Progress report

Normal and abnormal food intake

The control of food intake is of central importance in the maintenance of physiological energy balance. Nevertheless, knowledge of appetite control in man is fragmentary.

Food intake is altered according to prevailing energy requirements; when these are increased by, for example, lactation, growth, exercise or a cold environment intake is increased. Appetite control occurs on a basis of alternating hunger and satiety, the degree of hunger and the amount of food needed to produce satiety being altered by demands for energy at any given moment. This pattern provides a background but it can be modified or overridden by higher influences such as custom, pleasure and the psychological state of the individual.

Until recently the major control imposed on food intake was the availability of food as the abundance of food in the western hemisphere is a relatively new situation. In such circumstances fine control mechanisms to diminish slight, but chronic, overeating are not often called upon although short-term mechanisms to prevent gross overeating are still necessary. This may be important when considering why what seems, at first sight, to be a basic physiological mechanism should break down so frequently in the face of unlimited availability of food. The result of this breakdown is obesity.

Physiological Mechanisms Controlling Food Intake

APPETITE CONTROL CENTRES

Hypothalamus
In many species the hypothalamus is an important site at which energy requirements are translated into feeding behaviour. Bilateral lesions in the ventromedial nuclei result in hyperphagia and obesity whereas lesions in the lateral nuclei result in diminished appetite. The ventromedial nucleus acts as a satiety centre which controls a chronically active feeding centre in the lateral nucleus.

Other brain centres
Appetite is also influenced by areas of the brain outside the hypothalamus and the role of the extrahypothalamic sites has been comprehensively reviewed by Grossman. The limbic system provides an important pathway by which higher influences such as emotion, pain and custom can affect autonomic and hypothalamic function including appetite control.

CONTROL MECHANISMS
Appetite control can be differentiated into short- and long-term mechanisms. The short-term mechanisms regulate the size and frequency of meals and must act rapidly since satiety occurs even before absorption of a meal is
Normal and abnormal food intake

complete. Long-term regulation is poorly understood but there is indirect evidence\textsuperscript{14,15,16} that the appetite control centres are set to maintain a particular level of body fat stores and that in some unknown way there is a feedback to the hypothalamus from these fat stores. Knowledge of the mechanism of this feedback might be extremely helpful in a fuller understanding of appetite control in obesity. Presumably the long-term control mechanism adjusts the sensitivity of the short-term mechanisms according to the energy requirements of the individual.

Gastrointestinal tract

The hypothalamus receives information from the gastrointestinal tract which is of great importance in bringing about satiety. Sensory neurological input from the gut is extremely important in controlling food intake in some lower animals; thus denervation of the foregut of the blow-fly\textsuperscript{14} leads to such extreme hyperphagia that the gut may be ruptured by the quantity of food ingested. Fortunately vagotomy does not have the same effect in man.

The smell of food causes salivation, gastric secretion, increased awareness of hunger and alteration of activity in the hypothalamic feeding centres\textsuperscript{17}. Passage of food through the mouth results in a small degree of satiety\textsuperscript{18}.

Hunger is associated with epigastric pangs and these coincide with waves of contraction in the stomach\textsuperscript{19} (gastric hunger contractions). It seems reasonable that as these contractions result in hunger pangs they should be an important cue that food is required at that time; however, the evidence for the importance of hunger pangs in appetite control is conflicting. That frequency of hunger pangs is increased when the arteriovenous differences in glucose concentration is low\textsuperscript{20} and decreased when neurological activity in the satiety centre is high\textsuperscript{21} suggests a role in appetite control but they also show considerable automatism and may be unchanged in animals with severely deranged appetite control\textsuperscript{22}.

Gastric distension is important in the short-term control of intake and produces increased neuronal activity in the satiety centre\textsuperscript{23,24}, possibly mediated by vagal afferent fibres from stretch receptors in the stomach wall\textsuperscript{25}. Connexions exist between the nucleus of the vagus in the brainstem and the appetite centres in the hypothalamus\textsuperscript{26}. Distension of the bowel beyond the stomach influences food intake to a lesser degree\textsuperscript{27,28}.

Chemoreceptors in the gut are also involved in control of intake. Feeding is moderately depressed by distension of the small bowel with water, but when a nutrient such as glucose is added a much greater inhibition of feeding results\textsuperscript{29}. There are also chemoreceptors in the stomach and, in animals, the introduction of glucose solutions into the stomach alters neuronal activity in the region of the hypothalamic feeding centres\textsuperscript{30}. Recording from the vagi and mesenteric nerves after the instillation of glucose solutions into surgically resected specimens of human stomach and small intestine suggests the existence of similar chemoreceptors in man\textsuperscript{31}. These receptors are also sensitive, but to a lesser degree, to peptones, ethyl alcohol and caffeine. The role of pH receptors and osmoreceptors in appetite control has yet to be defined.

Gastrointestinal hormones are released into the portal circulation in response to food and some reach the systemic circulation. They may, therefore, be important in appetite control although their role is still unknown. Glucagon, because of its effect on the blood glucose levels, is an obvious candidate, and it has been shown that the intravenous injection of this
hormone increases electrical activity in the satiety centre of experimental animals. It is not known if enteroglucagon reaching the systemic circulation during and after a meal has important effects on appetite control. Intravenous injection of enterogastrene inhibits feeding in the mouse, whereas injections of secretin and cholecystokinin-pancreozymin are without effect.

**Blood glucose, temperature, and other factors**

In 1955 Mayer suggested that the hypothalamic feeding centres are ‘glucose-static’ and that their activity is controlled by glucose metabolism. Subsequent direct recording from these centres by Anand using microelectrodes has shown that neurological activity correlates well with blood glucose levels and even better with arteriovenous differences in glucose level.

In both man and animals food intake is affected by the ambient temperature, being increased when it is low and decreased when it is high. This relationship led Brobeck to propose that the control of food intake is ‘thermostatic’, suggesting that animals eat to provide energy to keep warm and that short-term temperature increases induced by ingested food are important in regulating the activity of the hypothalamic centres. There are undoubtedly temperature-sensitive neurones in the anterior hypothalamus and preoptic areas which influence the activity of the hypothalamic appetite centres, and temperature changes do occur in the hypothalamus as a result of eating. The role of these temperature changes in appetite control is, however, disputed but hypothalamic temperature sensitivity may be important in adjusting intake to environmental temperature.

Prostaglandins, serum amino acid levels and many hormones, eg, growth hormone, adrenal corticoids, oestrogens, progesterone and prolactin, have all been implicated in appetite control but in most cases their importance is unclear.

**Abnormalities of Appetite Control**

The relationship between weight gain and food intake is more complex than it would seem at first sight. When food intake is increased the metabolic rate is also increased and therefore only some of the excess calories are converted into stored energy. This mechanism may act as a useful buffer in the maintenance of constant energy stores and calculations of the excess food intake resulting in a certain degree of obesity can be misleading.

Anorexia may be unrecognized by patients or their doctors as an important factor in a disease process. Betts and Magrath recently drew attention to diminished food intake as an important aetiological factor in the growth retardation of uraemic children. Extreme weight loss can occur as a result of anorexia in patients treated with digitalis without the patients realizing the extent of their anorexia.

**Obesity**

Obesity resulting from inherited hyperphagia has been described in animals but not, as yet, in man.

Recently evidence has begun to accumulate of abnormalities of appetite control in the obese. Obese subjects are less aware of internal signals indica-
Normal and abnormal food intake

ting hunger or satiety, depending mainly on external cues, eg, visual, and are therefore poor at adjusting food intake to metabolic needs53.

Gastric motility does not differ in obese and non-obese subjects53 but there is a better correlation between episodes of increased gastric motility and sensations of hunger in the non-obese than in the obese, suggesting an insensitivity to this internal stimulus in the obese. A defect in the recognition of satiety may also occur54; prior feeding appropriately reduces subsequent intake in normal but not in obese subjects.

Obese subjects increase their food intake more than non-obese subjects if they find a particular food palatable55 but eat the same amount of unpalatable food as normal subjects. Normal subjects find that with the continued administration of sucrose solutions the sweet taste changes from a pleasant to an unpleasant sensation and this curtails intake. In obese subjects this change does not occur and may explain why palatability is a more potent influence on the intake of the obese than on that of the non-obese56.

The influence on intake of the amount of food presented has been elegantly demonstrated by Nisbett57. Obese and non-obese subjects, unaware of the object of the experiment, were left alone to fill in a questionnaire after taking part in a bogus physiological experiment during which they had missed a meal. They were given either one or three sandwiches on a plate and told that there were plenty more sandwiches available to them. Non-obese subjects ate the same amount whether they were left one or three sandwiches. Obese subjects ate significantly more than the non-obese when left with three sandwiches but less if left with one sandwich. This suggests that they are influenced by immediate availability and in addition are possibly less prepared to 'work' for additional food by getting it for themselves.

Visual cues are important in the obese to control intake. If obese subjects are given a milk shake in a graduated container they eat less if they can see the container than if it is hidden57. Normal subjects take the same amount in both situations. Hashim and Van Itallie58, using a machine that dispenses bland homogenized food with little taste directly into the mouth, have attempted to eliminate as many external cues as possible. They found that under these circumstances non-obese subjects maintain a normal intake but that obese subjects have a strikingly decreased calorie intake.

Experimental studies of the feeding behaviour of overweight neonates59 have suggested defects in appetite control somewhat similar to those of obese adults. The food intake of these babies is affected to a greater extent by palatability than that of infants of normal weight and they are less prepared to 'work' for food than normal when the size of the hole in the teat on their bottle is decreased. These results are interesting, since obese children often become obese adults.

Increased sensitivity to taste and unwillingness to work for food are characteristic of animals with hypothalamic hyperphagia60,61, and the abnormalities of appetite control in the obese human subject have a certain similarity, which leads to speculation about the role of the hypothalamus in the abnormalities in appetite of the obese.

**Psychiatric Disease**

Anorexia nervosa provides one of the most striking examples of deranged appetite62 but its basic mechanisms remain obscure. These patients have evidence of depressed pituitary and hypothalamic function63 but there is no
evidence that this is the primary defect. These patients have a marked disturbance of body image (the way they see their body) and persistently overestimate their dimensions. This may mean that they cannot appreciate their plight. It is of interest that patients with juvenile obesity who subsequently lose weight have a similar disturbance of body image and that patients with juvenile obesity who have lost weight in their teens are said to be particularly likely to develop anorexia nervosa. Body image is not disturbed in adult obesity.

The activity of the hypothalamic feeding centres can be altered experimentally by the administration of catecholamines both locally into the hypothalamus and systemically. There is indirect evidence that levels of hypothalamic monoamines, e.g., noradrenaline, 5 HT and Dopamine, are diminished in depression and therefore altered activity of the hypothalamic feeding centres resulting in anorexia can be implied. The tricyclic antidepressant amitriptyline has been reported as causing weight gain, possibly as a result of increased appetite, in patients in whom treatment was continued for several months after recovery from depression. It is possible that the tricyclic antidepressants produce this effect by increasing levels of free noradrenaline in the hypothalamus.

Diminished arteriovenous differences in glucose levels have been reported in severely depressed patients and return to normal after patients are treated with monoamine oxidase inhibitors. The reason for these diminished arteriovenous glucose differences is not known but such a reduction could result in a decrease in appetite as a consequence of altered activity in the hypothalamic feeding centres.

Abnormalities of appetite control also occur in many other psychiatric diseases, e.g., mania, anxiety and schizophrenia.

ORGANIC NEUROLOGICAL DISEASE
Organic lesions of the brain can result in severe appetite disturbances. They may act directly by interfering with structures involved in appetite control or indirectly by producing psychological changes on an organic basis. Striking abnormalities of appetite occur in some patients with hypothalamic tumours. In a series of 60 patients with hypothalamic disease 8% were grossly hyperphagic and 7% severely anorexic. Reeves and Plum described a woman who developed extreme hyperphagia and obesity as a result of a well circumscribed neoplasm which had destroyed the ventromedial hypothalamus and part of the median eminence, suggesting that this area may act as a satiety centre in man as well as in experimental animals. Voracious appetite may also occur in patients with temporal lobe epilepsy, after surgery to the temporal or frontal lobes, as a result of tumours, particularly in the frontal lobe, cerebrovascular disease, head injury and encephalitis. The Klein-Levine syndrome of episodic hyperphagia and hypersomnia is as yet unexplained.

GASTROINTESTINAL DISEASE
Anorexia is common in many gastrointestinal diseases but its extent is poorly documented and there has been little work on the basic mechanisms responsible. Inadequate food intake may have an important effect on the patient's clinical state, particularly if combined with an absorption defect.
Normal and abnormal food intake

In coeliac disease, weight loss correlates better with the degree of anorexia than with the extent of the absorption defect. Disease of the gastrointestinal tract may result in anorexia in many ways. Pain and discomfort associated with eating may occur, for example, as a result of obstructive lesions, and in some patients with peptic ulceration or gallbladder disease. Patients suffering from large and small bowel conditions associated with diarrhoea may avoid food because of the ensuing diarrhoea. Inflammatory and neoplastic disease may interfere with local autonomic reflexes and neurological input to the hypothalamic appetite centres by destroying local sensory receptors, nerve plexuses and afferent nerves; in addition they may depress appetite by their unexplained constitutional effects and by the depressant effect of pyrexia on the hypothalamic centres.

Taking increased amounts of food also occurs but is less common. Some patients with malabsorption from a variety of causes, for example, pancreatic disease, coeliac disease and Crohn's disease with small bowel resection, may develop hyperphagia and eat as much as 11 000 Kcals/day. It is possible that this excessive intake is an attempt to compensate for diminished absorption and this attempt may sometimes only serve to increase steatorrhoea with no absorptive gain. This overeating may easily escape notice unless a careful dietary history is taken when severe steatorrhoea is encountered. Some patients with peptic ulceration may eat excessively in their attempts to relieve abdominal pain.

OTHER ILLNESSES

It is not surprising, considering the many factors involved in the control of appetite, that disturbances of this control, particularly anorexia, occur frequently in disease states.

Emotional stress, fear and pain resulting from chronic illness may depress appetite, possibly through the connexions of the limbic system with the hypothalamus. Pyrexial illnesses may suppress appetite through the temperature-regulating sensitivity of the hypothalamus. The cause of the anorexia of neoplastic disease remains a mystery, and, although circulating anorexigenic substances have been sought, none have been definitely identified. Decreased plasma osmolality and disturbances of plasma electrolytes may decrease activity in hypothalamic feeding centres. This mechanism has been invoked to explain the anorexia seen in Addison's disease, advanced cardiac and liver disease and inappropriate ADH secretion. In liver disease and cardiac failure, it is, however, unlikely that changes in osmolality are the only cause of anorexia. In diabetes insipidus, where the plasma osmolality is high, increased food intake has been reported in association with the increased thirst. In general high plasma osmolality results in reduced appetite, as is seen in the much commoner situation of dehydration and after injection of sodium into the hypothalamus of experimental animals.

Increased appetite is much less common than anorexia. The hyperphagia of thyrotoxicosis is almost a physiological adjustment to the increased metabolic need. Corticosteroid overproduction and therapeutic administration results in increased appetite and weight gain but the mechanism of this increase in intake is not understood. Insulin administration and hypoglycaemia produce hunger and increased food intake probably by direct effects on the glucose-sensitive mechanisms of the hypothalamic feeding centres. The hyperphagia of uncontrolled juvenile diabetes cannot be explained in these
terms but could result from depleted fat stores stimulating intake by the postulated long term lipostatic 'control mechanism.'

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References

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