in regulating food intake: the gastrointestinal tract (GIT) and the brain. In addition, the adipose tissue and the islet cells in the pancreas play large part.

2.1. The Gastrointestinal Tract (GIT)

We have already seen that when food is placed in the mouth it stimulates oral and olfactory receptors. After the food is swallowed it proceeds down the gastrointestinal tract, passing in turn through the oesophagus, stomach, duodenum, small intestine, and the colon. In its course, a relay of receptors are stimulated which trigger an ordered release of peptides into the circulation (see below). In addition, the increase in volume, due to the presence of food and partly digested products, leads to mechanical changes in the gut wall which send messages to the brain via the vagus nerve. These *'preabsorptive'* stimuli are sometimes referred to as 'direct' controls which act on the central nervous system to affect the size of the meal being eaten. As they can influence meal eating in decerebrate animals they are thought to act on a 'central pattern generator' (cpg) in the brainstem. This is in contrast to 'indirect' controls which require an intact central nervous system and which can affect more than one meal. Examples of indirect control include diurnal changes in metabolism, those due to changes in body temperature, learned conditioned responses to certain foods and tastes, cognitive attitudes to foods, and social responses related to the availability of foods (see Chapter 2). The *postabsorptive state* describes the situation when the contents of a meal have been digested and the nutrients absorbed through the intestinal wall into the circulation.

2.2. The Brain

It has long been known that the hypothalamus plays a pivotal role in the regulation of feeding and body weight. In the 1950', lesions of the medial

part of the hypothalamus (VMH) in experimental animals were found to be followed by increased food intake and consequent obesity. By contrast, lesions of the lateral hypothalamus (LH) were noted to lead to animals virtually stopping eating (Anand and Brobeck 1951). These findings gave rise to the 'two centre' hypothesis of food intake regulation (Stellar 1954) which postulated that a 'feeding centre' in the lateral hypothalamus is controlled by inhibitory pathways from a 'satiety centre' in the medial hypothalamus. This hypothesis received some support from observations in humans. Tumours in the region of the fourth ventricle, which impinge on the medial hypothalamus in patients, leads to gross overeating, secondary to a voracious appetite. Those so afflicted became massively obese.

Within the medial hypothalamic area, the arcuate nucleus (ARC) plays a pivotal role in the regulation of feeding and body weight. The ARC is an elongated 'arc-like' collection of cells – hence its name. It contains two subsets of neurones which have been dubbed 'accelerator' and 'brake' respectively, depending on whether they contain 'orexigenic' (appetite stimulating) or 'anorexic' (appetite reducing) peptides (see below). The medial part of the ARC contains neurones that express the orexigenic peptides *neuropeptide Y* and *agouti related protein* (see below). The lateral part contains neurones which express the anorexic peptides melanocortin and cocaine and amphetamine-related transcript (see below). These neurones project to the melanin concentrating hormone neurones and the orexigenic neurones in the lateral hypothalamus. The arcuate nucleus is considered to lie outside the blood–brain barrier and is therefore accessible to substances in the circulation. The two groups of neurones interact with each other and with other hypothalamic areas such as the paraventricular nucleus. They also receive input from the periphery conveyed by peptides such as *cocaine- and amphetamine-regulated transcript* (CART) and *leptin* (see below). It is believed that the balance between the orexigenic and anorexic pathways in the hypothalamus is of pivotal importance in the maintenance of energy homeostasis (Sainsbury et al. 2002). The hypothalamic control of eating is implemented through its reciprocal connections with the caudal brainstem (Smith 1999).

In addition to these intra-hypothalamic and brain stem connections, the lateral hypothalamus (LH) has extensive projections to the cerebral cortex, suggesting that ARC-LH activation can lead to changes in cognitive function, including the awareness of hunger sensations.

In humans, imaging techniques such as positron emission tomography (PET), have revealed that the neuroanatomical correlates of hunger form a complex network of brain regions (Tataranni et al. 1999). In addition to the hypothalamus, the network includes the thalamus, several limbic and

para-limbic areas (the insula, hipocampus, para-hippocampal formation) and the orbito-frontal cortex (Del Parigi et al. 2002). Satiation, on the other hand, is associated with increased activation in the lateral orbitofrontal and temporal cortex (Hinton et al. 2004). The processing of extrinsic appetitive information, such as the smell and taste of food, involves activity in the vicinity of the amygdala and orbitofrontal cortex. These findings suggest that intrinsic homeostatic influences and extrinsic incentive factors act via different neural pathways, with areas of convergence in the amygdala and orbitofrontal cortex.

3. Peptides and Neurotransmitter Amines in the Regulation of Appetite, Eating and Body Weight

Our understanding of the regulation of appetite, food intake and body weight has advanced significantly in recent years with the discovery of a number of peptide molecules emanating from the gastrointestinal tract, adipose tissue and the central nervous system which appear to play a pivotal role (Wilding 2002). Much of this recent understanding has arisen from studies involving experimental animals, particularly pure-bred strains of rats and mice with selective genetic abnormalities. Parallel evidence from normal human subjects and from genetically compromised individuals, has indicated that such peptide systems play a similar major role in the regulation of eating and body weight in humans (Schwartz and Morton 2002; Small and Bloom 2004).

These peptides can be classified functionally into two types: *orexigenic* (appetite stimulating) and *anorexic* (appetite reducing). Some originate mainly in the periphery and are carried to the brain in the circulation. Those coming from the gastrointestinal tract include *cholecystokinin* (CCK) and *ghrelin* which act over a relatively short time frame to influence the size of individual meals. *Leptin* and *insulin*, released into the circulation in proportion to the amount of adipose tissue in the body, are more concerned with longer term regulation of body weight and energy homeostasis. The more recently described peptide $PYY_{3\text{-}36}$, emanating from the small and large intestine, has been found to act over an intermediate time frame. When administered to humans, it inhibits eating for up to 12 hours.

Other peptides which affect feeding behaviour are found in the hypothalamus. They include the orexigenic peptides *neuropeptide Y* (NPY) and *agouti-related protein* (AgRp), and the anorexic peptides *melanocyte-stimulating hormone* (MSH) and *cocaine- and amphetamine-regulated transcript* (CART) (see below).

3.1. Peptides Originating in the Periphery

3.1.1. Gut peptides (Naslund et al. 2001; Small and Bloom 2004)

Cholecystokinin (CCK) is a peptide released by the presence of food, particularly fatty food, in the duodenum and jejunum. As its name implies, one of its earliest recognised functions was the promotion of gall bladder contraction which releases bile into the intestine. This aids the digestion and absorption of fat. It also enters the circulation where it acts as a potent inhibitor of feeding (negative feedback) in experimental animals (Smith and Gibbs 1975) and in humans (Kissileff et al. 1981), but only after the ingestion of food (Holst 1997). It inhibits gastric emptying via the vagus, its effect being increased when the stomach is distended. CCK may act synergistically with leptin (see below). Co-administration of CCK peripherally and leptin centrally to experimental animals diminished food intake more than administration of either peptide alone (Matson and Ritter 1999).

Glucagon-derived peptides (GLP-1, GLP-2) are produced in L-cells of the intestinal mucosa of the ileum and colon (Holst 1997). GLP-1 inhibits gastric emptying. This may be the basis for its ability to increase satiety and reduce food intake in humans, thereby acting as an 'ileal brake' hormone. The effects of GLP-2 have not been as clearly characterised as GLP-1.

Ghrelin is a potent orexigenic peptide secreted by endocrine cells in the gastrointestinal tract, predominantly in the stomach (Eisenstein and Greenberg 2003). (The name 'ghrelin' is derived from the Proto-Indo-European root *ghre-* for growth and *–relin* for releasing substance.) Plasma levels of ghrelin fall when the stomach is isolated surgically in the Roux-en-Y gastric bypass in patients with morbid obesity. This fall in ghrelin level may underlie the reduction in hunger and food intake which patients experience after the operation. When exogenous ghrelin is administered to human subjects, it increases appetite and promotes food intake (Wren et al. 2001). Its orexigenic action is probably mediated by activating neurones in the ARC which co-express NPY and AgRP (Cummings and Shannon 2003). Plasma levels of ghrelin, which are reduced in obesity, rise after successful weight loss (Hansen et al. 2002).

$PYY_{3\text{-}36}$, which, though related chemically to the orexigenic neuropeptide Y (see below), is functionally an anorexic peptide. It is secreted by endocrine cells lining the distal small intestine and upper colon in amounts proportional to the calorie content of the food consumed (Batterham et al. 2002). In humans, infusion of normal postprandial concentrations of PYY(3-36) significantly decreases appetite and reduces food intake by 33% over 24 h. It possibly acts through the arcuate nucleus.

3.1.2. Peptides related to adipose tissue

Leptin Genetically obese mice (*ob/ob*) lack a blood-borne factor that regulates nutrient intake and metabolism. This factor, a 167 amino acid peptide, was given the name *leptin,* from the Greek word *leptos*, meaning thin (see Janeckova (2001) for review). The plasma level of leptin is closely related to the amount of fat in the body, being greater in the obese (Considine et al. 1996). Leptin levels rise and fall with loss or gain of adipose tissue; a loss of body fat leads to a decrease in the blood leptin level which, in turn, stimulates food-seeking behaviour in experimental animals. Conversely, gaining weight leads to an increase in the blood leptin level, and a reduction in food consumption. Thus plasma leptin acts as a 'lipostat', providing the brain with information about the body's fat stores. Of possible clinical relevance is the finding that leptin concentrations are higher in females than males from a very young age. This may reflect differences in body composition, with women likely to have a greater percentage of body fat than men, particularly subcutaneous fat. In experimental animals, leptin has been shown to act primarily on the hypothalamic region of the brain where it lowers the levels of NPY arising from neurones in the arcuate nucleus. Other hypothalamic targets of leptin include: *orexin*; *corticotropin-releasing hormone* (CRH); *proopiomelanocortin* (POMC). As well as reducing food intake, leptin has metabolic effects which increase energy expenditure, possibly via the sympathetic nervous system (van Dijk 2001).

Insulin is released into the blood from the beta cells in the pancreas in response to the rise in blood sugar following a meal. The amount released is to some degree related to the amount of body fat: the larger the adipose tissue content of the body, the greater the insulin release (Heini et al. 1998).

3.2. Hypothalamic Peptides

3.2.1. Orexigenic peptides

Neuropeptide Y (NPY) is a potent appetite stimulant expressed by neurones of the hypothalamic arcuate nucleus (ARC) that project to important appetite-regulating nuclei, including the paraventricular nucleus (PVN). It also inhibits thermogenesis. Repeated administration rapidly induces obesity. The ARC NPY neurones act homeostatically to correct negative energy balance. They are stimulated by starvation, probably mediated by falls in circulating leptin and insulin (which both inhibit these neurones),

and contribute to the increased hunger in this and other conditions of energy deficit. ARC NPY neurones may act independently as they mediate hyperphagia and obesity in genetically obese mice (ob/ob) and rats (fa/fa), in which leptin inhibition is lost through mutations affecting leptin or its receptor. Antagonists of the Y5 receptor (currently thought to be the NPY 'feeding' receptor) have anti-obesity effects. NPY is considered to be the final common pathway for the signaling cascade triggered by leptin (see below).

Agouti-related protein (AgRP) in the brain is expressed primarily in neurones of the ARC, where it is co-localised with NPY. AgRP is homologous with the 'agouti protein' found in the brain and other tissues of an agouti mouse (hence the name) with an autosomal dominant mutation which gives rise to a phenotype characterised by hyperphagia, late onset obesity, decreased thermogenesis and yellow hair. AgRP immunoreactive neurones project to neurones in the lateral hypothalamus which synthesise melanin concentrating hormone and orexin (see below). As stated above, AgRP neurones are among the targets for leptin in the CNS. The belief that it plays an important role in energy balance is substantiated by the finding that fasting induces its synthesis.

Orexins A and B are expressed in a distinct population of neurones in the lateral, perifornical and dorsal hypothalamus which have extensive projections to other brain areas (Rodgers et al. 2002). Orexin-A injected centrally stimulates eating, and prepro-orexin mRNA is up regulated by fasting and hypoglycaemia. Behaviorally, it suppresses the onset of satiety by modulating satiety signals from the gastrointestinal tract to the brain. Orexin neurones may be involved in stimulating feeding in response to falls in plasma glucose. These neurones are sensitive to nutritional state and to plasma leptin concentration and are involved in the short-term regulation of energy balance. Exogenous administration of orexins stimulates food intake in rats, possibly by acting synergistically with NPY.

Melanin concentrating hormone (MCH) acts as a functional antagonist to melanocyte stimulating hormone (see below) (Truant et al. 1972). Direct injection of MCH into the lateral ventricle of laboratory animals leads to an immediate increase in food intake.

3.2.2. Anorexic peptides

Melanocyte-stimulating hormone (MSH) is derived from pro-opiomelanocortin. It acts via melanocortin-4 receptors in the hypothalamus to inhibit feeding. It is thought to play an important role in mediating the action of leptin in the CNS (Tritos and Maratos-Flier 1999).

Cocaine- and amphetamine-regulated transcript (CART) is found in the periventricular nucleus of the hypothalamus. It inhibits food intake in laboratory animals by countering the action of NPY (Lambert et al. 1998).

Melanocortin-4 receptors (MC4-R) are expressed in various hypothalamic regions, including the ventromedial nucleus and ARC. Activation of MC4-R by agonists such as alpha-melanocyte- stimulating hormone (a cleavage product of pro-opiomelanocortin which is expressed in ARC neurones) inhibits feeding and causes weight loss. Conversely, MC4-R antagonists such as 'agouti' protein and agouti gene- related peptide (AGRP) stimulate feeding and cause obesity. Ectopic expression of agouti in the hypothalamus leads to obesity in the AVY mouse, while AGRP is co-expressed by NPY neurones in the ARC. Synthetic MC4-R agonists may ultimately find use as anti-obesity drugs in humans.

Corticotrophin releasing hormone (CRH), a peptide synthesised in the paraventricular nucleus, suppresses appetite and food intake in addition to its role in the regulation of the hypothalamic-pituitary-adrenal axis.

3.3. Hypothalamic Neurotransmitters

Within the lateral and ventromedial hypothalamus the neurotransmitter amines norepinephrine (NE), dopamine (DA) and serotonin (5-HT) play a complex synergistic role in the regulation of food intake and energy expenditure (Meguid et al. 2000). In the lateral hypothalamus of laboratory animals, increased release of NE and DA is associated with inhibition of feeding, whereas in the ventromedial hypothalamus it is associated with stimulation of feeding. By contrast, release of 5-HT in the ventromedial hypothalamus is associated with inhibition of feeding.

Animal studies have shown that stimulation of the lateral hypothalamus by glutamate and glutamate agonists, causes an intense, rapid, dose-dependent increase in food intake (Stanley et al. 1993). Receptors which respond to exogenous cannabinoid-1 (CB1) exist in the brain and appear to play a role in the regulation of appetitive behavior. Exogenously administered cannabinoid receptor agonists stimulate food consumption in animals and humans. Endogenous cannabinoid receptor agonists are present in the brain, and the brain level of these agonists increases with greater demand of food by rodents. Specific CB1 receptor antagonist compounds have been discovered that display high affinity and selectivity for the CB1 receptor. They inhibit both acute and long-term food intake in rodents and humans (see Chapter 3) (Black 2004). Neurons that express high levels of CB(1) receptors include GABAergic interneurons in the hippocampus,

amygdala and cerebral cortex, which also contain the neuropeptides cholecystokinin. Activation of CB(1) receptors leads to inhibition of the release of amino acid and monoamine neurotransmitters (Iversen 2003).

Conclusion

It is clear that the biological regulation of appetite and food intake derives from a complex set of physiological interactions taking place in a number of locations. These involve exogenous signals such as the sight, smell and taste of food, and a variety of endogenous mechanisms. The latter include satiety signals generated by ingestion and hormonal signals related to energy balance. Information about the energy and nutritional status of the body is continuously transmitted to the feeding and satiety centres in the hypothalamus by afferent autonomic nerves and by gastrointestinal and central neuroendocrine peptide mediators. Other relevant areas of the midbrain and forebrain further modulate this information stream entering the hypothalamic nuclei. Within the hypothalamus, the afferent information influences the release of DA and 5-HT from presynaptic neurones. The functional outcome depends on the postsynaptic neurones which are activated: whether they are neurones releasing orexigenic peptides such as NPY, orexin, or neurones releasing anorexic peptides such as MSH, CART or CRH. Leptin and insulin modulate the synthesis and release of DA and 5-HT from the presynaptic neurones.

If energy balance is to be maintained, the frequency of meal eating as well as the amount eaten at each meal must be controlled. The major determinant of meal size is the onset of satiety, which we have seen, is under tighter physiological control than meal frequency. The hypothalamic pathways involved in energy homeostasis interact with pathways involved in the response to satiety signals to adjust the size of individual meals (Schwartz et al. 2000). Within the hypothalamus DA appears to be associated with the initiation and maintenance of feeding whereas 5-HT is more concerned with satiation. It has been suggested that the interaction between DA and 5-HT within the lateral hypothalamus influences meal size, while the interaction between them in the ventromedial hypothalamus influences meal frequency (Meguid et al. 2000). When we begin to feel hungry again, and start thinking about the next meal, largely depends on the rate at which the inhibitory effects of repletion dissipate.

Unfortunately for overweight humans, the complex homeostatic mechanisms that regulate energy balance, which we have just reviewed, are much more effective in defending a low body weight from any further

fall, than in countering a significant increase in weight. This makes sense in evolutionary terms. Until very recent times, the risk of being malnourished was always much greater than that of being overweight. That still applies for much of the world's population. Thus, signals driving food-seeking behaviour when food supplies are limited, evolved as more powerful than those curbing food intake during times of plenty.

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Chapter 2

Psychological and Social Influences on Appetite and Eating Behaviour

Eating behaviour: when, where, and how much a person eats is governed as much, if not more, by psychological and social determinants as by physiological signals

1. Starting a Meal

While it is axiomatic that we need to consume sufficient food in order to survive ('eating to live'), much of our eating behaviour is generated more by desire than by need ('living to eat').

1.1. Sensory Stimuli

In the developed world, the desire to eat is just as often triggered by external cues, such as the sight of a delectable dish or the tempting aroma of food being cooked, as by subjective sensations of hunger brought about by metabolic needs (see Chapter 1). In practice, these external sensory stimuli trigger an increase in brain metabolism, particularly in the right orbito frontal cortex (Wang et al. 2004). They interact with internal signals reflecting the degree of satiety following the previous meal. The longer it has been since we have eaten, the less sated we are likely to feel. As the level of satiety falls and hunger increases, external stimuli become ever more potent triggers to begin eating. (Marcelino et al. 2001; Hetherington 2002). Cephalic phase responses (CPR) of the body are elicited by exposure to the sensory properties of food (e.g., sight, smell and taste) as well as by simply the thought of eating (Nederkoorn et al. 2000). They can be the direct result of sensory stimulation. The sight of food leads to activation in the right orbito-frontal cortex, a brain region involved with motivation and drive (Wang et al. 2004). Conditioned processes also play a role. CPRs are believed to optimize the digestion, absorption and use of ingested nutrients. Exposure to food increases salivation, gastric activity, heart rate, body temperature and insulin release. The magnitude of the response is directly related to the individual's state of hunger (Wooley and Wooley 1973). Some CPRs are experienced as 'craving' (see below).

1.2. Social Determinants

We tend to be creatures of habit. Much of our eating takes place in set meals taken at particular times of day. We often sit down to have a meal, not because we are hungry, but because it is what we consider to be the appropriate time for lunch or dinner. These times vary considerably from one society to another, as does the time of day at which the main meal of the day is taken. In some cultures this is at midday, in others in the evening.

Within these broad frameworks, other influences come to bear. Constraints are often placed upon us as to when we are able to begin a set meal. For example, demands of work determine when we can take a break for lunch, or the needs of others influence the time of family meals. Thus, we are often not free agents able merely to suit ourselves when it comes to eating a meal.

Another important social influence is the presence of others. We generally eat more in the company of friends, and 'restraint' (see below) may be lessened when others are present. The giving and sharing of food has a potent symbolic quality: it has been likened to the giving and receiving of love.

1.3. Mood State

Emotions can have a considerable effect on eating behaviour. Many people do not feel like eating if they are worried or depressed, while, conversely, others turn to food for solace when they feel miserable – 'comfort eating'. (See chapters on obesity and binge eating for further discussion of this issue.)

Major depressive disorder, when severe, is characteristically associated with a reduction in appetite, often sufficient to cause significant loss of weight. This is probably related to the alterations in central neurotransmitter activity (particularly that involving serotonin and norepinephrine), which occur in this disorder. Subjects with milder depressive disorder may, by contrast, eat more when depressed and gain weight (see Chapters 7 and 9). Those with 'seasonal affective disorder', who experience marked seasonal variations in mood, typically have an increase in appetite, and gain weight, in the winter months (see Chapter 8). This, too, may be related to fluctuations in brain serotonin activity (Wurtman 1993).

2. Continuing to Eat

A range of psychological and social factors can influence how much is eaten on a given occasion.

2.1. Taste and Texture of the Food

These two attributes determine the *palatability* of a given food, that is, how pleasurable it is to eat it. The greater the palatability of a food, the more we consume (de Castro et al. 2000). During the course of a meal, there is a shifting balance between the deliciousness of the food, which stimulates us to eat more of it, and the experience of increasing satiety, which inhibits further consumption. At the start, the balance is in favour of palatability but, as the meal continues, satiety increases and eventually brings eating to an end, no matter how delicious the food.

The sensitivity of taste receptors tends to decline with age. This is one of the factors causing elderly people to eat less and lose weight (see Chapter 11). Other changes implicated in the 'anorexia of aging' include a decline of opioid modulation of feeding, an increased sensitivity to satiety factors such as CCK and a slowing of gastric emptying (Chapman et al. 2002) (see Chapter 11).

2.2. Variety ("Variety's the Very Spice of Life, That Gives It All its Flavour." – Cowper 1785)

Palatability can be influenced by exposure. Even the most delectable food begins to pall on frequent repeated exposure, giving rise to 'sensory-specific satiety' (Hetherington and Rolls 1996). Introducing a novel food at that point can often stimulate further eating. Serving the same midday meal every day for 5 days leads to a decline in acceptance and intake of that meal (Meiselman et al. 2000).

2.3. Choice of Food

2.3.1. Cultural and religious aspects

The contents of a given meal in most societies is determined to a large degree by what is considered to be appropriate in that society for that particular meal. For example, in North America and much of the English speaking world, cereal, taken with milk, is a commonly accepted constituent of the first meal of the day (breakfast). The evening meal however is more likely to contain some cooked meat or fish. By contrast, meals in the Indian subcontinent would generally consist of quite different foods, which would themselves vary considerably from one region of the country to another.

Religious beliefs can also play an important part in what is eaten. Observant Muslims and Jews will not countenance eating pork while Hindus

eschew beef. Vegetarians avoid eating meat and fish, many because of ethical objections to the killing of animals for food.

Another determinant of food choice is advertising, Exposure to food advertising may influence choices towards foods of higher energy density and lower nutritional value. Foods that are heavily advertised are generally over-consumed relative to recommendations, while foods that are advertised less frequently are under-consumed.

2.3.2. Cost and availability

They often determine whether or not we eat a particular item of food. For example, caviar and *pate de foie gras* are considered to be highly desirable delicacies by many, but their extremely high price deters all but the most affluent from buying them.

2.3.3. Cognitive beliefs

People trying to lose weight by reducing their calorie intake ('restrained eaters') may deliberately avoid certain types of food because they think they are particularly fattening. Starchy foods, such as pasta and potatoes, are often misrepresented in this way. In fact, as we shall see in the chapter on obesity (Chapter 9) foods containing a high proportion of fat have a much higher energy density and thereby more likely to promote weight gain.

As may be expected, choice of foods reflects education. People with more education are more likely to consume a nutritionally healthy diet than those with less education.

2.3.4. Cravings

To have a craving for a particular food is to have an 'intense desire' for that food. In Western society the most commonly craved food is chocolate, although other energy dense foods such as cakes and biscuits appear high on the list (Rogers and Smit 2000). The concept of craving is often likened to addiction and those with a craving for chocolates referred to as 'chocoholics'. However, such cravings do not show many of the features of true addiction: there are no withdrawal symptoms if chocolate becomes unavailable and 'tolerance' does not develop, (i.e. chocolate 'cravers' do not develop the need for ever greater consumption of chocolate to achieve the same effect).

'Carbohydrate craving' has been defined as: "A ravenous appetite for a variety of sweet substances including chocolate, cake, pastry and ice cream" (Paykel et al. 1973). It has been suggested that it occurs as part

of a mood self-regulating system involving the neurotransmitter serotonin (5-hydroxy tryptamine), which is thought to play a pivotal role in the regulation of mood. According to this view, if the level of serotonin in the brain falls then mood becomes low. Serotonin is synthesised from the amino acid tryptophan which passes from the circulation into the brain through the blood–brain barrier. In this it competes with other amino acids. When the level of these other amino acids in the blood is high, less tryptophan is absorbed into the brain and less serotonin synthesised, leading to a fall in mood. Foods high in carbohydrate can overcome this effect and thereby facilitate the passage of tryptophan across the blood–brain barrier, so raising its concentration in the brain. This in turn promotes the synthesis of serotonin, which, according to the theory, produces an elevation of mood. Thus, consumption of carbohydrate can be viewed as a form of self-medication (Wurtman and Wurtman 1986). Unfortunately for this seemingly plausible notion, the evidence for it is "weak and contradictory". Dietary variations in the intake of carbohydrate and protein have very little effect on brain sertonergic function and occur far too slowly to account for any mood changes occurring within a short time after eating. Any effects of carbohydrate or protein meals on human brain serotonin are likely to be negligible under most circumstances (Young 1991).

An alternative, cognitive explanation of a craving for chocolate and other confectionary has been advanced (Rogers and Smit 2000). This suggests that dieters frequently have an ambivalent attitude to eating certain foods such as chocolate. Attempts to resist eating them frequently fail. When that happens the dieter takes refuge in the concept of a biologically determined need, such as that expressed in the carbohydrate craving hypothesis, to provide an acceptable explanation for their behaviour.

2.3.5. Restrained eating and dieting

Restricting one's calorie intake in order to lose weight, or to avoid gaining weight ('dieting') is becoming increasingly common, particularly among women in affluent cultures. According to recent population surveys, 39% women and 21% men say they are trying to lose weight; 24% of women and 8% men are actively dieting. Even higher rates were recorded when respondents were asked about their dieting history: over half of the women questioned (55%) and 29% of the men reported that they had tried to lose weight through restricting their calorie intake at some time in their life (Hill 2002). Chronic dieters exhibit what has been called a 'restrained eating style' and are often referred to as 'restrained eaters' a term coined in 1975 (Herman and Mack 1975). Restricting one's calorie intake over a

sustained period can have significant adverse psychological consequences. Restrained eaters are preoccupied with thoughts of food, they commonly exhibit increased emotionality and they are prone to bouts of disinhibited eating ('binges') (see Chapter 7). Their eating behaviour is more susceptible than that of non-dieters to social and emotional influences. In addition, some restrained eaters over-respond to palatability, and thereby increase their risk of gaining weight (Yeomans et al. 2004). "Dietary restraint seems to be fragile and easily disrupted" (Polivy 1996).

3. Termination of a Meal

The decision to terminate a meal is influenced by the interplay of a number of physiological and psychosocial factors. These include the somatically determined signals of satiety (see Chapter 1), the variety and palatability of the food being presented (see above), cognitive attitudes towards food, and social circumstances.

Eating ceases: "When the negative post-ingestive effects of satiety overcome the positive orosensory effects of the food" (Rogers and Smit 2000).

3.1. Cognitive Attitudes

Restrained eaters deliberately attempt to restrict their food intake by eating smaller portions, sampling fewer courses and by ending the meal before they reach the point of satiation.

3.2. Social Circumstances

In most cases we consume more food when we eat in the company of others than when we eat alone. But this is not always the case, as, for example, when we wish to avoid being thought a glutton by our companions or when we are conscious of our hosts' straitened financial circumstance. In general women feel more constrained by social circumstances than men (Kristen et al. 2002).

At certain times of the year such as Christmas and Thanksgiving, not only are we given license to eat large quantities of food, we are positively encouraged to do so. Conversely, at other times, members of certain religions are expected to be abstemious, even to the point of completely fasting for certain periods (e.g., Lent for Christians, Ramadan for Muslims, Day of Atonement for Jews).

There has been a growing trend in the developed world for an increasing proportion of the daily diet to be consumed outside the home, either in restaurants or from fast food outlets. Among adolescents and young adults this now accounts for up to 20% of their total energy intake. Eating in fast food outlets is associated with an increase in the intake of high-energy, high-fat foods. Another contributor to an increase in energy intake, particularly among the young, is the presence of commercially sponsored vending machines in schools and work places. Their ready availability encourages the consumption of high calorie sweetened drinks.

Another trend associated with eating out is an increase in portion sizes. "Super sizing' of portions is a trend that appears to be growing inexorably, particularly in the US. For example, the current McDonald's 'child size' soft drink is 12 oz.; the same serving in the 1950s would have been marketed as 'king size'. Portion sizes began to grow in the 1970s and the number of larger size meals rose sharply in the 1980s, and has continued steadily. (Interestingly, there is some national variation in this trend; portion sizes in French McDonalds are smaller than those in US McDonalds.) Evidence suggests that the availability of larger portion sizes increases total energy consumption among both normal-weight and overweight men and women (Rolls et al. 2002).

4. Conclusion

The determinants of eating behaviour in humans clearly involve a range of perceptual, cognitive and social factors. These all interact with the large array of physiological mechanisms regulating food intake, described in Chapter 1. Thus, how much we eat, when we begin eating and when we stop, as well as what we eat, are all governed by an extremely complex set of interactions.

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Chapter 3

Pharmacology of Appetite and Eating

Drugs can affect eating and energy balance in a number of ways. They can act centrally to increase or reduce the desire to eat (*orectics* and *anorectics*), or they can act peripherally by interfering with the absorption of nutrients from the gastrointestinal tract (see orlistat below). They can also affect body weight by influencing energy output.

In the brain, centrally-acting drugs affect neurotransmission by (a) inhibiting neurotransmitter synthesis; (b) inhibiting or promoting the release of neurotransmitters from presynaptic neurones into the synaptic cleft, where they act on post-synaptic receptors; (c) blocking the reuptake of neurotransmitters from the synaptic cleft back into pre-synaptic neurones; (d) inhibiting enzymes, such as monoamine oxidase, which are involved in the breakdown of neurotransmitter substances; (e) directly stimulating or blocking post-synaptic receptors. Other drugs modulate the action of the centrally-acting neuropeptides involved in the regulation of eating behaviour (see Chapter 1).

1. Drugs Reducing Appetite and Food Intake (Anorectics)

1.1. Centrally Acting Phenylethylamine Anorectics

Amphetamine was the first anorectic drug to be introduced into clinical practice. It was originally synthesised in the 1920's as a potential substitute for ephedrine and marketed under the trade name of *Benzedrine* for use as a nasal decongestant. Initially, it was thought to have very little, if any, effect on the central nervous system. However, within a relatively short time it was noted that, in contrast to what had first been thought, amphetamine had pronounced stimulant and mood elevating properties.

As a result, during the 1930's it came to be widely used in the treatment of narcolepsy and other fatigue states, where it was ingested in tablet form, as well as continuing to be administered intra-nasally as a decongestant. Unexpectedly, patients reported feeling less hungry after taking it and it was suggested it might have a place in the treatment of obesity. This suggestion was taken up by Lesses and Myerson in 1938, who conducted the first sucessful clinical trial of amphetamine in obese patients (Lesses and Myerson 1938). They reported that seven out of eight patients

who had taken amphetamine, lost weight without feeling hungry: "... on the one hand it decreases the appetite, and on the other so increases the sense of well being and of energy that physical activity is spontaneously increased." Thus began the complex saga of 'slimming drugs' (Silverstone 1982).

Benzedrine was shown to be the racemic mixture of two optical isomers: dextro- and laevo-amphetamine. The dextro-isomer was found to be the more potent of the two and was marketed as *Dexedrine*. The finding that the appetite suppressant activity of dextroamphetamine is paralleled by a significant reduction of food intake, has been amply confirmed (Silverstone and Stunkard 1968; Foltin et al. 1990). At first, it was hailed as an ideal drug for use in obesity. But, within a relatively short time, some of the very properties originally thought to be advantageous clinically, came to be recognised as carrying the potential for abuse, and it fell into disrepute. Despite its current unlicensed status as a treatment for obesity, pharmacological study of its actions on appetite and energy balance continue to shed light on the regulation of appetite and food intake.

Other, potentially less stimulant anorectic phenylethylamine compounds such as diethylproprion (*Tenuate*), phentermine (*Ionamin, Adipex-P*) and mazindol were introduced. All these compounds were found to increase the release of the catecholamine neurotransmitters norepinephrine and dopamine from presynaptic neurones in the brain. Subsequent studies in humans using selective dopamine receptor blockers such as pimozide, suggested that the stimulant effect of dexamphetamine was largely due to the release of dopamine. The anorectic effect appeared to be due to the enhancement of norepinephrine (NE) neurotransmission as it was attenuated by the NE receptor blocking drug thymoxamine (Silverstone 1992). Studies in laboratory animals however, have implicated DA pathways as being the more important in regulating food intake (Evans and Vaccarino 1987). They, in turn, may act by reducing the release of neuropeptide Y in the hypothalalmus (Kuo 2003).

In the early 1960's fenfluramine (*Ponderax*), another phenylethylamine compound, with a quite different pharmacological action, was introduced. It acted by enhacing the release of the indolamine neurotransmitter serotonin (5-hydroxytryptophan), rather than acting on catecholamine neurotransmitter pathways. Its anorectic activity was comparable to that of amphetamine but it was sedative, rather than stimulant. It, together with the dextrorotatory isomer, d-fenfluramine, became a recommended drug for the treatment of obesity. Weintraub had the seemingly bright idea of evaluating the combination of the sedative anorectic drug fenfluramine, with the more stimulant anorectic compound phentermine

(Weintraub et al. 1984). This combination (later to become known as fenphen) appeared to be more effective and better tolerated in comparative clinical trials than either drug given alone. The combination of fenfluramine and phentermine soon became extremely popular in the US. By 1996, over 18 million prescriptions for this combination were being issued annually. Unfortunately, the fenfluramine moiety of the combination appeared to cause pulmonary hypertension and/or mitral valve prolapse in some patients. It was withdrawn from the market in 1997.

The antidepressant drug fluoxetine (*Prozac*), another compound which promotes serotonergic neurotransmission in the brain, was also shown to reduce appetite and food intake in healthy volunteers (McGuirk and Silverstone 1990). It can be effective in the management of binge eating syndrome (see Chapter 6) and bulimia nervosa (see Chapter 5). Its use in uncomplicated obesity is more limited, as any beneficial effect wears off within a few months (Goldstein et al. 1994).

Shortly afterwards, the European pharmaceutical regulatory authority withdrew the licence for phentermine and all other stimulant anorectics in the treatment of obesity. In the US and Canada phentermine (*Adipex-P*, *Ionamin*), diethylproprion (*Tenuate*), phendimetrazine (*Bontril*), benzphetamine (*Didrex*) and mazindol (*Sanorex, Mazanor*) continue to be available for short term use in the treatment of obesity. Sibutramine (*Meridia*) [see below] is the only centrally acting anorectic drug licensed for long-term use in the US, and the only one licensed for the treatment of obesity by the European authorities. The pharmacological profiles of the more commonly used of these centrally acting appetite suppressants are given below; their clinical application is discussed in Chapter 9.

1.1.1. Diethylpropion

Diethylpropion (amfepraone) is a phenylethylamine with minor sympathomimetic properties and much less stimulant activity than amphetamine. In the brain it promotes the release of norepinephrine and, to lesser degree, serotonin. The drug is well absorbed from the gastrointestinal tract, with peak plasma concentrations occurring some two hours after oral administration. It is metabolised in the liver and has an elimination half-life of 8 hours. Diethylpropion has been shown to possses clear appetite suppressant activity. A single 50–70 mg dose lowers subjective ratings of hunger (as measured by a visual analogue scale) and food intake over an 8-hour period (Silverstone 1992).

1.1.2. Phentermine

Phentermine has a pharmacological profile similar to diethylpropion. It is well absorbed when taken orally, with a peak plasma concentration being reached within eight hours. Its elimination half life is 20–24 hours. A single 30 mg dose given to normal weight healthy volunteers significantly reduces hunger ratings and food intake (Silverstone 1982). The same effects are observed when phentermine is given to overweight women.

1.1.3. Mazindol

Mazindol has a different chemical structure from the phenylethylamine compounds considered above and a somewhat different pharmacological profile. Rather than promoting release of norepinephrine, it inhibits the neuronal reuptake of norepinephrine in the brain. In healthy human subjects a single oral dose of 1 mg reduces food intake significantly more than placebo for a period of eight hours (Silverstone 1982).

Studies of the pharmacological actions of the clinically available phenylethylamine appetite suppressants on the monoamine transporters involved in dopamine, norepinephrine and serotonin neurotransmission have revealed that they enhance neurotransmission via increased substrate release. They bind to transporter proteins and promote the efflux of transmitter from the presynaptic neurones by a process of transporter-mediated exchange. They also reduce the storage of transmitter in cytoplasmic vesicles. The various phenylethylamine appetite suppressants have a wide range of activities at monoamine transporters, with each drug exhibiting its own unique profile of action (Rothman and Baumann 2003). Phentermine (like amphetamine) is more potent promoter of norepinephrine release than dopamine release. Diethylproprion itself is inactive at monoamine transporters: it is its N-deethylated metabolite which is active. This acts by releasing norepinephrine and in blocking dopamine reuptake. Phendimetrazine similarly acts only after being converted to its metabolite phenmetrazine which is a potent releaser of norepinephrine and dopamine. Fenfluramine and its active metabolite norfenfluramine (both now withdrawn) are interesting from the pharmacological viewpoint; they both potently release serotonin and epinephrine (but not dopamine).

This group of drugs all have high bioavailabilty, a high distribution volume (4 l/kg), and are less than 20% bound to plasma proteins (de la Torre et al. 2004). Their elimination half-life is 6–12 hours.

1.2. Sibutramine

Sibutramine (*Meridia, Reductil*) has a different chemical structure and pharmacological action from the phenylethylamine derivatives considered above. It is a tertiary amine which inhibits the reuptake of both serotonin and noradrenaline, with dopamine reuptake also being inhibited, but to a lesser degree (Lean 2001). These actions lead to an enhancement of post-ingestive satiety and a reduction in hunger ratings in normal weight subjects for some four hours after administration (Chapelot et al. 2000). When given to obese patients for two weeks it reduces appetite ratings and leads to a reduction in food consumption (Barkeling et al. 2003). As well as reducing food intake sibutramine stimulates thermogenesis by activating the sympathetic nervous system.

1.3. Drugs Acting on Cannabinoid Receptors

Cannabis is known to stimulate appetite, and promote food intake ('the munchies'). The identification of cannabinoid (CB1) receptors in the brain allowed the development of selective antagonist compounds such as *Rimonabant*, which was found to suppresses food intake in laboratory animals (Colombo et al. 1998). Clinical trials have shown it to be significantly more effective than placebo in assisting overweight patients lose weight (see Chapter 8).

1.4. Anticonvulsants

Two anticonvulsants, *topiramate* and *zonisamide* were noted to cause weight loss in patients being treated for epilepsy with these drugs. They have both undergone preliminary trial as antiobesity treatments. In a 24-week, double-blind placebo controlled trial in overweight patients, those who received topiramate lost 6.3% of their bodyweight, compared a mean weight loss of 2.6% in those receiving placebo (Bray et al. 2003). A 16 week randomised placebo-controlled trial of zonisamide, treatment with the active drug led to mean weight loss of 6% of the body weight; significantly greater than the mean weight loss in the placebo group (Gadde et al. 2003).

1.5. Peptides

Derivatives of many of the peptides involved in the regulation of food intake, described in Chapter 1, have been investigated as potential therapeutic agents for use in the treatment of obesity (Halford et al. 2004).

1.5.1. Leptin

A randomised double-blind placebo controlled clinical trial of long-acting pegylated human recombinant leptin (PEG-OB) has been carried out in obese men attempting to adhere to a very low calorie diet. During the 45 days of treatment, 80 mg daily of PEG-OB daily led to a more pronounced reduction in appetite and greater weight loss than placebo (Hukshorn et al. 2003).

Axokine is a genetically engineered recombinant human variant of ciliary neurotrophic factor (rhvCNTF) that acts via leptin-like pathways in the hypothalamus. In animal models of obesity it has been shown to bypass leptin resistance. In an initial, dose-ranging, 12-week randomised placebo-controlled trial, patients who received daily subcutaneous injections 2.0 μg/kg of rhvCNTF lost an average of 3.4 kg compared to a mean loss of 0.1 kg in those receiving placebo injections (Ettinger et al. 2003).

1.5.2. Cholecystokinin (CCK)

Intravenous infusion of an octapeptide derivative of CCK decreases the level of hunger and reduces food intake in normal subjects (Kissileff et al. 1981). This effect is reversed by loxiglumide, a specific CCK-A antagonist (Gutzwiller et al. 2000).

1.5.3. Neuropeptide Y

A number of NPY receptor antagonists have been synthesised in the hope that they may be useful in the treatment of obesity. There are at least five types of NPY receptor subtypes (Chamorro et al. 2002). Thus far, the results with inhibitors of the NPY Y5 receptor subtype have been equivocal and no clearly effective anti-obesity compound has emerged (Levens and Della-Zuana 2003).

1.5.4. Glucagon-like peptide (GLP)

Glucagon-like peptide infused intravenously can reduce calorie intake of a test meal (Gutzwiller et al. 2004).

1.6. Centrally Acting Appetite Stimulants (Orectics)

A number of drugs have been found to stimulate appetite and promote an increase in body weight.

1.6.1. Cyproheptadine

Cyproheptadine (*Periactin)* is an antihistamine used for relieving symptoms of hay fever and other allergic conditions which was found to promote weight gain. We subsequently showed in a double-blind trial in normal subjects that this gain in weight was secondary to the drug's appetite stimulating effect (Silverstone and Schuyler 1975). This is thought to be due, at least partly, to its action as an inhibitor of serotonin receptors, as other antihistamine compounds do not usually affect appetite or body weight.

1.6.2. Antipsychotic drugs

Antipsychotic drugs used in the treatment of psychosis and mania commonly lead to significant weight gain. This effect was noted following treatment with chlorpromazine, the first antipsychotic compound to be introduced into clinical practice. Other antipsychotics of a similar phenothiazine structure were also prone to cause weight, particularly when administered chronically as a depot formulation (Silverstone et al. 1988). The more recently introduced second generation ('atypical') antipsychotics, such as clozapine (*Clozaril*) and olanzepine (*Zyprexa*), are particularly prone to cause significant weight gain and obesity (see Chapter 10). The inhibition of serotonin 5-HT_{2c} receptors, which offsets the likelihood of extrapyramidal symptoms (Casey and Zorn 2001) has been implicated in causing the significant weight gain which frequently accompanies treatment with some of these compounds (Allison and Casey 2001) (see Chapter 9). They also interact with the brain monoaminergic and cholinergic systems (Baptista et al. 2002).

1.6.3. Antidepressant drugs

Antidepressant drugs can lead to a gain in body weight. First generation antidepressants such as amitriptyline have long been known to do this (Paykel et al. 1973). Treatment with the newer, second generation antidepressant, mirtazepine is also often accompanied by increased appetite and weight gain. This drug acts by antagonizing adrenergic alpha2-autoreceptors and alpha2-heteroreceptors as well as by blocking 5-HT2 and 5-HT3 receptors. The appetite stimulation and weight gain are thought to be due to the central drug's action on 5-HT1A-mediated serotonergic transmission (Anttila and Leinonen 2001).

1.7. Peripherally Acting Antiobesity Drugs

Orlistat (*Xenical*) inhibits the action of the enzyme lipase in the intestine, thereby inhibiting the digestion and absorption of fats. This can lead to significant weight loss, but is often accompanied by flatulence, diarrhoea and oily stools. Its clinical application is described in Chapter 8.

1.8. Future Developments

With an ever increasing understanding of the way appetite and eating are regulated (see Chapter 1), more and more potential targets become available for the development of drugs designed to help patients overcome disorders of eating, appetite and body weight. At least 100 molecules are currently known to be in various stages of preclinical and clinical investigation for the treatment of obesity alone (Korner and Aronne 2004). They include compounds which affect the various signalling systems in the brain involved in energy balance: (a) leptin analogues, leptin transport and/or leptin receptor promoters, neuropeptide Y and agouti-related peptide antagonists, and a range of propiomelanocortin and amphetamine regulated transcript; (b) compounds which interact with pathways linking the gastrointestinal tract to the brain, such as those involving CCK, glucagon-like peptide-1, and ghrelin; (c) agents to increase resting energy output (Bays 2004).

The future for the emergence of new effective, safe compounds to help patients with eating disorders and obesity looks very promising.

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Part II

Disorders of Eating and Body Weight

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Chapter 4

Anorexia Nervosa

1. Clinical Features

Anorexia nervosa is the most life-threatening of the eating disorders and the most difficult to treat. The emaciated sufferer, typically an adolescent or a younger adult female, has an intense fear of gaining weight and becoming fat. As a result she steadfastly resists all attempts to induce her to eat and will often actively avoid treatment. The criteria laid down by version four of the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM IV) requires that: "the individual weigh less than 85% of that weight that is considered normal for that person's age and height". The World Health Organisation International Classification of Disease, edition 10 (ICD-10) stipulates that the individual have a body mass index (BMI) equal to or less than 17.5 kg/m^2. It should be noted however, that DSM IV adds: "these cut-offs are provided only as suggested guidelines for the clinician". Thus the figure of 85% of normal body weight should not be regarded as an absolute requirement for the diagnosis since: "it is unreasonable to specify a single standard for minimally normal weight that applies to all individuals of a given age and height. In determining a minimally normal weight, the clinician should consider not only such guidelines but also the individual's body build and weight history." This latter caveat rather takes the wind out of the sails of those who criticise the DSM IV for having too rigid a weight criterion for anorexia nervosa (Watson and Andersen 2003).

Weight loss in patients with anorexia nervosa is usually accomplished primarily through severely restricting food intake. In addition, many patients promote further weight loss by misusing laxatives and/or inducing vomiting. Many also exercise excessively. It should be noted that appetite is not usually deranged; patients say they experience reduced hunger and increased satiety after a test meal in the same way as normal subjects (Halmi and Sunday 1991). Thus, the label 'anorexia nervosa' may be a misnomer. Nevertheless, there is probably some impairment in the physiological regulation of food intake: for example, patients with anorexia nervosa were found to salivate less than normal women in response to food-related cues (LeGoff et al. 1988).

A frequent additional feature is a subjective distortion of body image. Although painfully thin, individuals will insist that they are 'too fat' and/or that their abdomen, buttocks or thighs are too large. Their self-esteem is highly dependent on their body weight and shape; they celebrate further weight loss as a laudable achievement.

For females who have reached the age of menarche, it is a requirement for a DSM IV diagnosis of anorexia nervosa that they should no longer be menstruating. Such amenorrhoea is a consequence of the major disturbance in endocrine function which takes place secondarily to the weight loss brought about by a sharply reduced calorie intake. The negative energy balance leads to a diminished secretion from the pituitary of the two gonadotrophic hormones: follicular stimulating hormone (FSH) and luteinising hormone (LH). This, in turn, lowers the ovarian output of oestrogen. Some authorities question the value of including amenorrhoea as a necessary diagnostic criterion. In at least two studies amenorrhoea did not discriminate between women with anorexia nervosa and women with all the features except amenorrhoea, across a number of relevant variables (Garfinkel et al. 1996; Watson and Andersen 2003). Furthermore, the clinical presentation of anorexia nervosa in male patients is otherwise very similar to that in women (Woodside et al. 2001).

According to DSM-IV, there are two recognised sub-types of the condition: (a) the *restricting type*, where weight loss is achieved by dieting, even to the point of fasting completely, plus, in many cases, rigorous exercise; (b) the *binge-eating/purging type* in which the individual regularly self-induces vomiting after eating and/or ingests an unwarranted amount of laxative. Some also take diuretics, thereby compounding the problems of malnutrition with those of dehydration. Patients with this type of anorexia nervosa are more likely than the restricting type to display other behaviours related to poor impulse control, such as substance abuse. Having said that, it should be recognised that the distinction between the two subtypes may not be hard and fast: transitions between them are not uncommon.

Patients with anorexia nervosa often experience depressive symptoms, (e.g., depressed mood, social withdrawal, irritability and insomnia), to a degree that would warrant a diagnosis of major depressive disorder. Some are also so preoccupied with thoughts relating to food and weight that they may be considered to be suffering from obsessive-compulsive disorder – checking every item of food against a table of calorie values. In this context it should be noted that childhood perfectionism is a particularly strong antecedent factor. In an interview study of 324 patients with anorexia nervosa some 70% revealed that they had experienced obsessional thoughts

and/or exhibited compulsive behaviour (Halmi et al. 2003). Whether these other problems should be considered as secondary to the eating disorder, or whether they should be regarded as co-morbid conditions in their own right, may have to wait on the outcome of treatment. If this is successful they usually resolve in parallel with improvement in the anorexic behaviour.

2. Epidemiology

Anorexia nervosa is typically a condition affecting young women. A recent review of the published literature on the incidence and prevalence of eating disorders among girls of high school age (12–20) in western developed countries gave prevalence rates for anorexia nervosa ranging from 0 to 0.9%, with a clustering between 0.3 and 0.7% (Hoek and van Hoeken 2003). In a large Canadian community sample the point prevalence of full syndrome anorexia nervosa was 0.66% in females of all ages (Woodside et al. 2001). It most frequently first becomes manifest between the ages of 14 and 18, after which the number of new cases falls off. The lifetime prevalence in females is of the order of 0.5%. Thus, approximately one woman in every two hundred exhibits this syndrome at some point in her life.

The incidence, that is the number of new cases reported per year, ranges from 4.2 per 100,000 women per year in the UK to 12.0 per 100,000 per year in the US. The incidence among 15–24-year-old women appears to have risen since 1974. After the age of 25, the incidence levels off to approximately 5 new cases per 100,000 women per year (Hoek and van Hoeken 2003).

Anorexia nervosa is much less common in males, the overall prevalence being approximately one tenth to one twentieth of that in females (Lindberg and Hjern 2003). In North America and Western Europe it is also less common among women belonging to ethnic minorities. Among a subset of a national sample surveyed in the US ($n = 2000$) none of the Afro-American women in the sub-sample met criteria for anorexia nervosa compared to 1.5% of the white women (Striegel-Moore et al. 2003).

3. Pathology and Pathophysiology

Many of the somatic features of anorexia nervosa arise as a result of the severe weight loss following sustained calorie restriction. In addition to amenorrhoea, patients often complain of constipation, and abdominal ‘bloating’ after food. This latter symptom further discourages eat-

ing, thereby exacerbating the problem of malnutrition. Some patients develop lanugo, a covering of fine downy bodily hair with a truncal distribution. Their limbs, in addition to being extremely wasted, may show petechiae and.the skin may appear yellow, secondary to hypercarotinemia. Self-induced vomiting, commonly seen in the purging type, can lead to hypertrophy of the salivary glands, particularly the parotid. This behaviour may also cause erosion of dental enamel and lead to lesions on the dorsum of the hand from the teeth scraping the hand and fingers during the self-induction of vomiting. General physical examination may reveal bradycardia, hypotension and peripheral oedema. Laboratory findings may show a normochromic normocytic anaemia and impaired renal function. Radiological examination often shows widespread osteoporosis resulting from a reduced calcium intake. Fasting gastric motility is generally found to be normal (Silverstone and Russell 1967; Diamanti et al. 2003) although gastric emptying can be prolonged (Hutson and Wald 1990).

Abnormalities in brain structure and function are seen early in the course of the illness in adolescents. Brain imaging studies reveal enlarged ventricles with a reduction in white matter (Swayze et al. 2003). These structural changes are may only be partially reversed on weight normalization (Stamatakis and Hetherington 2003). Functionally, regional cerebral blood flow is reduced, predominantly in the temporal lobe but also to lesser extent in the parietal, and orbitofrontal lobes (Chowdhury et al. 2003). Again, these abnormalities may be only partially reversed with weight gain (Rastam et al. 2001).

In addition to the alterations in gonadotrophic hormones described above, patients have an increased plasma cortisol, secondary to an elevation of corticotrophin releasing hormone (CRH) (Putignano et al. 2001). This is a factor in the reduction in bone density and increased liability to fractures seen in anorexia nervosa. Increased CRH inhibits the activity of the orexogenic neuropeptide Y (NPY) thereby further lowering the desire to eat.

Serotonergic pathways play a significant part in the pathophysiology of anorexia nervosa (Steiger et al. 2001). Altered serotonin activity, with reduced 5-HT_2 binding, persists after normalization of weight, eating behaviour and menstrual function. It has been suggested that this underlies the obsessive compulsive component of the syndrome.

4. Course and Prognosis

Anorexia nervosa is an illness with a serious course and outcome in many of the affected individuals (Steinhausen 2002). Follow up studies of pa-

tients who attended specialist referal centres indicate that the mean likelihood of full recovery is no greater than 50%. Or, to put it another way, only half of the patients presenting to such centres in adolescence will ever achieve normal weight and adopt healthy patterns of eating despite intensive treatment. Furthermore, for a condition affecting mainly previously healthy young women, it has a disturbingly high mortality. On average, one in every twenty patients treated is likely to die as a result of the illness, either from complications of severe malnutrition or from suicide. Of those ill enough to require hospital admission, the mortality rate is even higher.

The prognosis is best for younger patients presenting with a shorter history. The outcome is even better when there is a good parent-child relationship in a family of higher socio-economic status. In older patients, the greater the weight loss, the worse is the likely outcome. Failure to reach desirable weight during treatment also predicts a poor prognosis. In general, the binge/purging variant carries a worse prognosis than the restricting type.

5. Aetiology

Anorexia nervosa is a disorder in which biological, psychological and sociocultural factors have all been imputed to play a part. A recent neurodevelopmental model of the illness suggests that genetic predisposition interacts with early life experiences to produce changes in the hypothalamic-pituitary-adrenal (HPA) axis which may persist throughout life (Connan et al. 2003). According to that model, the prolonged elevation in corticotrophin releasing hormone (CRH) which results, leads to a derangement of appetite regulation and energy balance which becomes manifest around puberty. While the model provides a plausible explanation of the aetiology of anorexia nervosa, in truth, little is known about the biological components (Collier and Treasure 2004).

5.1. Heredity

There is clearly a hereditary element in the aetiology of anorexia nervosa. First degree relatives of patients show an increased prevalence compared to the base population: prevalence rates decline from first to third degree relatives (Woodside et al. 1998). That such family aggregation is not due simply to a shared environment and parental attitude is shown by the concordance rate within monozygotic twin pairs being significantly greater than in dizygotic twins. In a British twin study involving 25 monozygotic

(MZ) pairs and 20 dizygotic (DZ) pairs of female twins, one member of which suffered from anorexia nervosa, fourteen (56%) of the 25 MZ pairs were concordant compared to only 1 (5%) of the DZ pairs (Holland et al. 1988).

So far the search for candidates genes has not been particularly successful. However, when linkage analysis was carried out in families where at least two affected relatives were diagnosed as suffering from the restricting form of the illness, there was suggestive evidence of linkage on chromosome 1p (Gu et al. 2002).

5.2. Psychological

In their thoughtful and scholarly analysis of the aetiology of eating disorders Polivy and Herman consider that dissatisfaction with one's body is an essential element in the aetiology of anorexia nervosa (Polivy and Herman 2002). As they point out, it is difficult to imagine an eating disorder developing without it. In addition, cognitive distortions leading to obsessive preoccupation with weight and body shape can be important components. Such preoccupations can take up several hours of every day. Other important factors include being in a negative emotional state (depressed or anxious) and having low self-esteem.

Family pressures to be thin can play an important role, as can peer pressure. However, such influences probably only lead to an eating disorder in those who are vulnerable on other grounds. Traumatic experiences in childhood, such as being sexually abused, are commonly recounted in the developmental histories of patients who subsequently develop anorexia. But, as most women with a history of sexual abuse do not become anorectic, such experiences cannot be considered to be specific risk factors. They probably act by reducing self-esteem.

Whether or not the fear of fatness seen in patients with anorexia nervosa constitutes a true phobia is a matter of debate. Many patients, although reluctant to gain weight, do not have a true fat phobia (Ngai et al. 2000). In keeping with this view, we found that the change in skin conductance ('psycho-galvanic reflex') in response to food-related cues in patients with anorexia nervosa was much less than that seen in patients with other phobias when presented with relevant phobic related cues (Salkind et al. 1980).

Another phenomenological question relates to the distortion of body image commonly seen in patients with anorexia nervosa. Is the conviction that they are fat, which many underweight patients hold, against all objective evidence, a true delusion? Of possible relevance to this issue is the

PET scan finding that patients suffering from anorexia nervosa show an elevated blood flow in the middle temporal lobes bilaterally, a pattern similar to that seen in patients with psychotic disorder (Gordon et al. 2001).

5.3. Sociocultural

Until recently, anorexia nervosa was largely a disease of the affluent in white dominated societies. It is now no longer uncommon among other ethnic groups in the developed world; it appears to be related more to socio-economic status than any particular racial or cultural characteristic. Furthermore, the prevalence of anorexia nervosa is rising in many non-Western societies (Simpson 2002).

In conclusion, the aetiology of anorexia remains uncertain. There appears to be a broad range of risk factors, many of which are shared with other psychiatric conditions. Few, if any are specific for this illness.

6. Treatment

Successful treatment of anorexia nervosa is deemed to require a multidisciplinary approach, usually as an outpatient. This should include initial weight restoration where possible, followed by psychological therapies, such as interpersonal psychotherapy or cognitive behaviour therapy, together with nutritional counselling and encouragement aimed at promoting weight gain. Unfortunately, the effectiveness of these psychological treatments is somewhat variable (Kaplan 2002). Furthermore, 30–50% fail to complete the prescribed course and it has so far not proved possible to predict, with any degree of accuracy, which patients are likely to persevere, and which are likely to drop out of treatment. In younger patients, family therapy is often effective (Russell et al. 1987). Drugs have proved of limited value (Zhu and Walsh 2002; Casper 2002). First of all, patients often refuse to take oral medication, or hide it. Forcible systemic administration is rarely justified. Moreover, there have been relatively few randomised controlled trials (RCT) on which to base rational prescribing. When such trials are undertaken, the drop out rate tends to be high. Treatment with psychotropic drugs needs to be introduced cautiously because of the risks of cardiac side effects in these malnourished patients. Nevertheless, despite all the above limitations, drugs can have a potential role to play and should not be dismissed out of hand.

Three main classes of drugs have been considered in the treatment of anorexia nervosa: antipsychotics, antidepressants and antihistamines.

6.1. Antipsychotics

Chlorpromazine was used an adjunctive treatment in the 1960s with a certain degree of success in promoting weight gain, but its use was limited because of the high incidence of seizures it induced (Dally and Sargant 1966). Other antipsychotics with a more selective dopamine receptor blocking activity, such as *pimozide* and *sulpiride*, were found to lead to some weight gain, but did not affect the underlying psychopathology (Vandereycken and Pierloot 1982; Vandereycken 1984). With the advent of the newer, so-called 'atypical' antipsychotic drugs, which are less likely to cause extrapyramidal symptoms, there has been renewed interest in using antipsychotics in the treatment of anorexia nervosa. The results have not been particularly impreessive. In a 10-week, open-label study of *olanzapine* involving 18 patients, 10 gained weight; 4 failed to complete and the remaining 4 lost weight (Powers et al. 2002). Eighteen AN subjects who had engaged in open treatment with olanzapine, who were questioned retrospectively about their response, reported a significant reduction in anxiety, difficulty eating, and core eating disorder symptoms after taking olanzapine (Malina et al. 2003). While these two studies support the view that olanzapine may be useful in the treatment of anorexia nervosa, its definitive place in management must await the results of controlled trials. It is not clear which particular aspects of the illness olanzapine primarily addresses: whether it reduces anxiety associated with the fear of fatness, normalizes the distortion of body image, or has a direct appetite stimulant action.

6.2. Antidepressants

Early trials of tricyclic antidepressants yielded disappointing longer term results. This, together with their propensity to cause cardiac side-effects, sometimes leading to sudden death, led to them falling out of favour in the treatment of anorexia nervosa (Zhu and Walsh 2002). More recently, the generally safer serotonin reuptake inhibitor (SSRI) antidepressants have been the subject of clinical trials. *Fluoxetine* has been the most extensively studied. While the majority of studies failed to show efficacy in the acute treatment of AN (Strober et al. 1997; Attia et al. 1998), there are data which suggests that fluoxetine at higher doses (80 mg daily) may assist in preventing relapse during maintenance therapy (Kaye et al. 2001). Fluoxetine can also play a role in the reduction of obsessive-compulsive symptoms and depression in anorexic patients (Kim 2003). Another SSRI, *citalopram*, proved to be no better than placebo in promoting weight gain

when given to anorectic patients (Fassino et al. 2002). However, like fluoxetine, it improved depressive and obsessive-compulsive symptoms. *Venlafaxine*, an antidepressant drug which acts by preventing the reuptake of both serotonin and noradrenaline, was shown to be equal to fluoxetine in producing weight gain when combined with cognitive behaviour therapy (CBT) (Ricca et al. 1999). Moreover, it was more effective than fluoxetine in relieving anxiety symptoms.

A single-blind comparison of the antipsychotic drug *amisulipride*, the SSRI *fluoxetine* and the tricyclic antidepressant *clomipramine* in 35 anorectics of the restricting type showed amisulpiride to be superior to the other two compounds in promoting weight gain (Ruggiero et al. 2001).

In conclusion, while the core symptoms of anorexia nervosa appear to be largely refractory to psychotropic drugs, it would appear, on the basis of the limited trial data, that the newer antipsychotic compounds, such as olanzapine and amisulpiride, show promise. Antidepressant drugs can help to reduce the relapse rate after successful treatment (Casper 2002).

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Chapter 5

Bulimia Nervosa

1. Clinical Features

Bulimia nervosa was first described as discrete clinical entity by Russell in 1979 (Russell 1979). He referred to it as "an ominous variant of anorexia nervosa", although the abnormal eating behaviour described had been recognised for some time as a symptom occurring in the context of anorexia or obesity (Vandereycken 1994). Two criteria were originally required to make the diagnosis: "(i) an irresistible urge to overeat (bulimia nervosa) followed by self-induced vomiting or purging; (ii) a morbid fear of becoming fat". The majority of the patients in Russell's series had a history of anorexia nervosa, and were determined to keep their weight below a self-imposed threshold, although they were generally heavier than patients with anorexia nervosa and were more likely to be menstruating and be sexually active. In addition, severe depressive symptoms were common, with a high risk of suicidal behaviour.

Within a year of Russell's description, bulimia nervosa was included in version three of the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM III).

The criteria were modified only slightly for DSM IV where they read: "Repeated (at least twice a week) episodes of binge eating followed by inappropriate compensatory behaviours such as self-induced vomiting, misuse of laxatives, diuretics or other medications; fasting or excessive exercise." A 'binge' is defined as: "eating in a discrete period of time (e.g., within two hours) an amount of food that is definitely larger than most individuals would eat during a similar period of time under similar circumstances" – a somewhat imprecise definition open to wide interpretation. The choice of food eaten varies from patient to patient but typically includes sweet high calorie foods such as ice cream or cake, but quantity counts for more than content. During a binge, the individual typically consumes over 1000 calories, but there are large variations from patient to patient.

Although bulimia nervosa was originally described as a variant of anorexia nervosa, the two conditions are classified separately in DSM IV. The distinction between anorexia nervosa of the binge-eating/purging type and bulimia nervosa is based almost exclusively on the patient's body

weight: if it is below 85% of the norm the diagnosis is anorexia nervosa; if above, the diagnosis is bulimia nervosa. Thus, anorexia nervosa is "an exclusion criterion for bulimia nervosa which otherwise may be confused with bulimic type anorexia nervosa" (Polivy and Herman 2002). Another distinction which is sometimes drawn between the two conditions relates to the impulsivity displayed by patients with bulimia nervosa. They are more likely to be sexually promiscuous, to be drug abusers and to engage in delinquent behaviour. It may be such impulsiveness which causes a potential anorectic to binge. Binge/vomiting allows the individual to eat as much as she likes without having to pay the price of putting on weight. The clinical criteria required for a diagnosis of bulimia nervosa in the ICD-10 classification are very similar. However in ICD-10 bulimia nervosa takes precedence over anorexia nervosa, so that patients fulfilling the criteria are accorded the diagnosis even though their body weight may be very low. In the DSM-IV classification such patients would be diagnosed as anorexia nervosa, binge/purging subtype (Palmer 2004).

Most patients are ashamed of their eating and purging behaviour and go to great pains to keep it secret; eating furtively and urgently, without any ability to control it (this latter feature being required for the diagnosis). Vomiting is the most common compensatory behavior adopted to avoid the weight gain which would otherwise occur as a result of bingeing. Many also take excess laxatives and some promote diuresis with diuretic drugs. DSM IV also recognises a non-purging type of bulimia nervosa, where fasting or excessive exercise are used as compensatory behaviours.

2. Epidemiology

As with the other eating disorders, bulimia nervosa is some ten times more common in females than males. The prevalence of bulimia nervosa among young women in the United States is 1.1–4.2% (Kendler et al. 1991; Garfinkel et al. 1995).

3. Pathology and Pathophysiology

Although less malign than AN, BN does carry an appreciable risk to health, largely from electrolyte disturbance. The mortality rate has been estimated as being 1–2% within 10 years of diagnosis, but very few deaths can be directly attributable to the disordered eating (Quadflieg and Fichter 2003). There appears to be an increase risk of suicide and road traffic accidents, perhaps reflecting the predilection to impulsivity referred to above.

This sometimes takes the form of shoplifting of food items required to support bingeing

3.1. Peptides

The possible role in the pathogenesis of BN of gastrointestinal peptides involved in the regulation of feeding and body mass, such as leptin and ghrelin (see Chapter 1) has been the subject of much research. The plasma level of leptin was at first thought to be unaffected in patients with BN. However, a more recent finding indicates it may be reduced out of proportion to changes in body mass (Brewerton et al. 2000; Monteleone et al. 2002). The degree of reduction in the plasma level of leptin bore no relationship to average binge frequency in the first of these two studies although it did in the second. As plasma leptin appeared to be negatively correlated with the level of plasma cortisol, and was positively correlated with the rise in prolactin induced by l-tryptophan it was postulated that the decreased plasma level of leptin was related to dysregulation of serotonin in the HPA. This, in turn, may contribute to the disinhibited eating seen in BN. Another factor which may contribute to the aberrant eating behavior is the blunting of the ghrelin response to food observed in some patients (Monteleone et al. 2003). Another gastorointestinal peptide, gastrin releasing peptide which has a central anorexigenic activity, was found to be lower in the cerebrospinal fluid of recovered bulimics than in normal control subjects (Frank et al. 2001). This too might contribute to the episodic hyperphagia in BN.

Women suffering from BN tend to have an elevated level of serum cholesterol. The mechanism for this, and the consequences, are uncertain (Pauporte and Walsh 2001). It may partly explain the increased mortality. Disturbances in the functioning of the upper gastrointestinal tract have been reported in BN. They include: increased gastric capacity; diminished gastric relaxation; delayed gastric emptying; diminished release of CCK (Hadley and Walsh 2003). It is possible that such disturbances play a role in the perpetuation of the disturbed eating behaviour.

3.2. Neurotransmitters

Serotonin has been given a central role in the pathophysiology of bulimia nervosa (Kuikka et al. 2001). Challenge tests have revealed a blunted prolactin response to systemic administration of the 5-HT receptor agonists metachlorophenylpiperazine (mCPP) (Levitan et al. 1997) and dl-fenfluramine (Jimerson et al. 1997) in this condition. The higher the frequency of bingeing, the more blunted the prolactin response (Monteleone

et al. 2000). After recovery, the endocrine response to mCPP reverts to normal, suggesting that it is more likely to be a secondary state-related response to binging and purging than a primary marker of a predisposition to the aberrant eating and purging behaviour (Kaye et al. 1998; Wolfe et al. 2000). Further evidence of serotonergic dysfunction in BN comes from studies of platelets, which reveal enhanced 5-HT_{2A} receptor binding (Spigset et al. 1999). This may be related to the increased impulsivity observed in patients (Steiger et al. 2001).

In keeping with the presumed importance of serotonin in the pathophysiology of BN is the finding that a reduction in the synthesis of serotonin in the brain, brought about by a diet deficient in tryptophan, precipitates a loss of eating control and an increased concern with body image in recovered BN patients (Smith et al. 1999). Chronic depletion of plasma tryptophan may be one of the mechanisms by which dieting leads to the development of BN in vulnerable subjects.

Brain studies, using single photon emission computed tomography (SPECT), show that the availability of serotonin transporter is reduced in the hypothalamus and thalamus of patients with BN. The longer the duration of the illness, the more pronounced this reduction is likely to be (Tauscher et al. 2001).

4. Course and Prognosis

With appropriate treatment, some 50% of patients become symptom free and 25% are much improved, though still resorting to the occasional binge. Relapse rates after initially successful treatment are a disappointing 30% (Keel and Mitchell 1997). Overall, after 10 years, 33–50% show at least partial recovery, meaning that a majority remain afflicted for the rest of their life (Quadflieg and Fichter 2003). As may be expected, the outcome is related to severity; the more severely affected do less well. Younger age of onset is associated with a better outcome although age at presentation is no predictor (Reas et al. 2000).

5. Aetiology

Bulimia nervosa shows marked family aggregation. This is thought to be due to environmental factors interacting with genetic predisposition (see below).

5.1. Heredity

A growing body of twin studies have demonstrated that bulimia nervosa, in common with other eating disorders, has strong genetic determinants. Twin studies confirm that bulimia nervosa is familial, and they reveal the significant contributions of additive genetic effects in promoting the liability to bulimia nervosa. The concordance for narrowly defined BN in monozygotic twin girls was found to be 22.9% compared to 8% in dizygotic twins (Kendler et al. 1991).

The magnitude of the contribution of shared environment is less clear, but in the studies with the greatest statistical power, it appears to be less prominent than additive genetic factors, which account for 54–83% of the variance (Kaye et al. 2004). Furthermore, the behavioural components of BN such as bingeing and purging are themselves heritable. A linkage study has provided evidence of a susceptibility locus for BN on chromosome 10p (Bulik et al. 2003). Further evidence of the genetic contribution to the etiology of BN comes from a study in which genetic polymorphism of the serotonin-1B receptor gene was found to be associated with body mass in some women with BN (Levitan et al. 2001).

5.2. Psychosocial

Concern with one's body weight and shape, in common with the other eating disorders, is an invariable precursor of BN. Such concerns appear to be a necessary, but not sufficient factor in its pathogenesis. After all, a majority of adolescent and adult females in the developed world worry to some degree about their weight. What is it that distinguishes those who develop the pattern of bingeing and purging adopted by patients with BN? Included among the many explanations proffered are: (i) physiological and psychological stresses accompanying the menarche; (ii) family dysfunction; (iii) sociocultural pressures; (iv) personality variables. (These are not necessarily mutually exclusive.)

Dieting to reduce weight implies some degree of eating restraint. When such restraint is severe it can lead to a variety of associated psychological consequences, even in perfectly healthy and well-adjusted individuals. This was clearly demonstrated in a US study carried out in conscientious objectors by Keys and his colleagues during World War II (Keys 1950). In that study, healthy males of normal weight had their calorie intake restricted to 75% of their normal intake for six months. During this protracted period of semi-starvation the subjects became increasingly preoccupied with food, virtually to the total exclusion of other interests

(Franklin 1948). Of particular clinical relevance to the pathogenesis of binge eating was the observation that, after all restrictions on food intake had been lifted and the subjects' weight had returned to baseline, these previously normal eaters would gorge themselves in the presence of attractive foods. Like patients with bulimia nervosa, at such times they reported that their eating was 'out of control'.

People who habitually try to limit their calorie intake in order to lose weight ('restrained eaters') display many of the features shown by the subjects in Keys' experiments. They too are preoccupied with food-related matters (Polivy 1996). In addition, once restrained eaters break their diet, their self-control vanishes and their eating becomes uncoupled from energy needs; it is 'disinhibited'. In predisposed individuals, binge eating can also follow emotional distress.

5.2.1. Developmental changes

During puberty, the proportion of adipose tissue in females increases from being 8% of total body mass to 22%. The areas of most pronounced fat deposition include the abdomen, buttocks and thighs, areas which adolescent girls are particularly sensitive about. Such increases are most evident in girls who mature earlier, and who are therefore likely to be particularly self-conscious about them (Gowers and Shore 2001).

5.2.2. Family influences

Self-conscious anxiety, associated with the developmental changes just described, can be exacerbated by parental over-concern, particularly by mothers. Such over-concern occurs more frequently in mothers who themselves have, or have had, an eating disorder or who have been obese. As most family studies have been correlational, it is difficult to know whether family dysfunction contributes to the eating disorder, whether the distortions of eating behaviour in the affected daughter causes the family dysfunction, or whether some common other factor contributes to both (Polivy and Herman 2002).

The family dynamics may be viewed differently by mother and daughter. Bulimic daughters are more inclined to have a negative perception of family function than their mothers (Bonne et al. 2003). Teasing by siblings, especially brothers can also add to tensions within the family and further promote the eating disturbance.

5.2.3. Social pressures

Within the past 50 years in the Western world the ideal size and shape for women has increasingly become a slender figure. This societal view of the desirability of slimness has been energetically promoted by the media, to such a degree that young women cannot escape from the repeated exhortations to lose weight seen in every magazine or television programme aimed at a female audience (see Chapter 4). In the US women of Afro-Caribbean origin were, until recently, protected to some degree from such pressures. But no longer; socioeconomic status is now thought to be a more potent influence in all ethnic groups. This is reflected in peer pressure which is thought to account for up to a third of the variance.

5.2.4. Personality

Patients with BN are more likely to display traits of perfectionism, ineffectiveness and interpersonal distrust (Lilenfeld et al. 2000). Such traits are also more common among their first-degree female relatives. Another characteristic of BN is impulsiveness (Polivy and Herman 2002). Some dieters ('restrained eaters') who are perhaps more impulsive than others, rebel against their diet and indulge in a binge – 'kicking over the traces', as it were (Polivy 1996). Such dietary excess so runs counter to their concerns about not gaining weight that they take drastic steps to undo whatever 'damage' (weight gain) it may have caused – they self-induce vomiting or take laxatives to counter it. This in turn reinforces their view of themselves as being ineffective. They become miserable as result, thereby triggering off another binge in a vain attempt to elevate their mood or comfort themselves.

6. Treatment

Both psychological and pharmacological treatments are available for patients with BN.

Each has their advocates. On balance it appears that drug treatments are more cost-effective in the short term but may have less long-lasting benefits, with higher relapse rates (Keel et al. 1999). On the other hand, psychological treatments carry virtually no risk of untoward side effects but generally require greater resources of time and skilled personnel. A combined approach, using both psychological and pharmacological treatments, appears to be more effective than either given alone (Nakash-Eisikovits et al. 2002). The current recommendation for less severe cases is to start with an evidence-based self-help programme (Fairburn 1995;

Health 2004) and then proceed to either cognitive behavioural therapy where resources permit or to start treatment with a serotonin reuptake inhibitor (SSRI) such as fluoxetine (see below).

6.1. Psychological Treatments

Two forms of psychological treatment have been shown to be effective in the treatment of BN: cognitive behavioural therapy and interpersonal psychotherapy. Both have been found to be superior to traditional psychodynamic based therapy (Hay and Bacaltchuk 2003).

6.1.1. Cognitive behaviour therapy (CBT)

The cognitive behaviour therapy model for bulimia nervosa has the following major features:

(1) self monitoring of food intake and of binge eating and purging episodes, as well as the thoughts and feelings that trigger these episodes;
(2) regular weighing;
(3) specific recommendations designed to normalize eating behavior and curb restrictive dieting;
(4) cognitive restructuring directed at habitual reasoning errors and underlying assumptions that are relevant to the development and maintenance of the eating disorder;
(5) prevention of relapse.

Questions of relationships past and present, past experiences and emotional states play a much lesser role.

In this form of therapy, a range of cognitive behavioural procedures are used in a specific sequence of tasks and experiments set within the context of a personalised version of cognitive-behavioural theory of the maintenance of bulimia nervosa. Treatment is out-patient based and involves 15–20 sessions over about five months. CBT has been shown to be effective in a number of controlled clinical trials (Jones et al. 1993; Hay and Bacaltchuk 2003). It is either significantly more effective or at least as effective as any alternative form of psychotherapy (Hay and Bacaltchuk 2003). However, for some patients it is unnecessarily intensive, while for others it is not sufficient. This approach of guided self-help can be delivered solely using written materials, without any direct human involvement at all. Several studies have established the potential efficacy of

the use of such self-help books based on CBT in the treatment of binge eating (Carter et al. 2003). While they may be used alone they are probably more effective when additional guidance is offered (Palmer et al. 2002). CBT is generally underutilized, mainly due to the relative unavailability of therapists with specialized training in CBT for eating disorders in many countries.

6.1.2. Interpersonal psychotherapy (IPT)

IPT, which was originally developed in the 1970s for the treatment of depression, has been modified for use in a wide range of other conditions including BN (Weissman 1997). In contrast to CBT, IPT concentrates on the manner in which the patient deals with interpersonal relationships, rather than on the eating behaviour itself. It is a focussed, time-limited, manual-based treatment. In contrast to CBT, it emphasis the link between mood and the current interpersonal relationships of the patient.

Clinical trials have shown IPT to be effective in BN, with its benefits perhaps being longer lasting than CBT (Hay and Bacaltchuk 2003). It generally takes longer to achieve results comparable to CBT (Agras et al. 2000).

6.2. Drug Treatments

Over the years, both antidepressant and antipsychotic drugs have been used in the management of BN, with varying success. Meta-analysis of all the controlled clinical trials of pharmacotherapy published between 1980 and 1999, revealed that overall, such treatment led only to "moderate initial improvement for the average patient" (Nakash-Eisikovits et al. 2002).

6.2.1. Antidepressants

There are three main pharmacological classes of antidepressant compounds: tricyclic antidepressants (TCA), monoamine oxidase inhibitors (MAOI) and serotonin reuptake inhibitors (SSRI). Members of each class have been tried in BN. According to a survey of 19 controlled clinical trials, all are more effective than placebo, with little to choose between them in terms of efficacy (Bacaltchuk and Hay 2003).

Tricyclic antidepressants. (TCA) The anticholinergc side effects (dryness of mouth, constipation, increased sweating) associated with TCA (*imipramine, desipramine*) cause them to be poorly tolerated. They can only be recommended if other treatments have failed to reduce bingeing and/or purging.

Monamine oxidase inhibitors (MAOI). Patients taking MAOI such as *phenelzine* are required to modify their diet by avoiding foods with a high tyramine content, such as cheese. This makes them a less attractive treatment option. *Moclobemide* is a more recently introduced 'reversible' MAOI which does not require such strict dietary restrictions. It has not been approved for use in bulimia nervosa in the US.

Serotonin reuptake inhibitors (SSRI). These are currently the drugs of choice for the treatment of bulimia nervosa. The most frequently cited adverse effects include nausea, insomnia and diminution of sexual interest and/or impaired sexual function.

Fluoxetine was the first of this class of drugs to be introduced into clinical practice. It has been widely studied in the treatment of bulimia nervosa. In two large placebo controlled trials involving a total of 785 patients fluoxetine 60 mg daily proved superior to placebo and was more effective than 20 mg daily in reducing binge frequency and episodes of self-induced vomiting (Wood 1993; Goldstein et al. 1995). Despite side effects the drop out rate was low. Fluoxetine appears to be effective when given over the course of a year to patients who had a good initial response to the drug. They took longer to relapse than similar patients given placebo (Romano et al. 2002).

The combination of fluoxetine and CBT was found in one study to be more effective than CBT given as the sole treatment (Walsh et al. 1997), although this was not confirmed in another (Goldbloom et al. 1997). In patients who had failed to respond to CBT, fluoxetine significantly reduced the frequency of binge eating and purging (Walsh et al. 2000). It has also proved effective in patients seen in general practice, being better than guided self-help (Walsh et al. 2004).

Fluvoxamine showed therapeutic promise in an early open study (Ayuso-Gutierrez et al. 1994), and reduced the risk of relapse following a period of in-patient treatment (Fichter et al. 1996). However, in a more recent double-blind, placebo-controlled trial involving 276 female patients treated for one year, fluvoxamine, combined with varying degrees of psychotherapy, was no better than placebo in reducing binge frequency (Schmidt et al. 2004). Nor was it superior in inducing remission: 34% of the patients who received fluvoxamine throughout the year remitted, compared to 33% who had been on placebo. One finding in favour of fluvoxamine was that a greater proportion of patients taking the active drug achieved remission without additional psychotherapy. Against this small possible advantage, was the finding that fluvoxamine was much

more likely to cause serious side-effects, such as seizures and impaired liver function.

Sertraline In a small open study, five patients with bulimia nervosa binged less after being prescribed sertraline (Sloan et al. 2004). In a randomised, placebo-controlled trial of sertraline 100 mg daily for 12 weeks, the patients treated with sertraline had a statistically significant reduction in the number of binge eating crises and purging compared with those who received placebo (Milano et al. 2004). No patients withdrew from the trial because of side effects.

Citalopram When given at a dose of 20 mg daily for 8 weeks, binge eating episodes and mean scores in three EDI subscales (bulimia, ineffectiveness and interoceptive awareness) significantly decreased in the small number of bulimic patients to whom it was given (Calandra et al. 1999).

6.2.2. Other drugs

Roboxetine is an antidepressant which inhibits the reuptake of noradrenaline rather than serotonin. The results of a small open trial suggest it may hold promise as a treatment for BN (El-Giamal et al. 2000).

Odansetron is an antagonist of the serotonin receptor 5-HT3. Its main use is in combating the nausea and vomiting which frequently accompanies treatment with anti-cancer chemotherapy. In one short-term, 4-week placebo-controlled trial involving 26 patients with severe BN, odansetron 24 mg daily halved the frequency of binging and vomiting (Faris et al. 2000). Two other small clinical trials support the use of odansetron in BN (Fung and Ferrill 2001).

Inisotol is a precursor in the phosphatidylinositol (PI) cycle where it forms part of the second messenger system in serotonergic neurotransmission. In a small double-blind crossover trial 18 mg daily appeared to be more effective than placebo in 12 patients with BN (Gelber et al. 2001).

Olanzepine and other so-called ‘atypical’ antipsychotics are being evaluated in the treatment of BN. But, as such drugs can cause abnormal eating behaviour and weight gain (Theisen et al. 2003) they should therefore be tried cautiously, if at all (see Chapter 10).

Topiramate Following a number of case reports that topiramate, an anticonvulsant drug, benefited patients with BN, a more extensive double-blind placebo controlled trial was carried out in 64 outpatients (Hoopes et al. 2003). Given at a dose ranging from 25–400 mg/day topiramate reduced the frequency of binge episodes by 49%, compared to 28% in those

given placebo. It could well come to be used as a second line treatment for BN if further trials substantiate these findings.

Methylphenidate Stimulants, such as methylphenidate and amphetamine, are widely used in the management of attention deficit hyperactivity disorder (ADHD). Such drugs have long been known to reduce hunger, but have not been generally recommended for treatment of BN. A few patients who have symptoms of bulimia nervosa plus some co-morbid features of ADHD have noted that the addition of methylphenidate or amphetamine markedly reduced the frequency of binge eating (Drimmer 2003).

Naltrexone is an opiate receptor antagonist used in the management of addictive behaviours. In a double-blind placebo controlled crossover trial, naltrexone reduced binge/purge frequency in 18 out of 19 patients with BN (Marrazzi et al. 1995).

7. Conclusions

Of the various drugs which have been tried in BN, fluoxetine has the largest body of evidence in its favour. It is therefore the preferred treatment, perhaps combined with CBT. If this proves ineffective or is poorly tolerated, topiramate, methylphenidate or naltrexone might be tried.

With our increasing understanding of the ways appetite and eating are regulated in humans, even more effective pharmacological treatments of bulimia nervosa are likely to be developed in the relatively near future.

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Chapter 6

Binge Eating Disorder

1. Clinical Features

Binge eating was first described in a population of obese patients by Stunkard in 1959 (Stunkard 1959). As its name implies, binge eating disorder (BED) is characterised by repeated bouts of excessive food intake or 'binges' (see Chapter 3 for a discussion of the pathogenesis of bingeing). Although bingeing is also a prominent feature of bulimia nervosa (BN) and some types of anorexia nervosa (AN), BED differs from them in a number of respects. In contrast to AN, patients are typically overweight, many being frankly obese and show little or no eating restraint. BED differs from BN in that patients rarely, if ever, resort to compensatory behaviour, such as purging or vomiting following a binge. Patients with BED share with other eating disorders an exaggerated concern with body shape and size. It is categorised in DSM IV as an 'eating disorder not otherwise specified'.

As stated in the previous chapter, DSM IV operationally defines a binge as: 'eating in a discrete period of time (e.g., within any 2-hour period) an amount of food that is definitely larger than most people would eat during a similar period of time under similar circumstances'. Thus, it is not a precise term but depends to a large extent on societal norms and there is no general agreement on any objective criterion (Stunkard and Allison 2003). A prominent additional feature is 'a feeling of lack of control over eating during the episode' (e.g., patients cannot stop eating or moderate the amount consumed). A binge has been said to contain elements of both *impulsive* and *compulsive* behaviour. Binging is a psychologically rather than physiologically determined behaviour: patients frequently binge when they are not hungry and continue even after they are uncomfortably full. They tend to feel very self-conscious about their disturbed eating patterns and typically binge only in private (like in BN). While the frequency of binge eating can vary a great deal from week to week, in order to be considered as suffering from BED patients need to binge at least twice a week for six months.

While the level of associated psychopathology in BED is generally less than that seen in bulimia nervosa or anorexia nervosa, depression and anxiety are often present. According to some, making the diagnosis can

serve a useful secondary purpose in drawing attention to any such associated psychopathology (Stunkard and Allison 2003).

Patients with BED tend to have a greater degree of dissatisfaction with their body image than those with uncomplicated obesity and have lower self-esteem. They show less dietary restraint than patients with bulimia nervosa, and their eating behaviour has been described as more 'chaotic' (Grilo 2002).

2. Epidemiology

BED is reported to occur in 2–3% of women in the US and Western Europe (Grilo 2002); its prevalence correlates with the prevalence of dieting in the community. It has risen in recent years with the increasing preoccupation with body weight among women. The prevalence is much higher among women actively seeking treatment for obesity (de Zwaan 2001). The prevalence in men is approximately half that in women (i.e. twice as many obese women as men suffer from the disorder). While bingeing behaviour often starts in late adolescence, the full syndrome is not usually seen until adulthood. Overweight BED patients most commonly seek treatment when they are in their 40 s.

3. Pathology and Pathophysiology

The underlying pathophysiological mechanisms of binge eating are poorly understood but alterations in the monoaminergic systems are likely to play some role. Obese binge-eating women were found to have reduced serotonin transporter binding in the mid brain compared to obese women who did not engage in binge eating (Kuikka et al. 2001). Successful treatment restores the serotonin transporter binding to normal (Tammela et al. 2003). When subjects with eating disorders are exposed to food cues, more craving and physiological reactivity is found than in normal subjects (Bulik et al. 1996; Fedoroff et al. 1997; Karhunen et al. 1997).

Serum leptin concentrations in BED obese patients were found to be higher than in non-binge-eating obese patients (Adami et al. 2002). This indicates that binge eating behaviour is not triggered by a low plasma leptin level.

4. Etiology

Binge eating is strongly associated with being obese (see next section) and the factors which promote obesity (see Chapter 8) can also be seen to be linked to binge eating.

While heritability is an important factor in the aetiology of BED, it is less pronounced than for obesity and there seems to be only modest overlap in the genetic risk factors that increase liability to each condition (Bulik et al. 2003). According to a large-scale Norwegian twin study, binge-eating appears to be equally heritable in males and females (Reichborn-Kjennerud et al. 2003).

Binge eating is typically triggered by negative emotional states, occurring in the context of dietary restraint (Polivy and Herman 1985). Comparing the scores on the Eating Disorder Examination (EDE) showed that binge-eating obese patients had a significantly greater degree of weight and eating-related psychopathology than non-bingeing obese patients (Wilfley et al. 2000). Their concern with body shape and weight was equal to or even greater than that of patients with other eating disorders such as AN and BN. The BED sample scored significantly higher than a combined AN/BN sample on a number of items on the EDE. These included eating in secret (*eating concern*), dissatisfaction with weight and desire to lose weight (*weight concern*); dissatisfaction with body shape, discomfort at seeing one's body and avoidance of exposure, together with feelings of fatness (*shape concern*). On seven of the subscale items, the BED sample scored similarly to the combined AN/BN sample but significantly greater than the controls. These items included food avoidance (Restraint); fear of losing control, over eating, and social eating (Eating Concern); importance of weight and preoccupation with shape or weight (Weight Concern); and fear of weight gain and preoccupation with shape or weight (Shape Concern). These findings suggest that over concern with weight and shape may be an important diagnostic feature of BED, as it appears to cluster with the other features of BED and is not influenced independently by level of overweight.

5. Treatment

5.1. Psychological Treatments

Both cognitive behavioral therapy (CBT) and interpersonal psychotherapy (IPT) have been shown to be effective in the management of BED. A randomized comparison of the two treatments was carried out in 162 overweight patients meeting diagnostic criteria for BED (Wilfley et al. 2002). Recovery rates were similar in both treatment groups: 64 (79%) of the 81 patients receiving CBT and 59 (73%) of the 81 patients getting

IPT were said to have recovered from binge eating after four months treatment. Follow-up a year after the start of treatment revealed that 48 (59%) of those given CBT and 50 (62%) of those given IPT remained well.

For the less severely ill, a behaviorally directed weight loss approach is probably the treatment of choice for BED. In addition to its effect on reducing the frequency of bingeing, it leads to greater weight loss than either CBT and IPT (Saelens et al. 2002; Stunkard and Allison 2003).

5.2. Drug Treatments

Although drugs are frequently prescribed for patients with BED, there has been relatively little systematic examination of their efficacy (Health 2003; Appolinario and McElroy 2004). Three main classes of drugs have been evaluated in randomized controlled trials: antidepressants, appetite suppressants, and anticonvulsants (Appolinario and McElroy 2004).

5.2.1. Antidepressants

Many patients with BED display symptoms of, or have a past history of depressive disorder, and a number of different antidepressant drugs, mainly of the serotonin reuptake inhibitor type (SSRI) have been tried in its treatment (Carter et al. 2003).

Tricyclic antidepressants (TCA). *Desipramine* administered for 12 weeks reduced the frequency of binge eating in patients specified as suffering from 'non-purging bulimia nervosa' (presumably the same condition which later came to be called binge eating disorder) (McCann and Agras 1990). By contrast, *imipramine*, a related TCA, had no effect on binge frequency in a small eight-week trial (Alger et al. 1991).

Serotonin reuptake inhibitors (SSRI). Five SSRI antidepressant drugs have been included in at least one placebo-controlled randomized clinical trial in BED, with variable effect (see below). Side effects are similar for all SSRI. These include: gastro-intestinal symptoms, such as nausea and diarrhea; sexual dysfunction; a heightened sense of arousal.

Fluoxetine (Prozac) administered at a daily dose of 20 to 80 mg for six weeks was found to be significantly superior to placebo in reducing binge frequency and lowering body weight in a clinic sample of 60 patients with a DSM-IV diagnosis of BED (Arnold et al. 2002). However, a rather longer 16-week trial involving 52 patients failed to find any drug–placebo difference (Grilo, unpublished observation reported by Carter et

al. 2003). A behavior modification program plus fluoxetine was more effective than behavior modification alone in promoting weight loss in obese binge eaters (Marcus et al. 1990). However the combination was also more effective in promoting weight loss in non-bingeing obese patients, suggesting it was having little selective action on binge-eating *per se*.

Fluvoxamine (Luvox) is another SSRI which has been shown to be potentially effective in reducing binge frequency. Administered at a dose of 50–300 mg daily in a 9-week randomized placebo-controlled trial to patients with BED ($n = 85$), it had a significant effect on reducing the frequency of binge eating and lowering body weight (Hudson et al. 1998). But, side effects proved troublesome, leading to a higher drop-out rate among those receiving the active drug. In contrast, a smaller ($n = 20$) 12-week trial failed to differentiate between fluvoxamine and placebo in any treatment outcome measures (Pearlstein et al. 2003). Thus the efficacy of fluvoxamine in BED appears modest at best.

The combination of fluvoxamine and fluoxetine, with and without accompanying cognitive behaviour therapy (CBT) has also been evaluated (Ricca et al. 2001). 108 patients with formally diagnosed BED were randomly assigned to receive one of the five following treatment regimens for 24 weeks: CBT; fluvoxamine 300 mg daily (FVX); fluoxetine 60 mg daily (FLX); CBT + FVX; CBT + FLX (Ricca et al. 2001). Neither FVX nor FLX had any effect on BMI or eating disorder ratings. Only the combinations with CBT proved effective, with the effect being greatest in the CBT–FVX treated group.

Citalopram (Celexa), a highly selective serotonin reuptake inhibitor, was evaluated in a small ($n = 38$) randomized placebo-controlled trial. 19 patients with BED were administered 20–60 mg of citalopram daily or matching placebo (McElroy et al. 2003). Citalopram significantly reduced the frequency of binge eating and lowered BMI compared to placebo. It was generally well tolerated.

Sertraline (Zoloft) In a placebo-controlled trial of sertraline 50–200 mg daily administered for six weeks ($n = 34$), sertraline led to a significantly greater rate of reduction in the frequency of binges, clinical global severity, and body mass index as well as a significantly greater rate of increase in clinical global improvement compared to placebo (McElroy et al. 2000). Almost half the patients receiving sertraline (47%), but only 14% of those on placebo, stopped binge eating completely.

A meta-analysis of four published placebo controlled trials of SSRI showed that patients who had received active drug were more likely to

have reduced their frequency of bingeing by 50% (the combined estimate for the drug–placebo difference in the percentage of patients who reached this criterion of improvement was 23%) (Carter et al. 2003). The improvement rate in the placebo treated patients was 33%.

Serotonin and norepinephrine reuptake inhibitors. The only member of this class which has received regulatory approval is *venlafaxine* (Effexor). Venlafaxine is a phenethylamine bicyclic derivative, chemically unrelated to tricyclic, tetracyclic or other available antidepressant agents. In a retrospective review of 35 consecutively treated overweight or obese outpatients with BED, venlafaxine 75–300 mg daily given for 1 to 43 weeks appeared to reduce the frequency of binge eating and to lower body weight (Malhotra et al. 2002). Reported side effects included dry mouth, sexual dysfunction, insomnia and nausea As there have thus far been no published randomised controlled trials, its place in the treatment of BED must remain uncertain.

5.2.2. Appetite suppressants

The only appetite suppressant which has been approved for treatment of obesity in Europe is sibutramine. In the US, phentermine, diethylproprion and phendimetrazine are still available (See Chapter 9 for a fuller discussion of this issue). Following a promising open label evaluation, a 12-week placebo-controlled trial of sibutramine 15 mg daily was conducted in 60 obese outpatients who met DSM-IV criteria for BED (Appolinario et al. 2003). There was a significant reduction in the number of days with binge episodes in the sibutramine group compared with the placebo group; this was associated with an important and significant mean weight loss of 7.4 kg compared with a small weight gain in the placebo group. Sibutramine was also associated with a significantly greater rate of reduction in the Binge Eating Scale scores. Commonly reported side effects included dry mouth and constipation.

In a parallel laboratory study, seven adult subjects who had problems with binge eating were randomly assigned to receive alternating sibutramine and placebo for four weeks in a double-blind placebo-controlled crossover trial (Mitchell et al. 2003). There was a significant difference in the number of kilocalories consumed between the sibutramine and placebo conditions, with a significant reduction of intake during binge eating episodes on sibutramine.

5.2.3. Anticonvulsants

Certain anticonvulsants developed initially for the treatment of epilepsy, such as topiramate and zonisamide, have been found to have a beneficial effect in mood disorders, particularly bipolar disorder. In addition, patients treated with these compounds lose weight. They were therefore seen as potential therapeutic agents for use in obese patients with BED.

Topiramate. Its pharmacologic mechanisms involve modulation of voltage-dependent sodium and calcium channels, enhancement of g-aminobutyric acid (GABA) activity at a nonbenzodiazepine site on $GABA_A$ receptors, and blockade of kainate/AMPA glutamate receptors. A small open label trial involving 8 patients treated for 16 weeks with topiramate 150 mg daily gave promising results (Appolinario et al. 2002). This was followed by a larger ($n = 61$) double-blind placebo controlled trial of topiramate in patients with binge eating disorder and obesity (McElroy et al. 2003). Topiramate was administered at a flexible dose (median 212 mg daily) for fourteen weeks. Compared to placebo, topiramate led to a greater reduction in frequency of binge eating and in BMI. Side effects, particularly headache and parathesias, caused 6 (20%) of the patients being treated with topiramate to withdraw from the trial. Open label continuation of topiramate treatment was associated with enduring improvement in some patients but was also associated with a high discontinuation rate (McElroy et al. 2004).

Zonisamide. is a sulfonamide antiepilepsy drug with sodium and calcium channel-blocking actions. A small preliminary open label trial of zonisamide 100–600 mg daily in 15 patients with BED showed it to reduce the frequency of binge eating and lower body weight in the eight patients who completed the 12 week trial (McElroy et al. 2004).

6. Conclusions

For patients with moderately severe BED, treatment with cognitive behaviour therapy combined with an antidepressant of the SSRI type is the treatment of choice, If this proves ineffective, preliminary results suggest that possible alternative drugs, including venlafaxine, sibutramine and topiramate are potentially useful. Their definitive place in the treatment of BED awaits the outcome of further research.

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Chapter 7

Biological Rhythms and Disordered Eating

Eating behaviour, in common with many aspects of human activity, is yoked to a number of chronobiological rhythms which oscillate at varying frequencies. Some, such as the sleep-wake cycle, show regular and predictable fluctuations within the 24 hour day; their rhythm is said to be diurnal. Others, like the menstrual cycle in women, follow a monthly pattern. There are yet others which have an annual or seasonal periodicity. A number of clinical conditions have been described in which disturbances in eating and changes in body weight follow similar daily, monthly or yearly patterns.

1. Night Eating Syndrome – A Disorder with a Daily Periodicity

1.1. Clinical Features

In most societies, the large majority of people eat most of their food in set meals during the day. In the developed world, the typical pattern is to have a modest meal shortly after rising and before beginning the day's main activity. Next in order comes a meal at or around mid-day (lunch). The last set meal of the day is usually taken in the evening after work. The customary time at which each meal is taken varies widely from culture to culture, as does the composition of a typical meal. For example, in Norway, situated in northern Europe, the main evening meal is eaten at, or even before, 1800 h whereas in Spain, which is in southern Europe, this meal is rarely started much before 2100 h. The night hours are generally reserved for sleep.

Some people, however, depart markedly from this conventional diurnal pattern of eating. They consume over 50% of their total daily energy intake after 7pm, hence the name 'night eating syndrome' (NES). NES was first identified as a discrete clinical condition by Stunkard in 1955 (Stunkard et al. 1955), but went largely unrecognised until the 1990's, when several series of patients exhibiting the characteristic features of NES were described. The other features of this syndrome, in addition to nocturnal eating ('nocturnal hyperphagia'), are a lack of any desire to eat

in the morning ('morning anorexia') and difficulty in sleeping ('insomnia') (Birketvedt et al. 1999). The food consumed in the night typically has a large carbohydrate content. Its position in the American Psychiatric Association classification is in the category of 'Eating disorders – not otherwise specified'. Patients with NES rate more highly for depression and low self-esteem than other overweight dieters.

NES occurs most frequently in women who are overweight or obese. Whereas the prevalence is 1.5% in the general population, it is 9–15% in people attending weight-reduction clinics, rising to 25% among those classified as severely obese.

Patients who fulfill the diagnostic criteria for the Night Eating Syndrome need to be distinguished from others who, while they get up at night to eat ('Nocturnal eating'), do not display any of the other characteristics of NES (Ceru-Bjork et al. 2001). Such 'nocturnal eaters' suffer from a sleep disorder rather than an eating disorder. They usually display other symptoms of sleep disorder such as sleepwalking, obstructive sleep apnoea or restless legs (Schenck and Mahowald 1994). Night Eating Syndrome also needs to be clearly distinguished from Binge Eating Disorder (see Chapter 6) in which large amounts of food are consumed in a discrete period of time, during which patients experience loss of control, and from Bulimia Nervosa where 'binges' are typically followed by self-induced vomiting or purgation (see Chapter 5). Such behaviour is not seen in NES.

1.2. Biology

Endocrine studies have revealed that the normal nocturnal rise in the plasma levels of melatonin and leptin is attenuated in patients with NES (Birketvedt et al. 1999). Plasma levels of cortisol are raised during the day and the ACTH and cortisol response to corticotropin-releasing hormone (CRH) are diminished (Birketvedt et al. 2002).

1.3. Treatment

A variety of therapeutic agents have been tried in patients with NES but there have not been any randomised double-blind controlled clinical trials. From the limited data available it appears that serotonin reuptake inhibiting antidepressants SSRI are the most promising. A 12-week open-label trial of sertraline in seventeen patients (12 women, 5 men) showed, a significant reduction in the mean number of nocturnal awakenings, the number of ingestions and in the amount of food consumed after the evening

meal (O'Reardon et al. 2004). Five patients achieved full remission of symptoms.

Among other preparations which have been reported as being effective in small open studies are: benzodiazepine hypnotics; the anticonvulsant compound topiramate; melatonin; leptin.

Any firm recommendations as to treatment must await the outcome of randomised double-blind, placebo-controlled clinical trials in sufficient numbers of patients.

2. Premenstrual Syndrome – A Disorder with a Monthly Periodicity

2.1. Clinical Features

Premenstrual syndrome (PMS), as its name implies, is a constellation of symptoms which recur at monthly intervals during the seven to 10 days before the onset of menstrual bleeding and abate shortly after menstruation starts. The symptoms can be *psychological*, such as lowering of mood and irritability; *somatic*, such as breast tenderness, feelings of 'bloatedness' and signs of fluid retention; *behavioural*, such as changes in food consumption and in appetite. If the symptoms are severe, the condition may qualify for the DSM-IV label of 'Premenstrual Dysphoric Disorder' (PMDD). PMDD occurs in some 5% of normal women.

2.2. Biology

The changes in mood and appetite appear to be closely linked to the cyclical fluctuations in brain hormones which drive menstruation. In a series of normal women who completed daily ratings of mood, appetite and somatic symptoms, and in whom regular measurements of estradiol and progesterone were made, a strong correspondence was found between change in appetite and breast tenderness on the one hand, and the periovulatory and premenstrual phases of the monthly endocrine cycle on the other (Laessle et al. 1990). Appetite increased in the periovulatory and premenstrual phases, whereas no such correspondence was found between changes in mood and endocrine function. Eating behaviour follows the changes in appetite: data from diet diaries systematically completed over a period of two months, reveal that women with PMS show a significant premenstrual increase in their intake of fat, carbohydrate and simple sugars, that is, an increased intake of more palatable foods (Cross et al. 2001). An intriguing link between Premenstrual Dysphoric Disorder and seasonal affective disorder (SAD) (see below) was found in a Canadian

study (Maskall et al. 1997). 100 consecutive female patients attending a subspecialty psychiatric clinic who qualified for the diagnosis of PMDD, completed the Seasonal Pattern Assessment Questionnaire, modified to include items on the seasonality of premenstrual symptoms. Over a third (38%) of the PMDD subjects met criteria for SAD, compared to 8% of a non-clinical control group. Furthermore, 45 patients with PMDD noted moderate to severe seasonal changes in their symptoms.

2.3. Co-morbidity

A possible association between Premenstrual Dysphoric Disorder and two eating disorders (Binge Eating Disorder and Bulimia Nervosa) was examined in an Italian study in which 12 women with PMDD were compared with 10 women with eating disorder (6 BN, 4 BED) and 10 healthy women with no psychiatric diagnosis (Verri et al. 1997). The women with PMDD shared a 16.6% co-morbidity with the eating disorder patients, compared to the general population where such an association is present in only 2.3%. The shared co-morbidity could reflect a common pathophysiological disturbance, perhaps related to central serotonergic neurotransmission. In a similar vein, a close relationship between the physical and psychological symptoms of premenstrual dysphoric disorder was noted in a population of 107 obese patients, but not in matched control subjects (Zucchi et al. 2000).

2.4. Treatment

Antidepressants of the serotonin reuptake inhibitor type (SSRI) have been found effective in ameliorating the symptoms of PMS in over 20 randomised placebo-controlled clinical trials. Therefore, these drugs are currently considered the treatment of choice (Pearlstein 2002). Sertraline and fluoxetine have been the most widely studied. Their beneficial effects appear fairly quickly, suggesting that their pharmacological mode of action in PMS differs from that underlying their antidepressant action which takes longer to become manifest. A possible explanation for this difference is that SSRI act directly on brain neuroendocrine activity.

Side effects, such as insomnia, nausea, headache and problems with sexual function, can prove troublesome. One way of minimising such problems is to prescribe the drugs intermittently, restricting treatment to the luteal phase. This has been shown to be an effective strategy in a large-scale placebo-controlled clinical trial of sertraline 50–100 mg taken intermittently (Halbreich et al. 2002). Similar results have been obtained with

fluoxetine 20 mg and venlafaxine 75 mg, taken daily for 14 days before the expected date of the next period (Cohen et al. 2002; Cohen et al. 2004).

3. Seasonal Affective Disorder – A Disorder with a Yearly Periodicity

Changes in mood with the changing seasons has been recognised since the time of the ancient Greeks. And some 400 years ago Shakespeare's Richard III linked the chill of winter to feeling low and depressed, and the warmth of summer with happiness and joy, when he proclaimed: "Now is the winter of our discontent made glorious summer by this sun of York". In a more clinical context, Emil Kraepelin, the father of modern psychiatry, noted, in 1921, that certain of his patients with manic-depressive illness, showed a clear-cut seasonal pattern to their illness. They became depressed in the autumn and winter, often becoming manic when the warmth of summer arrived. In more recent times, Rosenthal and his associates in 1984 described a series of 29 patients attending a psychiatric clinic who regularly became depressed in the autumn or winter, with their mood lifting the following spring or summer (Rosenthal et al. 1984). What was of particular interest, in the context of disorders of eating and body weight, was that these patients, who were largely female, noticed that their appetite and weight both increased in parallel with their winter depression. He coined the term, 'Seasonal Affective Disorder' (SAD), to describe this syndrome. In their original paper, Rosenthal and his colleagues reported that the winter depression abated if patients spent time in a more southerly latitude. Thinking that this may be related to a longer daylight period, they tried the effect of sitting patients with SAD in front of a bright light source for at least two hours each morning, to considerable beneficial effect.

3.1. Clinical Features

During the period of the year (usually winter) that patients have a persistent lowering of mood, they also experience a series of what have been called 'atypical vegetative symptoms: fatigue, sleeping more, and overeating – often in response to a marked increase in appetite, particularly for foods with a high content of carbohydrate ('carbohydrate craving') – with a consequent increase in body weight.

The frequency with which these associated symptoms are reported to occur varies considerably between centres, ranging from nil to 9% (Magnusson 2000). In the original US series of 29 patients recruited mainly from advertisements placed in the Washington DC area, 66% had

increased appetite, 79% noted 'carbohydrate craving' and 76% gained weight in the winter months. In a UK series of 51 patients, recruited largely through referrals for a psychiatric consultation, 74% had an increase in appetite, 82% had 'carbohydrate craving' and 84% gained weight (Thompson and Isaacs 1988). By contrast, in a Swiss series of 22 patients, recruited in response to written requests from doctors and articles appearing in local newspapers, only 45% had an increased appetite in winter and 55% gained weight, although 77% reported 'carbohydrate craving'. It would appear that there is considerable diagnostic heterogeneity. SAD patients, according to their answers on the Dutch Eating Behaviour Questionnaire are more likely than control subjects to eat in response to emotional triggers. Furthermore, those patients with a high body mass index who are also 'restrained eaters' show a greater seasonal change in weight than others (Krauchi et al. 1997). This finding is in accordance with reports that emotional perturbation often disinhibits dietary restraint (Herman and Polivy 1975).

SAD is not recognised as a discrete condition in the diagnostic criteria of the American Psychiatric Association. Instead, it is referred to as a 'seasonal pattern specifier', which can be applied to patients who otherwise meet the diagnostic criteria for Major Depressive Disorder or Bipolar Disorder. The definition of a seasonal pattern specifier is: "a regular temporal relationship between the onset of episodes and a particular time of year (e.g., regular appearance of the Major Depressive episode in the fall or winter) with full remission also at a characteristic time of year." To meet this criterion, the onset of illness must have demonstrated the same temporal seasonal relationship in the previous two years, with no non-seasonal episodes having occurred over the same time period. Thus, less severe episodes of dysphoria, which recur seasonally should, strictly speaking, not be classified as seasonal affective disorder. Generally, a less rigorous definition of SAD is applied which is: "a condition of regularly recurring depression in the winter with a remission the following spring or summer" (Magnusson and Boivin 2003).

3.2. Epidemiology

How common is SADS? A local telephone survey in the US found that 92% of the survey subjects noticed seasonal changes of mood and behavior to varying degrees. For 27% of the sample seasonal changes were a problem and 4.3% to 10% of subjects, depending on the case-finding definition, rated a degree of seasonal impairment equivalent to that of patients with seasonal affective disorder. Rosenthal remarked: "It is apparent that

SAD represents the extreme end of a spectrum of seasonality that appears to affect a large percentage of the general population ... in the northern US." (Rosenthal, 1984 #938). There is, however, considerable variation from country to country, even within the same bands of latitude. For example, the reported mean prevalence of SAD is twice as high in North America than Europe (Mersch et al. 1999). Some of this variation clearly reflects diagnostic practice. In the US, there is perhaps a greater readiness to consider as an illness, what, in other places may be thought to be merely a normal variant. Whereas seasonal variation in mood is common, the clinical condition of SAD is less so. On the basis of 20 retrospective surveys, the prevalence of SAD in the general adult population, as defined according to the less strict criteria, ranges from almost zero to nearly 10% (Magnusson 2000). A recent survey in temperate Melbourne yielded a prevalence of less than 1% (Murray 2004).

The influence of latitude and photoperiod (timing and duration of daylight) appears to be less than originally believed. In a population of 526 adult female twins residing across the latitudes of Australia, who completed the Seasonal Pattern Questionnaire as well as three other instruments which examined mood and behaviour, self-reported seasonality did not correlate with latitude (Murray and Hay 1997). Similarly, in Ontario, Canada, latitude appeared to have no impact on the prevalence of the seasonal subtype of major depression (Levitt et al. 2000). Furthermore, even at the same latitude, according to a Norwegian study, the prevalence of seasonal symptoms can change over time (Skou Nilsen et al. 2004). These findings suggest that the influence of latitude on seasonality may be small; seasonal variation in affective state may reflect personality variables and genetic vulnerability more than meteorology (Mersch et al. 1999).

3.3. Biology

The presumed relationship of SAD to the photoperiod suggested that it may have something to do with the peptide melatonin, the secretion of which is entrained to the light-dark cycle. However, against this assumption, treatment with the beta-blocker propanalol, which inhibits the secretion of melatonin, failed to alleviate the symptoms. It is now believed that changes in central serotonin neurotransmission systems are involved. In keeping with this view, is the finding that intravenous administration of the 5-HT agonist meta-chlorophenylpiperazine (m-CPP) to patients with SAD, elevated their mood and reduced their desire for carbohydrate-containing foods (Jacobsen et al. 1994). In normal subjects it had no such effect.

SAD and bulimia nervosa are often co-morbid, and both independently can show a seasonal pattern (Ghadirian et al. 1999). Also, they both respond favourably to SSRI antidepressant drugs. It may be that both disorders reflect similar alterations in central serotonin neurotransmission (Silverstone 1993).

Seasonal alterations in taste, however caused, may mediate the increased desire for carbohydrate-containing foods. Consistent with this possibility was the finding that patients with SAD were less sensitive in detecting sweet taste in the winter than normal subjects (Arbisi et al. 1996). This difference disappeared in the summer.

3.4. Genetics

In an Australian sample of 4639 twins, genetic effects were found to account for 29% of the variance in seasonal symptoms in men and women (Madden et al. 1996). It has been hypothesised that the pathophysiology of SAD may be related to a 'thrifty gene' which regulates energy expenditure and intake to the availability of food. Such a gene would lead to a reduction in energy output in winter, when food supplies become less abundant in temperate zones. In support of this notion is the finding of an increased frequency of the hypofunctional 7-repeat allele of the dopamine-4 receptor gene in patients with SAD (and in patients suffering from Bulimia nervosa – see Chapter 6 and below) (Levitan et al. 2004). Another relevant finding is that polymorphism of the 5-HT2A receptor gene also appears to play a part in the pathogenesis of SAD and Bulimia nervosa (Sher 2001).

3.5. Treatment

3.5.1. Light box

The standard treatment for SAD is light therapy. The patient sits for 0.5–2 hours in front of a fluorescent light box of a luminosity of 2000 to 10,000 lux. While there are a number of studies attesting to its effectiveness light therapy is time consuming. Its use has been extended to a range of non-seasonal depressive conditions such as PMDD.

3.5.2. Drugs

In contrast to research on light therapy, there have been few systematic studies of the efficacy of antidepressant medications for seasonal affective disorder, despite the fact that antidepressants are a standard treatment

for major depression. Only three random controlled, double-blind clinical trials of selective serotonin reuptake inhibitors (SSRI) have been published to date. In a placebo-controlled trial of *fluoxetine* 20 mg daily, patients with recurrent major depressive disorder showing a seasonal pattern, obtained a small, non-significant, beneficial effect with the active compound, with a faster rate of improvement than placebo (Lam et al. 1995). A more recent, larger, placebo-controlled trial of *sertraline* 50–200 mg daily for eight weeks, showed it to be superior to placebo in ameliorating depression and anxiety (Moscovitch et al. 2004). This was despite a large placebo response. In the third study, *citalopram* proved more effective than placebo in preventing relapse following one week's successful light treatment (Martiny et al. 2004). Other compounds which have shown promise in open-label studies include *bupropion, trazadone, mirtazepine, moclobemide, reboxetine, l-tryptophan* and *tranylcypromine*.

In practice, almost half of the patients receiving light therapy are also prescribed an antidepressant drug (Pjrek et al. 2004). The effect of combining light treatment with an SSRI antidepressant, citalopram, has been evaluated in one small placebo-controlled trial (Thorell et al. 1999). The combination was found to be more effective than light treatment alone. In clinical practice, patients being treated with bright light therapy, are frequently prescribed additional antidepressants.

4. Conclusion

This intriguing syndrome, with its complex overlap of symptoms, has the potential to aid our theory-making about individual symptoms in related conditions. That is so, despite its uncertain etiology and variable prevalence.

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Chapter 8

Obesity

1. Clinical Features

Obesity is the number one nutritional problem in the developed world. It has been described as a pandemic of "global epidemic' proportions" with some 300 million people affected world-wide (Organization 1998).

It is a complex, multifactorial disorder characterised by an excess of adipose tissue in the body (Aronne 1998). The internationally accepted definition of obesity is based on the body mass index (BMI), which is the body weight in kilograms divided by the square of the body height in metres. According to The World Health Organisation and the US Preventative Task Force, an obese individual is one who has a BMI equal to or exceeding 30; one with a BMI between 25 and 29 is categorised as 'overweight'. People with a BMI of 35.0–39.9 are categorised as having 'severe' obesity, and those with a BMI of 40 or above as having 'very severe' or 'morbid' obesity. In the US, the National Health and Nutrition Examination Surveys (NAHNES I, II and III) define being *overweight* as having a BMI equal to or greater than that at 85th percentile for 20–27-year-old men and women: this corresponds to a BMI of 27.8 for men and 27.3 for women (Kuczmarski et al. 1994). Among those classified as obese, the pattern of distribution of the adipose tissue can also affect the long-term outcome; those who have a large proportion of their fat intra-abdominally ('visceral' or 'abdominal obesity') have a greater risk of developing serious medical conditions than those whose fat lies mainly subcutaneously (see below). The pattern of distribution is reflected in the ratio of the body circumference at the waist to that at the hips – the waist/hip ratio (W/H). A W/H greater than 0.95 in men and 0.8 in women is associated with increased morbidity.

It is now widely accepted that obesity is a disease in its own right, with clear genetic as well as environmental determinants (Jung 1997). As a report from the Royal College of Physicians of London emphasises: "Obesity must therefore be considered a serious medical issue rather than a perversity of current fashion" (Physicians 1998). Obesity is clearly a disease, in the same sense as hypertension and atherosclerosis are diseases, and constitutes a major health problem (Bray 2004).

2. Epidemiology

Despite an increasing public awareness of the dangers of being obese, reinforced by a succession of reports from an ever-increasing number of expert committees, the prevalence of obesity, particularly abdominal obesity, is actually *rising* at a disturbingly rapid rate in the developed world. It has increased relentlessly each decade since 1960. In the US, over 30% (i.e. almost a third of the adult population) can be classified as obese (Flegal et al. 2002). This figure has almost doubled in the past 20 years, with the increase being greatest among African Americans. A similar pattern is emerging in most countries in Western Europe (Seidell & Flegal 1997). In England, for example, the prevalence of obesity in adult males almost trebled between 1980 and 2000, increasing from 6% to 17% in males, and more than doubled in females, rising from 8% to 21% (Prescott-Clark & Primatesta 1998). Of particular concern is the continuing increase in overweight among children and adolescents in the US (Jolliffe '04) and the UK (Jebb '04). World-wide, the prevalence of being overweight has risen to 1.7 billion, with 312 million being in the obese category (James et al. 2004).

These alarming trends do not reflect public apathy or ignorance: in the US 43% of women say they wish to lose weight and over a third are actively engaged in the attempt (Kruger et al. 2004). Similarly, one third of younger European women are actively attempting to lose weight. It should be recognised, however that many of these women are of perfectly normal weight. Indeed, a considerable proportion of women (7.6%) whose BMI is less than 18.5, a level at which undernutrition is a real risk, are actively attempting to lose weight: they are clearly driven more by fashion than by any clinical imperative.

3. Etiology

When energy intake, as food eaten, exceeds energy output, as exercise or metabolic processes, the excess is stored as triglyceride in adipose tissue. Such an imbalance between intake and out put may be due primarily to an increased food consumption or to a reduced energy expenditure, or both. Heredity and environment each play a part in determining the imbalance which does not have to be large in absolute terms: a weight gain of 10 kg from age 25 to 55 requires only a 0.3% daily excess of intake over expenditure.

3.1. Genetics

Despite the burgeoning of obesity world-wide, it is still only a minority who become clinically obese (see above). Thus: 'there is individual variation with a secular trend'. Genetic factors are believed to play a major role in such variation, according to twin, family and adoption studies (Damcott et al. 2003). It has been calculated that up to 80% of the variance in body mass can be attributed to genetic factors.

In the majority of cases, the hereditary influences are mediated through a number of genes (polygenic) each with a modest effect. Thus far, over 430 gene sites have been identified as possibly playing a part in the pathogenesis of obesity. In only a small minority of cases the obesity can be attributed to a single gene, and in those there are usually a number of other major abnormalities present. Four levels of genetic determination have been postulated: (a) single gene (rare), (b) strong genetic predisposition, (c) slight genetic predisposition, (d) genetically resistant.

3.2. Environmental Pressures

The alarming rise in the prevalence of obesity, observed in the developed world in recent years, cannot plausibly be attributed to any change in genetic composition. It has all happened far too quickly for that. Thus, it must therefore be largely due to environmental factors which have affected both sides of the energy equation: food consumption having increased and energy expenditure decreased. In the relatively affluent countries of the developed world during the past four or five decades, there has been an unremitting pressure encouraging people to eat more and more. Year by year, portion sizes in fast food outlets have grown larger, price inducements have become increasingly tempting, and food advertisements ever more seductive. And ready supplies of high calorie foods have become increasingly available in schools, colleges, factories and offices. In parallel with these increased pressures to eat more, the opportunities for taking regular exercise have diminished. Sidewalks have disappeared from suburban communities, children are discouraged from walking to school and young and old spend more and more of their leisure time engaged in passive, non-energy expending pursuits, such as watching television or playing computer games.

3.3. Psychological

There is no clear psychological determinant of uncomplicated obesity. It cannot in itself be considered as an eating disorder. However, certain types

of disordered eating behaviour, such as binge eating (see Chapter 6) and the night eating syndrome (see Chapter 7) occur most often in obese people. It is difficult in such cases to know which came first, the disordered eating behaviour or the obesity. Certainly, chronic dieting ('restrained eating'), as practiced by many obese people, can lead to disruption of normal calorie regulation with physiological hunger signals becoming dissociated from eating (Polivy 1996). The majority of those seeking treatment for obesity, but by no means all obese people, have been described as: "... food preoccupied, distractible, binge-prone and unhappy". While it is generally agreed that strict dieting is an early step in the development of anorexia nervosa and bulimia nervosa, we do not know what distinguishes those dieters who go on to develop these conditions from those who do not. It should be noted that most obese individuals do not engage in aberrant eating behaviour.

4. Pathology and Pathophysiology

The amount of triglyceride in the adipose tissue the body (i.e. how fat a person is) represents the cumulative sum, over time, of the difference between energy intake (as food) and energy expenditure (as exercise and resting metabolism). Excess triglyceride leads to hypertrophy of the fat cells in the adipose tissue which has been said to be the defining pathology of obesity.

The evidence is now overwhelming that obesity, defined as an excessive storage in the form of fat has adverse effects on health and longevity (St-Onge and Heymsfield 2003). It causes or exacerbates a large number of health problems, both independently and in association with other diseases (Physicians 1998). The greater the degree of obesity, particularly abdominal obesity, the greater the risk.

The distribution of fat in abdominal obesity is similar to that seen in Cushing's syndrome, where there is an excess secretion of cortisol from the adrenal gland. Detailed endocrinological testing has revealed subtle disturbances in the diurnal regulation of the HPA axis leading to elevated cortisol secretion in the majority of obese men, but not in all. This latter group has a reduced secretion of testosterone and growth hormone which might be responsible, as both these hormones antagonize the effects of cortisol on visceral fat accumulation. The reduced testosterone and growth hormone levels are probably the consequence of a different aberration in the regulation of the HPA axis. In women, visceral obesity is probably a consequence of increased HPA activity leading to increased androgen secretion from the adrenal glands.

Leptin is another peptide the secretion of which relates to the amount of adipose tissue in the body (see Chapter 1). But the increased level of leptin seen in obesity appears to have little if any physiological effect in humans.

In addition to disturbances in endocrine function, the sympathetic nervous system is probably involved in the pathogenesis of an 'arousal syndrome' involving neuroendocrine and autonomic centres (Davy 2004).

4.1. Morbidity

Obesity plays significant role in the pathogenesis of a number of physical conditions (Lawrence and Kopelman 2004). These include diabetes mellitus, hypertension, coronary heart disease, some forms of cancer, gall bladder disease, respiratory disease, and osteoarthritis. In addition, being obese can lead to profound psychological disturbances and can have a major impact on social relationships and employment prospects.

4.1.1. Diabetes mellitus

Obesity gives rise to a perturbation of the hypothalamic–pituitary axis (HPA) and an increase in insulin resistance (the 'metabolic syndrome'). In people who are mildly obese the risk of developing non-insulin dependent diabetes mellitus is twice as high as in those of normal weight; this increases to a five-fold increase in the moderately obese and 10-fold increase in the severely obese (BMI $>$ 40) (Pi-Sunyer 1993). 95% of women with a BMI of 35 or more, develop diabetes, in men with a similar degree of obesity, 45% become diabetic. A prospective study in Scandinavia showed that having a BMI $>$ 30 was associated with a 10-fold rise in the relative risk of becoming diabetic. An Israeli study similarly found a higher incidence of diabetes in 50–59-year-old men who have a BMI $>$ 27 (Medalie et al. 1975). With the seemingly inexorable rise in the prevalence of obesity in most developed countries it has been estimated that within 10 years, the number of people world-wide with diabetes mellitus is likely to double, reaching a total of over 221 million (Kopelman & Hitman 1998).

4.1.2. Hypertension

An association between obesity and a raised blood pressure (hypertension) was clearly demonstrated in the Build and Blood Pressure Study undertaken by the Metropolitan Life Insurance Company some 40 years ago (Company 1960). Since then several other large-scale investigations have confirmed this relationship. In a representative epidemiological sample of some 10,000 US residents the prevalence of hypertension (blood

pressure greater than 160/95 mmHg) was almost three times as common in individuals classified as being overweight (see above) than in their non-overweight contemporaries; the excess was even greater in overweight people aged 20–45 (Havlik et al. 1983). A 18-year prospective study of 5127 residents of Framingham, Massachusetts showed a highly significant association between an increase in weight and a rise in blood pressure (Chiang et al. 1969). In a Scandinavian study of 67,000 adults, systolic blood pressure rose 2 mmHg for every 10 kg increase in weight (Bjerkdal 1957).

4.1.3. Heart disease

It is now generally accepted that obesity is an *independent* risk factor for coronary heart disease, over and above its effect on blood pressure and serum cholesterol (Eckel 1997). A prospective 8-year follow-up study of 115,000 women who were initially free of heart disease demonstrated that those who were obese (BMI $>$ 29) were 3.3 times more likely to develop serious heart disease than those who were not obese at the outset (Manson et al. 1990). Obesity is clearly a strong risk factor for coronary heart disease in middle-aged women; 40% of the risk of developing coronary heart disease in this population can be attributed to obesity.

4.1.4. Cancer

A prospective American Cancer Society study found an increase in the mortality rates for colorectal and prostate cancer in overweight men and for endometrial, gallbladder, cervical, ovarian and breast cancer in overweight women (Lew 1985). An association with obesity is now firmly established for breast cancer in post-menopausal women, as well as for endometrial cancer and for renal cell cancer. Obesity may also play a part in the pathogenesis of colorectal, prostatic and pancreatic cancers in men (Caroll 1998).

4.1.5. Locomotor disability

Osteoarthritis of the hips and knees is a frequent complication of obesity.

4.2. Mortality

Life insurance statistics have long shown that obese people do not live as long as those of a normal body weight. This has now been confirmed by the findings of two large-scale follow-up studies in the US: in one, a representative sample of 750,000 men and women was followed for 12

years (Lew & Garfinkel 1979); in another 115,195 healthy women were followed for 16 years (Manson et al. 1995). Both showed a significantly increased mortality rate among those who were defined as obese; the greater the degree of overweight, the greater the excess mortality. In the Framingham Heart Study, the risk of death within 26 years increased by 1% for each extra pound (0.45 kg) increase in weight between the ages of 30 and 40, and by 2% between the ages 50 and 60 (Lissner et al. 1991). The consequences of being obese are even more dire in younger people. Because they have a longer risk period the young lose proportionally more years of life for every degree of overweight. Similar associations between obesity and decreased longevity have been found in Norway (Waaler 1984) and in Canada (Rabkin et al. 1997).

4.3. The Psychological and Social Consequences of Obesity

Overweight individuals are discriminated against from childhood onwards (Gortmaker et al. 1993; Fabricatore and Wadden 2004). Children as young as six years describe a silhouette of an overweight child as being someone who is, "dirty, stupid, lazy and ugly", and are disinclined to play with them or have them as friends. During their adolescence, obese young people suffer torments from being the butt of insulting jibes and from failing to be chosen by any of their peers as participants in out of school activities. Such discrimination continues in college or university where the overweight find it more difficult to be accepted by the more prestigious universities simply because of their size. On leaving college they find it more difficult to get a job than their slimmer contemporaries, and, when they do find work, they often have to settle for a lower salary. This may be a partial explanation of the common finding that obesity is more prevalent among the socio-economically disadvantaged in the developed world.

Despite being the object of such discriminatory attitudes throughout their lives only a minority of obese people suffer from significant psychiatric symptoms such as depression. In a survey of two populations in London which I carried out in the 1960s I found no excess in psychopathology among the obese (Silverstone 1968). A similar lack of an association between obesity and major depression or anxiety in the general population has been observed in a number of more recent US and European studies, supporting my somewhat unexpected earlier findings (Fabricatore and Wadden 2004; Hasler et al. 2004). However, among those seeking treatment for obesity, there is a much higher prevalence of psychopathology, particularly depression.

4.4. The Economic Costs of Obesity

With the increasing prevalence of obesity in the developed world there has been a major escalation in the economic costs attributable to the condition. In 2003 in the US the direct medical costs alone, attributable to obesity, reached a total of $75 billion (Finkelstein et al. 2004). And they form only a part of the overall cost. In calculating the overall cost of an illness such as obesity one needs to take into account the direct costs attributable to obesity itself, those cost arising from obesity-related illnesses (personal health care, hospital care, allied health services, medication) and the indirect costs of being obese (unemployment, reduced output and sickness benefits). In making these estimates, assumptions are required regarding the degree to which obesity contributes to the aetiology of co-morbid conditions such as type 2 diabetes and what proportion of their costs can be attributed to obesity. For example, in the case of type 2 diabetes it has been assumed that in women in the US, 94% of the morbidity is attributable to obesity, and that this accounts for over 50% of the direct costs associated with it (Colditz 1992). In like manner, 77% of the morbidity accompanying hypertension has been attributed to obesity at an annual cost of over $1.5 billion. Summing all the direct and indirect costs thought to be due to obesity and obesity-related conditions gave a total annual cost of $99.2 billion in the US in 1995, it is likely to be much greater now. These costs represent over 5% of the total national expenditure on health (Wolf and Colditz 1998). Similar calculations have been made in a number of other countries including the UK, Australia, Canada, France, Germany, The Netherlands, New Zealand and Sweden (Hughes and McGuire 1997; Katzmarzyk and Janssen 2004; Levy et al. 1995; Swinburn et al. 1997; Kurscheid and Lauterbach 1998; Kortt et al. 1998). In these countries a minimum of 2–3% of the total annual health expenditure has been attributed to obesity and obesity-related conditions. In confronting such daunting sums Wolf & Colditz (Wolf et al. 1998) were moved to conclude: “The economic and personal health costs of overweight and obesity are enormous and compromise the health of the United States”.

5. Treatment

The primary objective of treatment in obesity is to promote a loss of body weight over a prolonged period and, thereby improve health and reduce the risk of the associated morbidity. As obesity is a chronic condition, clinically effective treatment must be planned to ensure that any weight loss is maintained over the longer term. Short term weight reduction should only

be seen as merely the first step in a prolonged treatment programme; but a necessary first step nevertheless. In order for weight loss to occur, there has to be a negative energy balance, that is, energy intake has to be lower than energy expenditure. To achieve this goal, dietary restriction, to promote a reduction in energy intake, should be accompanied by an increase in energy output through regular exercise.

For successful long-term reduction of body weight, realistic goals need to be agreed at the outset by the patient and his or her health provider. Many patients have unrealistic expectations about how much weight they are likely to lose in a given period; many believe they should be able to lose 25% of their initial weight in a relatively short period of dieting. However, even a reduction of 10% of the total body weight can make a significant impact on the indices of morbidity such as glucose tolerance and blood pressure (Knowler et al. 2002). Defining, and meeting, a modest series of short-tem goals is likely to prove effective, and acceptable to most dieters (Wadden et al. 2003). Success in meeting such goals will positively reinforce dieting and exercise behaviour, leading to longer-term maintenance of a reduced body weight with its attendant advantages in health and longevity. Small alterations in dietary intake over a longer period usually prove more effective long-term than rigorous short-term restriction (Munro & Cantley 1992). For most overweight people a target weight loss of 0.5–1 kg (1–2 lb) per week is the most that can be expected over any length of time. It needs to be emphasised that a person weighing 100 kg (220 lbs) will obtain worthwhile benefits from losing as little as 10 kg (22 lbs) *provided this loss is maintained*.

5.1. Dietary Restriction

For weight loss treatment to be successful, patients need to be motivated to make a change in energy balance. Most subjects under the age of 40 who seek weight reduction do so mainly in order to improve their appearance, those who are over 40 do so more from a wish to improve their health. Patients should be informed about the principles underlying dietary treatment, the rate of weight loss which can be realistically expected, and to recognise what is an achievable goal. A realistic expectation for weight loss, assuming each kilogram of human adipose tissue provides 7000 kcal, is an energy deficit of 500 kcal per day which will lead to a weight loss of 0.5 kg (just over 1 lb) per week. Those who are obese, that is with a body mass index (BMI) of 30 or greater often need to lose well over 30 kg to be in the ‘normal weight’ range. Thus they need to achieve an overall energy deficit of more than 200,000 kcal. Since going on a 1000 kcal diet is likely

to produce a daily deficit of about 1000 kcal, it is clear that significant weight loss will take many months of perseverance and determination to resist the many physiological and psychological pressures to eat. People vary a lot in their readiness to change their behaviour and it is often helpful to determine how prepared to do this a given individual is; questionnaires have been developed for this purpose.

At any one time in the US 38% of the entire female population and 24% of the male population report that they are trying to lose weight (Kruger et al. 2004). Most of these people are not clinically obese; only 27% have a BMI greater than 30 whereas 36% of dieters have a BMI below 26 (Levy and Heaton 1993). These latter individuals, who have absolutely no medical need to lose weight, are trying to achieve some idealised body shape and size. As Hilda Bruch pithily put it some 50 years ago: "In our society slenderness is next godliness" (Bruch 1957). Her aphorism remains as true today as it was when first expressed.

To meet this seemingly insatiable demand for weight reduction, a vast range and variety of dietary programmes have been promoted to help people lose weight. Virtually all of these diets are designed with the objective of producing a negative energy balance, and can be classified into four main categories:

(i) Very low calorie diets which contain no more than 800 kcal per day. They are usually marketed in the form of a liquid formula containing all essential nutrients. They are not recommended for the routine treatment of obesity. Regular medical monitoring is advisable and the longer-term results over the succeeding year are no better than those achieved with more conventional reducing diets. They should only be followed for a limited period, and always under professional supervision. In my view their use is best restricted for people with severe obesity in helping them to get off to a good start.

(ii) Eating one or two low-calorie 'real' meals per day, or substituting one or more meals with commercially available limited calorie meal substitutes, usually taken in the form of specially formulated drinks or meal bars. These have the advantage of simplifying food choice. This approach can be combined with pharmacological treatment.

(iii) Limiting the intake of normal foods to provide a predetermined total number of calories per day; this is usually in the range of 1200–1600 kcal. To monitor their dietary intake patients are encouraged either to weigh all the food they eat or, more commonly, to calculate their daily intake using food chart ('calorie counter').

There are a number of variants of this general approach such as *The Atkins Diet*, which largely eschews carbohydrate-containing food, and

The GI Diet which favours foods with a low 'glycemic index' (i.e. the intake of which are not followed by a rapid rise in glucose leading to insulin release). Many form part of a comprehensive commercial slimming plan.

For obese binge-eaters additional psychological help is nearly always required (see Chapter 6).

For the majority of obese people, a calorie restricted diet based on nutritious and appetising foods is the most suitable; it is likely to be more successful if it is tailored to meet the needs, expectations and life-style of the individual trying to lose weight. The details of the diet, and how to monitor energy intake, are best explained by someone who has received formal training in these matters. For weight maintenance, a low fat, high fibre diet, which is nutritionally adequate, is best.

An exercise regime is often added to dietary programmes. While the immediate effects of exercise on weight loss may be small, modest increases in activity lead to more successful maintenance of dietary-induced weight loss (Grilo et al. 1993). Furthermore, exercise improves all-round health and induces a sense of well-being.

5.2. Behavioural Treatments

Behavioural weight loss treatments for obesity are designed to help patients modify their eating patterns and to increase their level of activity (Wadden 1993). Eating and exercise habits are analysed and problem behaviours identified. Patients are then encouraged to limit their exposure to situations (such as watching television while eating) that distract them from monitoring their eating. They are typically administered on a group basis.

A key element in this approach is detailed self-monitoring of all the foods eaten during the course of a day together with their calorie value. Patients are also instructed to note the situations in which they eat and to describe any emotional feelings associated with eating. In addition, patients are instructed to keep a record of an exercise taken. Patients are then helped in defining strategies to modify any systematic dysfunctional behavioural patterns identified by the self-monitoring process. They are also provided with sound nutritional information.

Behavioural weight loss programmes greatly help in promoting adherence to a reduced calorie intake and lead to more prolonged maintenance of weight loss. However even with this approach weight loss is frequently not maintained. On average, patients regain a third of their initial weight loss, although some do manage to consolidate their improvement.

5.3. Surgical Approaches

Gastrointestinal surgery is now widely used for the treatment of *severe* obesity (Buchwald et al. 2004). There are two main surgical objectives: (a) to reduce the amount of food the stomach can hold – *gastric restriction*; (b) to reduce the amount of intestinal absorption through bypass operations – *malabsorption procedures*. Operations of the first type include various forms of gastroplasty, in which the size of the stomach is reduced by stapling part of its walls together, and gastric banding. Here, a small belt is applied around the stomach just below the oesophagus to create a small gastric reservoir with a limited outlet. It has the advantage of being readily adjustable as an outpatient procedure.

Despite the obvious drawbacks of having to undergo an abdominal operation plus the associated dangers of anaesthesia in the very obese, most patients are pleased at the outcome. The results have been shown to be much better than for medical treatment in a randomised trial (Sjostrom et al. 1999). Surgery should be reserved for super-obese patients (BMI over 40), in whom the danger of associated morbidity from conditions such as diabetes mellitus and coronary heart disease are particularly high. The majority of obese subjects, who have a BMI between 30–40 should, in my view, be treated more conservatively.

6. Drugs in the Treatment of Obesity

"The goal of all anti-obesity drugs is to induce and maintain a state of negative energy balance until the desired weight loss is achieved" (Campfield et al. 1998). Drugs can play a useful part in this endeavour by assisting patients to reduce their energy intake, or to increase their energy output, or a combination of the two. In the United States alone, over two million people take an antiobesity drug during the course of a year (Kruger et al. 2004).

Drugs used in the treatment of obesity are of two main types: (a) those which reduce food consumption by lowering the desire to eat (anorectics); (b) those which reduce absorption of nutrients from the small intestine. The former include drugs which act on the brain mechanisms regulating appetite and hunger (*appetite suppressants* – see Chapter 3) and those which provide the gastrointestinal tract with a substantial amount of zero-calorie bulk, usually in the form of cellulose (*bulk agents*). Bulk agents, such as guar gum, have not proved more effective than placebo in the treatment of obesity (Pittler and Ernst 2001). They will not be considered further.

6.1. Appetite Suppressant Drugs (Anorectics)

Centrally-acting appetite suppressant drugs have had a very chequered course over the past 70 years or so. The first such compound to be introduced into clinical practice was amphetamine, which had been first conceived as a synthetic alternative to ephedrine for use as a nasal decongestant. When taken orally it was unexpectedly found to reduce hunger and increase alertness – a seemingly ideal combination of properties for the treatment of obesity, and was introduced into clinical practice for this indication in the early 1930s. Unfortunately, its stimulant and euphoriant properties soon led to it becoming a popular drug of abuse, and it fell out of favour. Beginning in the 1950s, a number of other short-acting appetite suppressants with fewer stimulant effects were introduced, most of which are still available in the US, but not in Europe (see below). Fenfluramine, a non-stimulant phenylethylamine appetite suppressant compound, which acted via central serotonergic rather than noradrenergic pathways, was introduced into Europe early in the 1970s and later into the US. It enjoyed a considerable vogue in the 1990s, particularly when given in combination with the stimulant anorectic phentermine. However, the combination was found to cause cardiac and pulmonary problems and was withdrawn in 1997 at the instigation of the US Food and Drug Administration (FDA).

To obtain FDA approval in the US, an appetite suppressant drug has to produce a weight loss, over and above that produced by placebo treatment, of at least 5% of body weight. The only centrally acting appetite suppressant currently licensed for longer term use (i.e. longer than three months) in the US is sibutramine. Anorectic drugs which are currently licensed for short-term obesity treatment in the US include *phentermine*, *diethylpropion*, and *mazindol*. The European Agency for the Evaluation of Medicinal Products (CPMP) requires a weight loss of 10% of body weight over placebo. The only appetite suppressant currently approved in Europe is sibutramine.

Anorectic drugs, given as part of an integrated dietary programme, can be of real benefit in helping obese patients who are medically at risk (Linne and Rossner 2004).

6.1.1. Centrally acting appetite suppressant drugs approved for longer term use Sibutramine (*Meridia*)

Sibutramine is a dimethylamine derivative which is a centrally acting inhibitor of the presynaptic reuptake of noradrenaline and serotonin. It undergoes extensive metabolism in the liver. After a 15 mg dose, the peak

plasma concentration is reached in 2.5–3.5 hours. In healthy adults the excretion half-life is 14–19 hours, being slightly longer in the elderly (McNeely and Goa 1998).

Clinically, sibutramine was initially investigated as a potential antidepressant, but was soon noted to reduce food intake, so further clinical testing focused on obesity. A single 15 mg dose of sibutramine given to normal volunteers significantly increased the feeling of satiety and reduced food intake for several hours following a meal (Chapelot et al. 2000). Following 14 days treatment at a dose of 15 mg daily the amount eaten at a lunch-time meal by 36 obese patients was reduced on average by 16% compared to placebo. Within individual patients the amount by which food intake was reduced in this short-term study was found to correspond to the amount of weight lost over the next 10 months continuous treatment with sibutramine (Barkeling et al. 2003). In addition to reducing food intake, sibutramine increases the resting metabolic rate, via thermogenesis (Hansen et al. 1998; Persky et al. 2004).

Numerous clinical trials of sibutramine as a treatment for obesity have been conducted. They ranged from 8 to 104 weeks in duration. Generally, sibutramine was taken orally at a dose of 10–20 mg, the commonest being 15 mg daily. In a large US multi-centre trial 1463 obese patients were treated for 24 weeks with 10, 15, 20 or 30 mg sibutramine daily or placebo, of whom 683 patients completed (Bray et al. 1999). Weight loss was dose related. At six months, the mean percentage weight loss in the placebo group was 1.2% of their body mass; on 1 mg/day it was 2.7%; on 5 mg/day it was 3.0 %; on 10 mg/day it was 6.1%; on 15 mg/day it was 7.4%; on 20 mg/day it was 8.8%; on 30 mg/day it was 9.4%. Those losing weight showed a concomitant increase in HDL cholesterol and a reduction in LDL cholesterol. Blood pressure showed a variable small increase. A longer, two-year, trial involving 499 obese patients was conducted in eight European centres (James et al. 2000). It was carried out in two phases: during the first six months all patients were prescribed an individualised diet calculated to produce an energy deficit of 600 kcal/day and treated with sibutramine 10 mg daily; patients who lost 5% or more of their body weight in this initial six months period were randomly assigned to receive either 10 mg/day sibutramine or matching placebo for a further 18 months. The dose could be increased to two tablets daily if weight regain occurred during the course of the trial. Of the patients who were allocated to receive sibutramine in the second phase, 89 (43%) maintained their first-phase weight loss, compared to only 16% of the placebo group. A meta-analysis of 29 placebo-controlled trials, involving a total of

almost four thousand obese patients found sibutramine to have a consistently greater effect than placebo on body weight (Arterburn et al. 2004).

In overweight patient with type 2 diabetes, treatment with sibutramine led to weight loss accompanied by an increase in insulin sensitivity, with greater glycaemic control (McNulty et al. 2003). Patients who lost 10% or more of their body weight showed significant decreases in both HbA(1c) and fasting plasma glucose. Health-related quality of life was also improved (Kaukua et al. 2004).

The most commonly reported side effects of sibutramine are dry mouth, constipation and insomnia (Nisoli and Carruba 2000). A small increase in heart rate and blood pressure is common; this persists as long as treatment continues. This action can be mitigated by the concomitant administration of a beta-adrenergic blocking agent, such as metaprolol (Ersoz et al. 2004). While sibutramine has been used successfully in patients with pre-existing hypertension, all patients receiving it require continued close clinical monitoring.

6.1.2. Centrally acting apetitite suppressant drugs approved for short-term use

The anorectic drugs which are currently licensed for short-term (i.e. 3 months or less) obesity treatment in the US are *phentermine*, *diethylpropion* and *mazindol*. They reduce appetite and lower food intake via their action on noradrenergic and dopaminergic pathways. While they all have some stimulant properties they only very rarely give rise to problems of dependence. In Europe their approval has been withdrawn, inappropriately in my view. Indeed, as recently as 2000 The UK Committee on Safety of Medicines advised: "There are no major health concerns in relation to phentermine and diethylproprion". Regulatory agencies would appear to have imposed unrealistic standards of efficacy on appetite suppressants, stipulating that they should promote long-term weight loss, while restricting their use to the short-term. In other words, they are expected to be effective long after they have been stopped. The major charges levelled against these sympathomimetic anorectic drugs are:

The rate of weight loss slows with time (this is usually attributed to tolerance developing). While it is true that the rate of weight loss plateaus after some 5 to 6 months of continuous treatment, this happens with most, if not all, weight loss regimes (even surgical). It occurs partly because the body adapts to a lowered calorie intake by reducing the resting metabolic rate; thus there comes a time when the lowered energy intake is matched by the reduced energy output and weight loss ceases. Hardly the fault of

the drug. In fact, true drug tolerance rarely develops. In a study designed to investigate this point, we allocated a series of obese patients into three groups: one group received diethylpropion 75 mg daily continuously for four months, another group received active diethylpropion in the first and third months and placebo in the intervening months, the third group received active diethylpropion during the second and fourth months with placebo in months one and three (Silverstone 1974). If tolerance were the predominant cause of the falling rate of weight loss seen over time, then the patients in the third group who received diethylpropion for the first time in the second month should have shown a greater drug effect than those in the first group who had been receiving it continuously. They did not, the weight lost was almost identical. The same was true in the fourth month; those who had been receiving the drug continuously during the previous three months lost no less weight in that month than those who had only taken diethylproprion during the second month. Similar results have been obtained with the intermittent administration of phentermine. These findings support the intermittent prescription of appetite suppressant drugs over many months rather than short-term continuous use.

6.1.3. When the patient stops taking the drug, he or she regains the lost weight

Weight regain after stopping anorectic drug treatment reflects the release from the continuing anorectic effect which these drugs exert for as long as they are taken, despite no further weight loss occurring. The fact that the drugs cease to work when they are no longer being taken is hardly surprising; this is a totally unrealistic expectation of any drug.

6.1.4. Anorectic drugs lead to drug dependence and abuse

Physical dependence leading to clear-cut withdrawal symptoms is only rarely seen. Psychological dependence on the drugs currently approved for use in the US, especially when they are taken intermittently (see below), is similarly uncommon (Bray 1993). The great majority of patients who have been prescribed appetite suppressant drugs approved for use in obesity have little or no difficulty in stopping.

6.1.5. Phentermine (*Ionamin*, *Adipex*)

Phentermine is a sympathomimetic phenylethylamine compound which has a potent appetite suppressant effect through increasing the release of noradrenaline from central presynaptic neurones. It has been clinically available for over 40 years and has consistently remained among the most

widely prescribed antiobesity medications (Stafford and Radley 2003). In the 1990's there was a fashion for prescribing phentermine in combination with the serotonergic agent fenfluramine, a combination generally referred to a 'fen-phen'. However, fenfluramine was withdrawn because of its toxic effects on the heart and lungs. Phentermine was fully exonerated from any blame for these effects.

There have been 17 double-blind placebo-controlled trials of phentermine 30 mg daily in obesity, involving some 1000 patients. In every single one of these trials the mean weight loss among those taking phentermine was at least twice as great as among those on placebo.

Glucose tolerance and lipoprotein profile has been shown to improve in parallel with phentermine-induced weight loss. In one small comparative trial, it proved more effective than diethylproprion. Intermittent administration of phentermine (alternate one month on phentermine, one month on placebo) was shown to be as effective as continuous administration over a 9-month treatment period (Steel et al. 1973).

Side effects are those expected of any sympathomimetic agent: dry mouth, palpitations and insomnia. Phentermine has an excellent safety record with a low potential for dependency. This is lowered even further with intermittent administration.

6.1.6. Diethylproprion [Amfepramone] (*Tenuate*)

Diethylproprion is a diphenylethylamine compound which promotes the release of noradrenaline (and to lesser extent, dopamine) from presynaptic neurones. It was introduced into clinical practice for the treatment of obesity over 40 years ago. A number of clinical trials have shown it to be significantly more effective than placebo, although less effective than phentermine or mazindol, in helping obese patients lose weight. As noted above, it does not lead to tolerance. Side effects are mild. Some patients experience mild stimulant symptoms and tachycardia. The risk of dependence has proved to be low.

6.1.7. Mazindol (*Sanores*, *Teronac*)

Structurally, mazindol is related to the tricyclic antidepressants; it is not a phenylethylamine derivative. Like sibutramine, it inhibits the reuptake of noradrenaline and dopamine into presynaptic neurones rather than promoting their release. It also inhibits the reuptake of serotonin. Mazindol was introduced into clinical practice in the 1970s. Clinically, it reduces hunger awareness and lowers food intake. A number of double-blind clinical trials have shown mazindol 2 mg daily to be significantly more ef-

fective than placebo in assisting obese patients lose weight. In a 12-week comparative trial patients lost more weight on mazindol than diethylpropion (Murphy et al. 1975). Although not a phenylethylamine, it does have a pronounced stimulant activity. There are some concerns regarding its safety when given to patients with pre-existing cardiac problems.

6.2. The Value of Appetite Suppressant Drugs in the Treatment of Obesity

Anorectic drugs can play a useful role in the overall management of obesity, provided it is recognised that the rationale of such treatment is to provide assistance to patients trying to keep to a restricted calorie diet. Therefore they should only be given in conjunction with appropriate dietary information and advice, which itself should be reinforced at frequent intervals and accompanied by instruction in the range of strategies which have been found to assist patients avoid overeating (behaviour modification). Further, such drugs should be restricted to those medically at risk either through the severity of their obesity, (i.e. a body mass index of 30 or more) or those who suffer from a serious complication of being overweight, such as having non-insulin dependant diabetes or hypertension. Their place in promoting weight loss purely for cosmetic purposes is questionable.

6.3. Drugs Which Act by Reducing Digestion and Absorption of Nutrients from the GI Tract

Orlistat (Xenical) is a partially hydrated derivative of endogenous lipstatin. It acts peripherally by blocking the activity of pancreatic lipase, an enzyme which breaks down dietary fat into a form where it can be absorbed from the small intestine (McNeely and Benfield 1998). When administered by mouth it leads to a 30% reduction in the amount of fat absorbed. Although treatment with orlistat can lead to significant weight loss (Sjostrom et al. 1998) troublesome side-effects, secondary to the high concentration of fat in the intestinal contents, include anal leakage of oily material, faecal urgency and increased frequency of defecation sometimes with incontinence (Birkbeck 1999). Balancing efficacy against side effects, the optimal oral dose was found to be 120 mg taken three times daily. It is suggested that multivitamin supplements be taken by patients on orlistat to offset the reduced absorption of the fat soluble vitamins D and E.

A number of multi-centre trials have been carried out in the US and Europe, four of which extended over two years (Padwal et al. 2003). In

the European trials the mean weight loss on orlistat was 10.3 kg compared to 6.1 kg on placebo; in the US trials the corresponding figures were 8.8 kg on orlistat and 5.8 kg on placebo A systematic review of 19 placebo-controlled trials revealed a modest comparative advantage of orlistat over placebo: after one year the mean weight loss on orlistat was 2.44 kg greater than on placebo; after two years it was 2.51 kg greater (O'Meara et al. 2004). Despite its unpleasant side-effects over 75% of the participants in long-term trials persisted with treatment. In double blind comparative trials, the mean weight loss in patients taking orlistat was generally less than in a comparison group taking sibutramine: being 2.7 kg after one year on orlistat compared to 4.3 kg on sibutramine (Padwal et al. 2003).

Orlistat has been found to be effective in the management of obese patients with co-morbid type II diabetes mellitus. Not only did the diabetics lose more weight on orlistat, the plasma levels of glycosylated haemoglobin (a measure of diabetic control) fell by 0.2% after 1 year on orlistat compared to a rise of 0.3% on placebo (Miles et al. 2002). Both orlistat and sibutramine appear to be equally effective in this group of patients, although sibutramine is better tolerated (Derosa et al. 2004).

6.4. Combinations of Antiobesity Drugs

In a small, open-label 12-week trial, the combination of orlistat (120 mg tid) and sibutramine (10 mg daily) proved to be more effective than orlistat alone, but not significantly better than sibutramine alone, in reducing BMI (Aydin et al. 2004). The combination of sibutramine, orlistat and the anticonvulsant drug topiramate (see below) has been assessed in small open trial in five obese patients (Anghelescu et al. 2002). First, orlistat (120 mg three times a day) was given as a monotherapy. Then sibutramine (15 mg in the morning) and topiramate (in a dose dependent on clinical response) were added for a total duration of 48 weeks. A further 48-week maintenance and relapse prevention treatment period with topiramate monotherapy followed the discontinuation of orlistat and sibutramine. This outpatient treatment procedure was tolerated well, although side effects occurred in all patients depending on the phase of the treatment regimen. After 96 weeks, the mean body mass index had fallen to 25.7 ± 1.2 kg/m. This type of combined treatment clearly warrants further study.

6.5. Cost/Benefits of Drugs in Obesity

Even modest weight loss, *provided it is maintained*, brings appreciable advantages in terms of health and health costs (Goldstein 1992). Most

authorities now agree that a loss of some 10% of baseline weight will decrease many of the risk factors associated with obesity and suggest that is a realistic target to aim for (Obesity 1995, 1996). Given that, in the US alone, there are at least 300,000 deaths per year which are attributable to obesity, large numbers of people are likely to benefit from even a small reduction in the level of risk (Manson and Faich 1996). That this is so, was shown in a prospective study of over 52,000 women; intentional weight loss in those women who were obese and had coexisting conditions, primarily diabetes and hypertension, reduced mortality by 20% (Williamson et al. 1995). Similarly, a 10 kg weight loss (i.e. between 5–10% of initial body weight for the great majority of obese people who are medically at risk) will: (a) reduce systolic blood pressure by 10 mmHg and diastolic pressure by 20 mmHg; (b) reduce the risk of developing diabetes by 50%, lead to a fall in fasting blood glucose of 30–50% and a 15% fall in HbA 1c; (c) lower serum cholesterol by 10%, LDL cholesterol by 15% and triglycerides by 30% with a corresponding increase in HDL cholesterol of 8% (Jung 1997). Thus, the drug-induced health benefits outlined above are likely to have a significant effect on the huge financial burden of the illness (Avenell et al. 2004).

6.6. Psychotropic Drugs

Although psychotropic agents are not approved by the FDA for the treatment of uncomplicated obesity, they are often prescribed for this indication in clinical practice. Furthermore they have proved of value in those eating disorders, such as binge eating disorder, which are usually associated with obesity (see Chapter 6) (Appolinario et al. 2004). The SSRI antidepressant, *fluoxetine*, in particular, has proved to be an effective medication in promoting weight loss in obese patients with type 2 diabetes mellitus (Norris et al. 2004). In uncomplicated obesity, the effect of fluoxetine is more limited, as its beneficial effect is relatively short-lived (Goldstein et al. 1994).

Two antiepileptic drugs have also been found effective in assisting obese patients lose weight. *Topiramate*, 64–384 mg daily, was significantly more effective than placebo in three clinical trials, with the effect lasting over the course of a year's treatment (Astrup and Toubro 2004). The drug was generally well tolerated, with adverse events, such as paresthesia, being mostly related to the central nervous system.

Zonisamide acts by blocking sodium and calcium channels and promoting serotonergic and dopaminergic neurotransmission. It can benefit patients with uncomplicated obesity as well as those with binge eating

syndrome (see Chapter 6). In a 16-week randomised, double-blind trial ($n = 60$) patients on zonisamide 400–600 mg daily lost 6.2% of their initial body weight compared to a 1.6% loss in those taking placebo (Gadde et al. 2003).

6.7. Drugs in Development

As noted in Chapter 1, a number of endogenous peptides such as CCK, leptin and peptide YY3, suppress appetite and food consumption when given to human subjects. As currently formulated they require to be given by systemic injection, this limits their therapeutic application. Efforts are under way to develop analogues which can be taken by mouth. Of more immediate promise is the cannabinoid receptor antagonist *rimonabant* (*Acomplia*). In one large multicentre phase III trial, 1036 obese patients with dyslipidaemia and a BMI of 27–40 kg/m^2 were randomised to double-blind treatment with either rimonabant (5 or 20 mg per day) or placebo for 1 year (Cleland et al. 2004). All patients were required to follow a reduced calorie diet. Patients in the high dose rimonabant group lost an average of 20 lbs compared to 5 lbs in the placebo group, with 44.3% of those on rimonabant losing at least 10% of their body weight. Moreover, the number of patients classified as having metabolic syndrome in the rimonabant 20 mg group, was reduced from 52.9% at baseline to 25.8% at one year. Rimonabant 20 mg was also associated with a significant reduction in waist circumference, a lower plasma level of triglycerides and C reactive protein and an increase in HDL-cholesterol. A large multi-centre European–US study, involving 1500 overweight and obese patients, compared rimonabant 20 mg daily to rimonabant 5 mg daily and to placebo. After one year, the mean weight loss in patients on the 20 mg dose of rimonabant was 8.6 kg compared to 3.6 kg in those on placebo and 4.8 kg in those on a daily dose of 5 mg rimonabant (Black 2004). There was a concomitant rise in HDL cholesterol fall in plasma triglycerides greater than that due to weight loss alone. Side effects included nausea and dizziness.

A large number of other centrally and peripherally-acting compounds are currently under investigation (see Chapter 3).

7. Course and Prognosis

Obesity is a life-long condition; it is a chronic disease like diabetes and hypertension. Unfortunately, the great majority of obese individuals who lose weight regain it. “Obesity is rarely cured; however, palliation is a realistic goal” (Bray 1993). A major factor in limiting continuing weight

loss is the reduction in energy output which accompanies a reduction of body weight. The body is geared to defending its mass and resist loss.

Despite the inbuilt metabolic mechanisms countering attempts to lose weight, longer term treatment with drugs clearly assists the maintenance of a lower weight. Weight which has been lost during active treatment is usually regained when such treatment is stopped. A review of 20 clinical trials lasting six months or more concluded: "The agents alone or in combination with adjunctive treatment were significantly more effective than were placebo or dietary treatment alone in producing weight loss. The benefits of extended treatment appear to outweigh the risks for those patients who are unable to lose sufficient weight without pharmacologic therapy ..." (Goldstein and Potvin 1994). A good case can therefore be made for longer term treatment with appetite suppressant drugs; the National Task Force on the Prevention and Treatment of Obesity (Obesity 1996) agrees: "Long-term pharmacotherapy, when combined with appropriate behavioural approaches to improve diet and increase physical activity helps some obese patients lose weight and maintain weight loss for at least a year". Such a view runs counter to many licensing requirements that, if anorectic drugs are to be used at all, they should only be given for a short time, say three to four months. In other chronic conditions such as hypertension or diabetes long-term treatment is the norm, not the exception. However, before such a strategy can be fully justified for newer drugs, we would need data about the efficacy and safety of the prolonged use (over a year) of appetite suppressant drugs. As far as the older drugs, such as phentermine, are concerned, one would have thought that any unexpected untoward long-term effects would have been revealed by now. In any case, intermittent treatment with either phentermine or diethylpropion, which has been proved to be effective in helping obese patients lose weight in double-blind, placebo-controlled trials, would even further reduce the likelihood of any adverse consequences from longer term treatment (Silverstone 1992).

It is unlikely that any single therapy will work as a sole treatment over the long-term. What is likely to be more effective is using a range of therapeutic interventions which can be combined and/or alternated over years. Such a policy of 'ringing the changes' is likely to be more effective in maintaining motivation and prolonging success than any one treatment on its own. Imaginative choreography of a variety of treatments is what is required. The informed application of anorectic drugs can play a valuable role in this endeavour.

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Chapter 9

Drug Related Obesity

Many of the drugs used in psychiatric practice to treat major mental illnesses (psychotropics) can lead to a significant increase in body weight, amounting in many cases to frank obesity (Zimmermann et al. 2003; Schwartz et al. 2004). Not only is this undesirable in itself, it frequently prompts patients, particularly women patients, to stop taking their medication, with potentially disastrous results. The classes of psychotropic drugs which are particularly prone to cause significant weight gain are antipsychotics (particularly some of the so-called 'atypical' antipsychotics), certain antidepressants and some mood stabilisers.

1. Antipsychotics

As their name implies these are drugs used in the treatment of psychotic disorders, such as schizophrenia and mania, in which delusions and/or hallucinations are a prominent feature. Antipsychotic drugs are often categorised into two main classes: 'typical' and 'atypical', largely depending on whether they are likely to cause extrapyramidal symptoms, such as tremor, stiffness and lack of emotional facial expression. The 'atypical' antipsychotics (sometimes referred to as 'atypicals') are less likely to cause extrapyramidal symptoms. Both the desired antipsychotic action and the unwanted extrapyramidal symptoms are thought to be due mainly to blockade of central dopamine D_2 receptors. In the case of the atypicals, concomitant inhibition of serotonin 5-HT_{2c} receptors can offset the likelihood of extrapyramidal symptoms developing (Casey and Zorn 2001). However, this action on serotonin pathways is implicated in causing the weight gain which frequently accompanies treatment with many of these compounds (Allison and Casey 2001).

1.1. Typical Antipsychotics

The so-called 'typical' antipsychotics, such as chlorpromazine (*Largactil, Thorazine*) and trifluperazine (*Stelazine*) were introduced into psychiatric practice in the 1950's. Other drugs in this category are, thioridazine (*Melleril*), and haloperidol (*Haldol*, *Serenace*). In addition, fluphenazine (*Modicate*), flupenthixol (*Depixol*) and haloperidol (*Haldol decoanate*), which

are administered as a long-acting intramuscular depot injection, are frequently employed in the long-term management of chronic schizophrenia. All these compounds are prone to cause extrapyramidal side effects. In addition, weight gain, largely brought about by a drug-induced increase in appetite, was recognised early on as a common side effect accompanying treatment with these compounds (McIntyre et al. 2001). Thioridazine is the most likely of them to cause weight gain; haloperidol the least likely (Allison and Casey 2001). On average, patients on these drugs gain some 4 kg in the first three months of treatment. Depot injections are particularly prone to cause obesity. In our sample of 226 patients treated with depot antipsychotics, 42% of the male patients and 49% of the females became obese (Silverstone et al. 1988; Ganguli 1999).

It is believed that the weight gain observed in patients being administered 'typical' antipsychotics is related to the antagonist action of these drugs at acetyl choline, serotonin and histamine-1 receptors.

1.2. 'Atypical' Antipsychotics

1.2.1. Clozapine Clozaril

Clozapine drug was first introduced for the treatment of schizophrenia in the 1960s. While it proved very effective and caused fewer extrapyramidal side effects than the other antipsychotics available at the time, it was later found to lead to potentially fatal agranulocytosis, and was withdrawn from the market. However, subsequent clinical trials using gradually escalating doses accompanied by close clinical and haematological monitoring, showed it to be effective in patients with chronic schizophrenia who had failed to respond to other antipsychotic drugs. This led to clozapine becoming re-established as the treatment for otherwise drug-reistant schizophrenia. Unfortunately, patients taking clozapine frequently gain a great deal of weight. In one study involving 51 patients treated over 12 months, 70% gained a mean of 7.5 kg (Briffa and Meehan 1998). In other trials, one third to one half of the patients treated with clozapine gained more than 10% of their pre-treatment weight, with most of the weight gain occurring in the first 12 weeks of treatment (Zimmermann et al. 2003).

1.2.2. Olanzapine (Zyprexa)

Significant weight gain is also a prominent side effect accompanying olanzapine treatment. Over half the patients treated are affected (Sprague et al. 2004). This often leads to reduced compliance, with subsequent relapse

of psychotic symptoms. The increase in weight is mainly due to an increase in calorie intake, secondary to an increased appetite, rather than to a reduction in energy expenditure (Gothelf et al. 2002). Insulin resistance, leading to type II diabetes, which is not always weight-related, and hyperlipidemia are other troubling consequences of treatment with olanzapine, and clozapine (Melkersson and Dahl 2004; Sprague et al. 2004).

The precise pharmacological mechanism by which clozapine and olanzapine promote an increase in food intake is uncertain (see Chapter 3). Olanzapine is known to affect 19 receptor sites involved in the regulation of food intake (see Chapter 1). 5-HT_{2c} receptors probably play a key role. Leptin may also be involved, as, unlike what happens in drug-free patients, there is little correlation between the amount of weight gained and the level of leptin.

1.2.3. Risperidone (Risperdal)

Risperidone, can cause modest weight gain which does not appear to be dose related (Nasrallah 2003). It is less troublesome in this respect than either clozapine or olanzapine; patients gain a mean of 2–3 kg in the first 10 weeks and 3–6 kg over the longer term. Weight gain is more likely in younger patients (Safer 2004). This may be related to the drug's higher affinity for 5-HT_{2a} receptors and its lower affinity for 5-HT_{2c} receptors.

1.2.4. Quetiapine (Seroquel)

Results from several clinical trials have shown that short-term quetiapine treatment is accompanied by modest weight gain that is not dose-related (Nasrallah 2003). When quetiapine is used as a long-term monotherapy it is weight-neutral.

1.2.5. Ziprasadone (Geodon)

Ziprasadone is an effective antipsychotic with less propensity to cause weight gain than risperidone (Addington et al. 2004). It is a potent 5-HT_{1a} receptor agonist and 5-HT_{2c} antagonist as well as being an inhibitor of serotonin reuptake. These multiple actions on serotonin pathways are probably responsible for it being weight neutral.

1.2.6. Aripiprazole (Abilify)

Aripiprazole is a clinically effective antipsychotic drug which acts as a partial agonist at D2 and 5-HT1A receptors and an antagonist at 5-HT2A receptors. It does not cause significant weight gain in most patients (Gupta

and Masand 2004). In a comparative, 6-month clinical trial of olanzapine and aripiprazole, only 14% of the patients on aripiprazole gained weight compared to 37% of those on olanzapine. Overall, the mean weight loss in those taking aripiprazole was 1.37 kg, compared to a mean weight gain of 4.23 kg in those receiving olanzapine. Increases in serum cholesterol and triglyceride levels paralleled the weight gain (McQuade et al. 2004).

Thus, there appears to be a hierarchy of antipsychotic drugs with differing propensity for causing weight gain. It is very high for clozapine and olanzapine; high for quetiapine, zotepin, chlorpromazine, and thioridazine; moderate for risperidone and sertindole; and lower for ziprazidone, amisulpiride, haloperidol, fluphenazine, pimozide, and molindone (Baptista et al. 2002). Furthermore, clozapine and olanzapine are the most likely to impair glucose tolerance and produce a worsening lipid profile; therefore they should be used with caution in patients with pre-existing diabetes and hyperlipidemia. Ziprasidone and aripiprazole are the least likely of the atypical antipsychotics to have adverse effects on body weight, blood sugar and blood lipids.

1.3. The Management of Antipsychotic-Induced Weight Gain

The first stage in the management of antipsychotic-induced weight gain is to try to prevent it occurring in the first place. Patients taking these drugs should be encouraged to maintain a suitable diet and make adjustments to their life style, such as taking regular exercise. The FDA now requires all patients being treated with an atypical antipsychotic drug to have regular monitoring of blood sugar levels and of plasma lipids. If weight gain has already occurred, the need for dietary intervention is even more pressing. This should be supervised by a trained dietician, and form part of a comprehensive behaviour modification programme (Birt 2003). In parallel, the antipsychotic medication should be reviewed. If there are no clinical contraindications, an antipsychotic with a low propensity to promote weight gain, such as ziprasidone (*Geodon*) or aripiprazole (*Abilify, Abilitat*), should be substituted.

If weight gain remains troublesome despite these measures, the addition of an antiobesity drug may be considered. However, there are a number of potential problems associated with prescribing an antiobesity drug to a patient with psychotropic-related weight gain. These include pharmacokinetic interactions, whereby the anti-obesity drug interacts with the pre-existing psychotropic medication, causing an alteration in its plasma level. If this rises, toxic side effects may occur; if the plasma level falls, the

therapeutic action of the psychotropic is likely to be prejudiced. Pharmacodynamic interactions (in which one drug interferes with the therapeutic action of the other) may give rise to unforeseen consequences. With these considerations in mind, and if the previous measures prove unsuccessful, cautious introduction of an antiobesity drug may be justified to help counter the socially undesirable and health-threatening weight gain. Unfortunately, there have been relatively few good intervention studies to help guide prescribing in this area.

Of the antiobesity drugs currently available, sibutramine (*Meridia*) (see Chapter 10) may be considered (Werneke et al. 2002). Should this be prescribed, blood pressure needs to be monitored closely. In addition, should a patient also be taking an SSRI antidepressant, there is an increased risk of the serotonin syndrome (hypertension, tachycardia, myoclonus, and confusion). An alternative anti-obesity drug is the lipase inhibitor, orlistat (*Xenical*). But the potentially antisocial side effects of that drug may further increase stigma and counter attempts at rehabilitation. Other drugs which have been reported as being helpful in reducing antipsychotic induced weight gain include: amantidine (*Symadine; Symmetrel*), an antiparkinsonian agent; nizatidine (*Axid*), a histamine H_2 receptor antagonist; topiramate (*Topomax*) an anticonvulsant with agonist activity at 5-HT_{2c} receptors (Faulkner et al. 2003). In addition, reboxetine (*Edronax, Vestra*) a norepinephrine reuptake inhibitor antidepressant, has been shown to reduce olanzapine-related weight gain (Poyurovsky et al. 2003). There have been no systematic trials of any of these medications in antipsychotic-induced obesity.

2. Antidepressants

Major depressive disorder, particularly when it is of the melancholic type, is typically accompanied by a lowering of appetite and a disinclination to eat. This can lead to significant weight loss during the course of the illness. With successful treatment with an antidepressant drug, the mood lifts and appetite returns, leading to a regain of the weight lost. Such weight gain, which is part of the process of recovery, must be distinguished from that which can occur as an unwanted side effect of the antidepressant medication. Certain patients with so-called ‘atypical depression’ display what have been called ‘reversed vegetative symptoms’, such as somnolence (rather than insomnia) and increased appetite leading to weight gain (rather than anorexia and weight loss).

Several antidepressant drugs are noted to cause a significant increase in body weight, over and above that due to recovery. That is not only

undesirable in itself, it often leads to the patient discontinuing taking the medication, with a consequent return of the symptoms of depression (Fava 2000). In one prospective six-month study, 44% of the patients on amitriptyline and 70% those on nortriptyline stopped taking their medication because of weight gain (Zimmermann et al. 2003).

The antidepressant drugs are generally classified according to their chemical structure (e.g., 'tricyclic antidepressants' [TCA]) or according to their pharmacological action (e.g., 'monoamine oxidase inhibitors' [MAOI]; 'serotonin reuptake inhibitors' [SSRI]). Certain other antidepressants, which do not fall into the above categories, are sometimes referred to as 'atypical' antidepressants (see below).

2.1. Tricyclic Antidepressants (TCA)

Were the first compounds found to be effective in the treatment of severe depressive illness and were introduced into clinical practice in the 1950s. Pharmacologically, they inhibit, each to a variable degree, the reuptake of noradrenaline, dopamine and serotonin by presynaptic neurones in the brain. They can thus be considered as 'non-specific reuptake inhibitors', although they are rarely referred to as such; the chemical descriptor 'tricyclic' (from the three conjoined benzene rings which forms their core structure), having become the name by which they are known.

2.1.1. Amitriptyline (Tryptizol, Elavil)

Soon after its introduction, amitriptyline was found to cause significant weight gain, often secondary to an increased desire for sweet foods (Paykel et al. 1973). It is the most likely of the tricyclic antidepressants to do this (Fernstrom 1995). In one study involving 51 women who were taking amitriptyline, the average weight gain was 4 kg, in another it was 7 kg; the amount gained being related to the dose.

2.1.2. Imipramine (Tofranil)

Weight gain, although it occurs during treatment with imipramine, is less consistent. Some 13% patients treated with imipramine for 33 weeks on average, had a 10% increase in body weight; 15% of patients in another trial had a weight gain of 4.5 kg or more after 16 weeks of treatment (Fava 2000).

It is probably relevant that the antidepressant drugs with a high affinity for alpha-adrenergic receptors are associated with weight gain, whereas those with a lower affinity, such as serotonin reuptake inhibitors (SSRI), are not (Virk et al. 2004).

2.2. Monoamine Oxidase Inhibitors (MAOI)

Of the monoamine oxidase inhibitors, phenelzine (*Nardil*) is the most likely to cause weight gain (Zimmermann et al. 2003). Treatment with moclobemide (*Manerix*), a reversible inhibitor of monoamine oxidase A, is not accompanied by any consistent increase in body weight (Silverstone 1993).

2.3. Selective Serotonin Reuptake Inhibitors (SSRI)

In general, weight gain is not a problem with SSRIs. Of those currently available, only paroxetine has been consistently noted to cause weight gain (Zimmermann et al. 2003). In a double-blind comparative clinical trial of fluoxetine, sertraline and paroxetine, 25% of patients assigned to treatment with paroxetine experienced a an increase in their body weight of 7% or more, compared to 6.8% on fluoxetine and 4.2% on sertraline (Fava et al. 2000).

2.4. Other Atypical Antidepressant Drugs

2.4.1. Bupropion (Wellbutrin)

Bupropion is more frequently associated with modest weight loss rather than weight gain (Croft et al. 2002). This is hardly surprising, given its close chemical similarity to the appetite suppressant compound diethylproprion.

2.4.2. Mirtazepine (Remeron)

Mirtazepine has specific noradrenergic and serotonergic receptor activity. It also has significant histamine H_1 and serotonin 5-HT_2 receptor blocking activity which probably underlay its propensity to cause weight gain, both acutely and in the long term (Cassano and Fava 2004).

2.4.3. Nefazodone (Serzone)

Nefazodone is a relatively weight neutral antidpressant (Sussman et al. 2001). Because of its liability to cause liver failure it has been withdrawn from the market in Canada.

2.4.4. Venlafaxine (Effexor)

Venlafaxine is an antidepressant drug which selectively inhibits the reuptake of noradrenaline and serotonin. It does not appear to be associated with weight gain (Silverstone and Ravindran 1999).

2.5. Conclusion

Of the antidepressants, the most likely to cause weight gain are the tricyclics amitriptyline, imipramine and clomipramine, plus mirtazepine. The SSRI, with the possible exception of paroxetine, are unlikely to do so (Zimmermann et al. 2003).

3. Mood Stabilisers

3.1. Lithium

Long term treatment of bipolar disorder with lithium commonly leads to weight gain. Up to a quarter of patients in long-term follow-up studies become clinically obese (Chen and Silverstone 1990). The weight gain, which adversely affects compliance, is due mainly to an increased consumption of high-calorie sweetened drinks brought about lithium-induced thirst (Elmslie et al. 2001). In a double-blind placebo-controlled trial, 13 of 21 patients (62%) on lithium gained at least 4.5 kg in the first year of treatment, compared to only one of the 12 patients (8%) on placebo (Peselow et al. 1980). In normal subjects, lithium has no direct effect on appetite or food intake (Chen et al. 1992).

3.2. Anticonvulsants

Following the observation in 1973 that the anticonvulsant drug carbamazepine was effective in the treatment of acute mania, a number of other anticonvulsants have been evaluated as treatments for bipolar disorder. Many of them (carbamazepine, valproic acid, and its derivative sodium valproate, and gabapentin) cause weight gain (Jallon and Picard 2001; Keck and McElroy 2003). Others, such as lamotrigine and topiramate, are associated with weight loss, with topiramate having been recommended as an adjunct to dietary treatment for psychotropic-induced obesity.

3.2.1. Carbamazepine (Tegretol)

Reports of weight gain with carbazepine have been variable. Gains of 10 kg or more have been reported in up to 20% patients being treated with carbamazepine, while others have reported little or no weight gain (Jallon and Picard 2001; Vanina et al. 2002). Carbamazepine is less likely than lithium to cause weight gain. In a 12-month double-blind controlled comparison of lithium and carbamazepine in the prophylaxis of bipolar disorder, we found that the patients receiving carbamazepine tended to

lose weight, compared to those on lithium who generally gained weight (Coxhead et al. 1992).

3.2.2. Sodium valproate and divalproex (Depakote, Epival)

Significant weight gain is a frequent accompaniment of treatment of bipolar disorder with valproate (Chengappa et al. 2002; Vanina et al. 2002). Among patients with epilepsy taking valproic acid as an anticonvulsant 70% gained 4 kg or more in a median period of 27 months (Corman et al. 1997). In a 47-week study comparing olanzapine and valproate in the treatment of mania, the patients who received valproate gained a mean of 1.2 kg compared to 2.8 kg in those who received olanzapine (Tohen et al. 2003). In women, such valproate-related weight gain may be accompanied by hyperandrogenism and polycystic ovaries (Isojarvi et al. 1996).

3.2.3. Gabapentin (Neurontin)

This analogue of gamma aminobutyric acid (GABA) has been found to have modest antidepressant effects in bipolar patients (Ketter et al. 2003). Among patients with epilepsy, a weight gain of more than 10% of base weight was reported in 23% of those taking gabapentin (DeToledo et al. 1997).

3.2.4. Topiramate (Topomax)

Topiramate appears to be effective in the management of bipolar depression and, possibly, in the prophylaxis of bipolar disorder. It does not cause weight gain, if anything it leads to weight loss (Chengappa et al. 2002). When combined with olanzapine, topiramate prevents long-term weight gain (Vieta et al. 2004).

3.2.5. Lamotragine (Lamictal)

Lamotragine has been shown to be effective in the treatment of bipolar depression. It does not cause weight gain (Bowden et al. 2004).

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Chapter 10

Eating Disorders and Obesity in Childhood and Adolescence

1. Eating Disorders

The eating disorders, anorexia nervosa and bulimia nervosa frequently begin in adolescence, particularly around puberty. Symptoms of anorexia nervosa can appear even earlier (Watkins and Lask 2002). The essential features of adult anorexia nervosa in adults (an intense fear of weight gain; a belief that one is too fat, although of normal weight; emaciation – being less than 85% of expected weight for height and age) also characterise the condition in younger patients. The exact prevalence of anorexia nervosa in childhood is uncertain, as no reliable epidemiological studies have been undertaken in this age group. What does appear, however, is that, among younger patients, boys constitute a larger proportion of those afflicted (19% of cases), than in older adolescents where they make up 5–10% of the total (Hawley 1985). Bulimia nervosa is rare in childhood.

1.1. Diagnosis

The DSM-IV criteria for anorexia nervosa do not always apply in children and young adolescents. Children may become malnourished, and therefore at risk, more quickly than adults. In such cases, the diagnosis must be based on a failure to grow and gain weight, rather than an actual weight loss. A weight at, or below, the 5th percentile for age and height is a cause for concern. There are three available sets of criteria for making the diagnosis in children and young adolescents:

(i) The American Psychiatric Association's Diagnostic Manual for Primary Care (DSM PC) – child and adolescent version;
(ii) The Eating Disorder Examination adapted for children (Bryant-Waugh et al. 1996);
(iii) The Great Ormond Street Eating Disorder Criteria (Nicholls et al. 2000).

1.2. Pathology

Structural changes in the brain, which are only partly reversible, have been observed using MRI. In one study, 13 adolescent girls (mean age 15.2 years) with restricting AN, who were receiving inpatient care, showed a significant reduction in total gray and white matter volumes compared to matched controls. These abnormalities persisted after recovery (Katzman et al. 1997).

Brain function in anorexia nervosa has been examined using SPECT. In one study, 13 out of 15 children and adolescents aged 8–16 (14 girls, 1 boy), diagnosed as having anorexia nervosa according to DSM-IV criteria, showed reduced blood flow to one or other of the temporal lobes (8 left, 5 right). In the three patients who were re-examined after recovery, the abnormality remained (Gordon et al. 1997).

1.3. Course and Prognosis

The presence of eating problems in childhood or the appearance of a frank eating disorder in adolescence greatly increases the risk of having an eating disorder in adult life. In one Swedish series of 51 patients presenting with anorexia in their teens, 25% showed symptoms of an eating disorder when examined at age 24 (Rastam et al. 2003). However, half had appeared to have recovered completely. A fatal outcome is extremely rare.

1.4. Treatment

Any treatment program, to be used in the management of an eating disorder in childhood or early adolescence, should closely involve the family. Family members need to be provided with full information about the condition together with the therapeutic objectives, of which weight gain is a major element. A multidisciplinary approach is advised. This should include nutritional information and guidance together with cognitive-behavioural psychotherapy. There has been almost no systematic evaluation of the role of pharmacological treatments in younger patients with eating disorders and they are not generally recommended in this age group. No drug has yet been shown to be effective in the acute treatment of anorexia nervosa, and bulimia nervosa is uncommon before late adolescence. There may be justification for the use of an SSRI antidepressant if there is a marked lowering of mood (Kotler and Walsh 2000).

2. Obesity

Obesity has now become a major public health problem among children and adolescents in the developed world. Obesity is defined in childhood, as in adults, by the proportion of the body weight which is adipose tissue. For most purposes this corresponds to the body mass index (see Chapter 9). A child whose body mass index (BMI) is greater than that of 85% of children of similar age and gender in his or her community, is considered to be overweight; if it is greater than 95% of other children of similar age and gender, that child is defined as obese (Kiess et al. 2001).

2.1. Epidemiology

The number of obese children in the developed world has increased alarmingly in recent years. In 1970 in Europe, less than 5% of children were obese; today well over 10% are. In the US the proportion of children categorised as obese doubled between 1988 and 2000. According to the 1999–2000 National Health and Nutrition Survey (NAHNES) over 10% of children age 2–5 are obese; among those age 6–19 the prevalence rises above 15% (Ogden et al. 2002). In New York City the situation is particularly bad: among children attending elementary school, 24% are obese, with children from Hispanic (31%) and Afro-American (23%) families having higher rates than children from Caucasian (16%) or Asian (14%) families (Thorpe et al. 2004).

2.2. Etiology

2.2.1. Changes in life style

The recent disturbing rise in the prevalence of childhood obesity is thought to be due to a combination of a change in eating habits and a reduction in the level of activity. “Put simply, our current culture consistently and powerfully sends two opposing messages: ‘it’s good to eat’ and ‘it’s bad to be fat.’ (Schwartz and Puhl 2003). As far as eating is concerned, in the US, children’s consumption of sugar-containing soft drinks and high fat fast foods has almost trebled in recent years.

Reduction in energy expenditure probably plays an equally important role in the pathogenesis of childhood obesity. In much of the developed world children no longer walk to school. Fewer are engaged in physically demanding games and sports with less emphasis being placed on such activities in many schools. Compounding this reduction in physical activity is an increase in the amount of time spent in sedentary pursuits, such as

watching television or playing computer games. It is estimated that children in US households currently spend over three hours a day watching TV. A Swiss study found that the use of electronic games was significantly associated with obesity, independently of confounding factors (Stettler et al. 2004). Children, especially girls, of socially disadvantaged families are at greater risk. Breast feeding has "a small but consistent protective effect" (Arenz et al. 2004).

There are three critical periods for the development of childhood obesity: during gestation; the time of the 'adiposity rebound' age 4–6, when BMI increases after an initial fall in early life; adolescence. An earlier adiposity rebound is associated with increased fatness in adolescence (Baur and O'Connor 2004). A longitudinal prospective study, from birth to age 7, of 11,000 children born 1991–92, carried out in the south west of England, showed that childhood obesity is related to the mother's level of education, the child's birth weight, whether or not the mother smokes, parental obesity and the amount the family watches TV (Ness 2004).

2.3. Genetics

2.3.1. 'Simple' obesity

This is a multifactorial condition in which environmental and genetic factors interact. Twin studies suggest a heritability of fat mass (fraction of the age adjusted phenotypic variance accounted for by genetic factors) of between 40% and 70%, with a concordance of 0.7–0.9 between monozygotic twins compared to 0.35–0.45 between dizygotic twins. While these associations may in part be explained by sharing the same childhood environment, a number of studies have described a closer relation between the weights of adoptees and their biological parents, than with their adoptive parents. This suggests that there is an important hereditary component in the etiology of obesity in childhood and adolescence. Whether this mediated mainly through changes in energy output or energy input remains uncertain. Recent studies, however, have indicated that genetic variation in energy output plays a major role via mitochondrial uncoupling proteins in muscle (Harper et al. 2002). This finding may go some way to explaining why some children are fatter than others.

2.3.2. Single gene obesity

Only in relatively rare conditions, can the obesity be attributed to a single gene or group of genes. These include human congenital leptin deficiency,

and mutations in the pro-opiomelanocortin gene and the melanocortin receptor (Clement et al. 2002). Patients with congenital leptin deficiency have been successfully treated with injections of leptin.

The *Prader–Willi syndrome* (PWS) results from the absence of expression of the paternally derived alleles of maternally imprinted genes in a critical region on chromosome 15 (Goldstone 2004). It has a prevalence of 1 in 10,000–25,000 live births. PWS is characterised by: intellectual disability; severe muscle hypotonia, a voracious appetite leading to relentless food seeking and overeating, gross obesity, hypogonadism, short stature and skeletal deformities such as small hands and feet, kyphosis, scoliosis and osteoporosis. There are two types: in one, there is foetal growth retardation, and severe hypotonia is noted at birth; in the other type, abnormalities are not evident much before the age of two, when overeating starts to become a major problem. Developmental delay, together with the other characteristics listed above, are also noted at this time. PWS is associated with a deficiency of growth hormone, and treatment with growth hormone improves linear growth and leads to an increase in muscle mass, bone mineral density and physical performance (Lee 2002).

In later life PWS is frequently associated with compulsive behaviour such as skin picking, hoarding, concerns with symmetry, ordering and arranging (Dykens and Shah 2003). Such behaviour might reflect an underlying disturbance in central serotonin neurotransmission as patients are responsive to treatment with serotonin reuptake inhibitors (Dimitropoulos et al. 2000).

2.3.3. Hypothalamic lesions

Damage to hypothalamus following trauma or compression by a neoplasm can cause obesity, which is often stubbornly resistant to treatment.

3. Pathology

3.1. Medical

As in adults, obesity in childhood is associated with a number of serious medical conditions. These include high blood pressure, impaired glucose tolerance (often leading to frank type II diabetes mellitus) and dyslipidaemia. It used to be thought that only adults were at risk for type II diabetes mellitus. In recent years however, with the rapidly rising number of severely obese children in the developed world, type II diabetes is becoming increasingly recognised in this age group. The proportion of

all cases of diabetes who present in childhood and adolescence rose from 4% to 20% in the 10-year period 1990–2000 (Baur and O'Connor 2004). A recent epidemiological survey estimated that the combined prevalence of childhood type II diabetes and maturity onset diabetes in 16-year olds in the UK is 0.39 per 100,000 (Ehtisham et al. 2004). Children from ethnic minorities are particularly at risk.

Other medical problems include gallstones, fatty liver and oesophageal reflux.

3.2. Psychosocial

Obese children are at a considerable social and psychological disadvantage from stigma and social rejection. They are discriminated against by their contemporaries and by many adults. In keeping with this sad state of affairs, they tend to have low self-esteem, which may go on to frank symptoms of depression. They are frequently the butt of bullying and, paradoxically, many obese girls become bullies themselves.

4. Treatment

Treatment should be based on encouraging and assisting the obese and overweight child to reduce his or her calorie intake, and increase energy output through exercise. It has been found that a concerted collaborative effort using a behavioural approach which involves the child, his or her family and school is the most likely to achieve success (Wilson et al. 2003). The aims of such treatment programs are to develop healthy eating habits and encourage increased physical activity Those who adhere to such a programme often do well; unfortunately most do not comply.

Drugs are generally not recommended in the treatment of childhood obesity and no controlled trials of antiobesity drugs have been carried out in children in recent years. Orlistat (*Xenical*), which is not absorbed from the gastrointestinal tract and has no systemic side-effects, has been used successfully in a small pilot study involving 11 severely obese prepubertal children aged 8–12 (Norgren et al. 2003). The US Food and Drug Administration has recently approved the use of orlistat 120 mg tid for the treatment of overweight and obese 12–16 year olds. Both it, and another antiobesity drug, sibutramine, (see Chapter 3) are undergoing placebo-controlled trials in children and adolescents.

If drugs are used they should be combined with ongoing behaviour therapy and nutritional counselling involving the family.

Children suffering from type II diabetes may benefit from the hypoglyemic compound metformin if standard diet and exercise programmes prove unsuccessful. Two patients in Japan with Prader–Willi syndrome, have been reported as benefiting from the centrally-acting appetite suppressant, mazindol.

5. Prognosis

Unfortunately, both the short term and the long term prognosis for obesity in childhood is not good. Most overweight children remain overweight. Furthermore, childhood overweight is significantly associated with severe obesity in adult life with all the medical complications that brings (Ferraro et al. 2003).

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Chapter 11

Disorders of Eating, Weight and Appetite in Later Life

1. Anorexia of Aging

The most common eating-related concern in the elderly is that of not eating enough to maintain nutritional balance. This is largely a result of the decline in appetite (often referred to as 'age-related anorexia'), which frequently accompanies aging. Healthy older people are generally less hungry and become sated more rapidly than younger persons (Sturm et al. 2003). This often leads to an unintentional reduction in food intake, causing a failure to preserve steady state levels of body weight and energy stores, even in the absence of obvious ill health. The decline in food consumption becomes particularly prevalent after the age of 75. According to the National Health and Nutritional Survey carried out in the United States (NHANES III), the average daily calorie intake among 80-year olds is 30% less than that of those in their 20s. Much of this reduction in intake parallels the fall in energy output associated with advancing years. However, in many, the fall in intake exceeds the fall in output, leading to a loss of weight. Much of the weight which is lost reflects a reduction in lean body mass more than a reduction of adipose tissue. The ensuing protein-energy malnutrition causes muscle weakness and reduced mobility, which further compound the problems of ageing. It is also a major cause of morbidity and increased mortality. Unfortunately, age-related anorexia and weight loss often goes unrecognised and untreated. Over 5% of the elderly population living in the community have been found to be malnourished; this proportion rises to 30% among residents of nursing homes in the US.

The anorexia of aging can be due to a variety of psychosocial, physiological and clinical factors.

1.1. Psychological

One of the causes of the anorexia of aging is the loss of the motivation to eat, which is frequently secondary to a depressed mood. In fact, depression is one of the most important treatable causes of weight loss among the elderly in both community and institutional settings. It should always be

considered as a possible cause of failure to thrive. Bereavement, followed by a debilitating grief reaction, is a common precipitant of depression in older people.

When they occur, depressive symptoms should be treated actively using a combination of cognitive-behavioral therapy and an antidepressant drug. Of the available antidepressants, selective serotonin reuptake inhibitors (SSRIs) have the most favourable combination of efficacy and side-effect profile for the elderly, regardless of the presence of medical co-morbidities. Although the dual agent venlafaxine has been proposed as an alternative agent for older patients who are either non-responders or partial responders to SSRIs, the frail elderly may be particularly vulnerable to its side effects (Hayes 2004).

1.2. Social

With advancing years comes loss or deterioration of social networks (Donini et al. 2003). One's friends and contemporaries die off, or move into sheltered accommodation some distance away, making visiting less easy. Travel becomes more difficult, particularly if driving is restricted because of failing eyesight or other infirmity. Stopping work compounds the problem as it cuts off another set of social contacts. Thus, loneliness is a frequent accompaniment of old age.

With the loss of earnings, relative poverty may become an issue, particularly for those having to live on a small fixed income, or having to get by on welfare. Hospitalization, or having to live in a nursing home or other institution, brings its own set of social consequences. Living alone can also prove difficult. With increasing infirmity come an inability to shop, an inability to feed oneself, and inability to prepare and cook meals, all of which can contribute to decreased food intake. Old people living in nursing homes often do not particularly care for the food provided or are put off by their fellow residents' eating habits. One way of addressing some of these problems is providing 'meal mates', young people who volunteer to provide company and encouragement to elderly people in institutions (Robinson et al. 2002).

1.3. Physiological

A blunting in taste and olfactory sensitivity, which commonly accompanies ageing, tends to make food less appetising and reduces the motivation to eat. One way to address this problem is to make sure the food is presented in an attractive manner and that it is tasty. Commercially available

taste enhancers can amplify the taste of the food presented, and thereby promote eating.

The central feeding drive, mediated by neuropeptides such as neuropeptide Y (see Chapter 1), declines with age. Such disturbances in the physiological mechanisms regulating food intake impair the ability of older people to increase their energy consumption to compensate for a previous period of undereating (Roberts et al. 1994). Plasma levels of ghrelin, a peptide produced by the stomach which acts as a stimulus to eating (see Chapter 1), fall with increasing age, further reducing the drive to eat (Rigamonti et al. 2002).

Satiety mechanisms also are affected by the ageing process. The elderly become sated earlier in the meal due to a decrease in the adaptive relaxation of the fundus of the stomach, resulting in early filling of the antrum. Another factor leading to early satiation is a rise in the level of cholecystokinin (CCK). Not only is the secretion of CCK increased, sensitivity to its action rises (Chapman et al. 2002). Both these factors lead to elderly people ingesting smaller meals, which they eat slowly. Despite these findings, some believe that reduced basal hunger and appetite may be a more important cause of the anorexia of aging than increased meal-induced satiety. That view is based on the observation that voluntary food intake in older subjects was not suppressed by the ingestion of an oral nutrient preload in undernourished older subjects to the same degree as in younger subjects (Sturm et al. 2003).

1.4. Clinical

1.4.1. Physical illness

Common medical conditions in the elderly such as gastrointestinal disease, malabsorption syndromes and acute and chronic infections often cause a loss of appetite. Another common problem is ill-fitting dentures. All these situations need to be addressed to promote adequate nutrition.

Many drugs used for the treatment of physical illness affect appetite. Mostly they reduce it. Thus, a possible iatrogenic cause should be considered in the management of otherwise unexplained loss of weight in the elderly.

1.5. Treatment

A necessary first approach in the management of the anorexia of aging is to be aware of the possibility of its presence. Always consider it when

presented with an elderly patient who is of less than optimal weight. Treatment efforts should be directed towards providing a nutritionally sufficient diet and giving frequent encouragement to eat.

2. Eating Disorders

2.1. Anorexia Nervosa

Although people with a lifelong history of anorexia nervosa frequently live to a relatively old age, the illness rarely has its onset in this age group. However, there are exceptions. A series of patients who fully met DSM-IV criteria for the various types of eating disorder, and whose illness began in later life, have been well described (Beck et al. 1996). In keeping with these findings, a survey of undernourished elderly males revealed a high preponderance of abnormal attitudes to eating and body image (Miller et al. 1991).

The age record to date for anorexia nervosa is probably held by a woman in New York, otherwise in good health, who presented with all the features of anorexia nervosa for the first time at the age of 92 (Mermelstein and Basu 2001). Such presentations of what has been termed 'tardive anorexia', can confront geriatricians with a difficult diagnostic dilemma, if the possibility of an eating disorder is not borne in mind. Typically, the eating disturbance is triggered by a severe life stress, such as a bereavement. In other cases, patients who had an eating disorder in adolescence, but had been well for years, can have their condition rekindled in the course of a grief reaction in late life (Gowers and Crisp 1990).

Treatment should be multifaceted and include the following components: (i) dietary management; (ii) cognitive-behavioural therapy focused on body image, food, and weight related constructs; (iii) resolution of any underlying social and family problems. Pharmacotherapy with an SSRI is often beneficial in addressing co-existing obsessional or depressive symptoms. A word of warning: when prescribing for the elderly anorectic the dose of psychotropic drug must be adjusted to take account of the patient's physical condition and reduced metabolic and renal function.

2.2. Bulimia

Typical bulimia nervosa very rarely arises for the first time in the elderly. However bulimic behaviour can be a symptom of Parkinson's disease (Rosenberg et al. 1977). Effective treatment of the underlying condition usually leads to complete resolution of any eating problem.

Excessive eating may also be associated with dementia, especially in those whose dementia is characterized by wandering behaviour (Smith et al. 1998). Restricting access to food usually proves an effective strategy for dealing with this symptom.

3. Obesity

The elderly form an ever-increasing proportion of the population in the developed world, with those aged over 65 accounting for over 15%. On average, BMI rises until the age of 65 and then starts to fall, largely reflecting a loss of muscle mass (Elia 2001). Furthermore, with increasing age, adipose tissue replaces fat-free mass. Thus, in older subjects, BMI does not reflect the amount of fat in the body in the same way it does in younger people.

3.1. Causes

Most cases of obesity seen in older subjects simply reflect the extension of a long-standing problem into later life. However, troubling weight gain can occur for the first time in the elderly. Two common causes of this are a reduced energy output, and medications which stimulate eating.

3.1.1. Reduced energy output

Many people find that their mobility becomes less as their age advances. Not only do they become less robust, locomotor problems, often secondary to arthritic conditions, supervene. These further restrict the opportunities for exercise. If calorie intake is not reduced to compensate for reduced energy expenditure, weight gain is likely to ensue, sometimes to the point of frank obesity. To prevent this happening, as well as to reverse any unwanted weight gain, dietary counselling should be offered.

3.1.2. Medication

Certain drugs, particularly some tricyclic antidepressants such as amitriptyline, increase the desire for sweet foods. If this goes unchecked, considerable weight gain can result. This further impairs mobility, leading to even more weight gain. Other drugs, particularly antipsychotics like olanzapine have an even greater propensity to cause weight gain (see Chapter 10).

3.2. Mortality

The effect of weight gain on mortality in the elderly is uncertain. Obesity has less of an effect on mortality than it does in younger subjects and the optimal BMI is higher.

3.3. Treatment

The case for weight reduction is less pressing in the overweight elderly, unless obesity-related complications such as diabetes, arthritis or respiratory disease are present. In such cases, appropriate dietary advice and a controlled exercise programme are recommended. Centrally-acting appetite suppressant drugs, such as sibutramine (see Chapter 8), are not generally recommended in this age group because of their effects on the cardiovascular system. If they are prescribed, close monitoring is required. Orlistat may be helpful, but its gastrointestinal side effects can prove to be a problem, particularly if bowel control is already compromised. No clinical trials of these drugs have been carried out in the elderly, who are usually excluded from such studies.

4. Conclusion

It is clear that no age group is free of vicissitudes in eating and body weight. Eating behaviour exemplifies a complex bio-psycho-social activity, which can be readily deranged at any point in the life cycle. It is perhaps remarkable that so many people get by without major problems.

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