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EDITORIAL

The case for biology in the aetiology of anorexia nervosa[1]

It is now common to view anorexia nervosa as a multi-determined syndrome in which physical, psychological, family and sociocultural factors interact to produce the illness. Such a compromise position is difficult to refute. However, the components of this complex model neither explain nor account for the epidemiological and clinical features of the condition.

A popular cultural thesis is that the victim of anorexia nervosa is struggling to change her body in an attempt to deal with the contradictory requirements of the female role in late twentieth-century Western societies (Chernin, 1986; Orbach, 1986; Edwards, 1987). However, this thesis cannot account for the numerous clear descriptions of the condition which date from the middle of the nineteenth century (Marcé, 1860; Gull, 1873; Lasègue, 1873), or even earlier (Morton, 1694).

A common assumption held by many who argue for the importance of socio-cultural factors, is that there have been marked increases in the incidence of anorexia nervosa, over the last two or three decades. The evidence that anorexia nervosa, as opposed to bulimic disorders, has increased in incidence in parallel with the vast social changes of the last two centuries is, however, controversial. Although there is no doubt that case registers show an increase in anorexia nervosa over the last few decades (Kendell *et al.* 1973; Jones *et al.* 1980; Szmukler *et al.* 1986; Willi *et al.* 1990) this is probably an artefact, due to increased awareness of the condition and recognition of its psychological basis. When rigorous case-finding procedures were used (Lucas *et al.* 1988) no significant trends in incidence were found in the 45 years spanning from 1930 to 1979, although in a later paper which included the years 1980–5 a twofold increase in 15–24-year-old females was found (Lucas *et al.* 1991).

The vivid case descriptions of anorexia nervosa in Hong Kong (Lee, 1991) serve to remind us that the form of the illness does vary between cultures; 'fear of fatness', in particular, is not universal. It was argued, at the NIMH-sponsored conference on cultural issues for DSM-IV, that anorexia nervosa can be found in developing countries if this criterion is omitted (Littlewood, 1992). At the same conference the proposal to classify anorexia nervosa as a 'culture bound' category was rejected. It is possible that the prevalence of anorexia nervosa is reduced in non-Western cultures but definitive studies have not been performed; rather, there has been a large series of case reports (from Asia: Buhrich, 1981; Ong *et al.* 1982; Kope & Sack, 1987; Khandelwal & Saxena, 1990; Gandhi *et al.* 1991, and Africa: Nwaefuna, 1981; Buchan & Gregory, 1984) and within ethnic minorities (Africans/USA/Caribbean/UK: Jones *et al.* 1980; Pumariega *et al.* 1984; Silber, 1984; Robinson & Anderson, 1985; Thomas & Szmukler, 1985; Holden & Robinson, 1988) and Asians: Bryant-Waugh & Lask, 1991; Mumford *et al.* 1991).

Family models of aetiology have inspired new approaches to treatment of anorexia nervosa in the last decade. Abnormal family interactions have been observed but whether these are either causal or specific is far from certain (Humphrey *et al.* 1986; Kog & Vandereycken, 1989). An important deficit in both the familial and cultural models is the failure to account for individual susceptibility, which leads in some to the development of anorexia nervosa in the context of general environmental hazards.

A biological model of the aetiology of anorexia nervosa, although currently out of fashion, is not new (Russell, 1970). In the early part of the twentieth century there was diagnostic confusion between pituitary insufficiency and anorexia nervosa (McCullagh & Tupper, 1940; Escamilla & Lisser, 1942). Later, the hypothalamus was implicated in the origin of anorexia nervosa following

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observations that lesions of the lateral hypothalamus of rats lead to a life threatening avoidance of food (Anand & Brobeck, 1951). More recently, data from twin studies suggest that genetic factors may account for a substantial part of susceptibility to anorexia nervosa (Holland *et al.* 1984, 1988; Treasure & Holland, 1991). Thus, at the close of the twentieth century it is useful to re-examine the biological hypothesis.

WHAT FEATURES SHOULD BE PRESENT IN A MODEL OF ANOREXIA NERVOSA?

The features to be explained by any biological substrate include the following: (*a*) a disturbance in the homeostatic control of appetite such that weight regulation is impaired (this is discussed in more detail below); (*b*) hypothalamic–pituitary gonadal and adrenal dysfunction (most of the other endocrine abnormalities and hypothalamic dysfunction can be simply explained as the sequela of weight loss); (*c*) the sex ratio (10:1 female:male) in the incidence of anorexia nervosa; (*d*) the peripubertal time of onset; (*e*) the presence of psychosexual immaturity (Meyer, 1961; Crisp, 1967); and finally, (*f*) the onset following psychological stress (Gull, 1873; Schmidt *et al.* 1992).

THE CONTROVERSY ABOUT APPETITE IN ANOREXIA NERVOSA

A problem with appetite and eating in anorexia nervosa may appear to be self-evident, but there is disagreement about whether appetite is disturbed. In the early accounts of anorexia nervosa (Lasègue, 1873; Gull, 1874) a lack of appetite was considered to be the primary disturbance. Ryle (1936) suggested that there was a 'perpetuation of the initial loss of appetite by refusal of food until loss of appetite develops into a veritable revulsion against food'. However, recent psychiatric texts imply that the form of the illness has changed; Fairburn (1983) comments that 'their appetite for food persists (except in longstanding cases) and for this reason the term anorexia is inappropriate'. Certainly in underweight cases of anorexia nervosa, central (Kaye *et al.* 1988*a*, 1990*a*, *b*) and peripheral (Pirke *et al.* 1985; Ploog & Pirke, 1987; Casper *et al.* 1988; Broberg & Bernstein, 1989) physiological parameters which indicate 'biological' hunger are increased. However, evidence from experimental studies suggests that the identification and interpretation of these signals may be dysfunctional (Silverstone & Russell, 1967; Coddington & Bruch, 1970); ratings of hunger are lower and the perception of fullness is higher in patients with anorexia nervosa, compared with controls (Robinson *et al.* 1983; Hetherington & Rolls, 1988, 1991). On the other hand, the preoccupation with food (supermarket gazing, cooking for others) and eating behaviours akin to those described in the literature of starvation (Keys *et al.* 1950; Solzhenitsyn, 1963; Vonnegut, 1969; Irvin, 1983) suggest that there is a psychological drive to eat but that this is either denied or is inadequate to compensate for the level of starvation present. There is no doubt that there is a profound disturbance in the homeostatic controls over nutritional state but the level of this dysfunction is unknown.

From the features which are described above it is reasonable to propose a model in which anorexia nervosa arises as a result of an abnormal interaction between sex steroids and the CNS system controlling appetite. Of all the neurotransmitter systems involved in the control of appetite, serotonin is of greatest interest as its spectrum of activity spans many of the clinical features noted above: moreover, many 5-HT pathways show sexual dimorphism. Morley & Blundell (1988) highlighted the possibility that 5-HT and corticotrophin-releasing hormone were important candidates involved in the neurochemical aetiology of anorexia nervosa. More specifically, an animal model, immobilization-stress anorexia, which involves 5-HT pathways has been proposed as an analogue for human anorexic conditions (Donohoe, 1984; Dourish *et al.* 1987; Kennett *et al.* 1987*a*, *b*).

5-HYDROXYTRYPTAMINE AND APPETITE

The evidence that 5-HT is critically important in appetite control comes from a wide variety of

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sources (see Blundell & Hill, 1991; Curzon, 1992, for reviews). For example, D-fenfluramine decreases appetite and increases satiety probably by an effect on 5-HT-1C receptors (Hill & Blundell, 1990, 1991; Curzon *et al.*, 1992): this effect is countered by metergoline, a 5-HT receptor antagonist (Goodall & Silverstone, 1988).

The control of appetite by 5-HT shows quantitative differences between the sexes. Chronic fenfluramine infusion has a greater hypophagic effect in female than in male rats (Rowland, 1986). Repeated exposure to immobilization stress (see above) leads to a persistent reduction in food intake in female rats only (Kennett *et al.* 1986; Haleem *et al.* 1988). Furthermore, the hypophagic effects of M-chlorophenylpiperazine (M-CPP, a direct acting 5-HT agonist) and RU 24969 are greater in female than male rats deprived of food for 24 hours (Haleem, 1988). Overall, these studies suggest that the role of 5-HT in decreasing appetite is more pronounced in females. In humans also, sex hormones appear to influence the effect of 5-HT on appetite. For example, the effect of L-tryptophan and D-fenfluramine on food intake varies with the stage of the menstrual cycle (Leiter *et al.* 1987; Hill & Blundell *et al.* 1991).

5-HT AND STRESS

In addition to its central role in appetite, 5-HT is involved in other behavioural responses analogous to the precipitating psychogenic factors in anorexia nervosa. Arousal and stress in rats increases central 5-HT release (Kalan *et al.* 1989; Dunn & Welch, 1991). Immobilization-induced anorexia in the rat is reversed by 5-HT-1A agonists (Dourish *et al.* 1987). The endocrine response to prolonged chair restraint in monkeys (increased ACTH, and cortisol and reduced LH and testosterone levels) is similar to that found in anorexia nervosa (Norman & Smith, 1991). It is interesting to note that in these animal models, female rats are more vulnerable to the behavioural effects of stress such as loss of appetite.

5-HT LINKED NEUROENDOCRINE PATHWAYS

5-HT linked neuroendocrine pathways also show sex-related differences. In women, but not men, weight loss enhances the release of prolactin in response to L-tryptophan (Goodwin *et al.* 1987). Prolactin release by D-fenfluramine or buspirone is increased mid-menstrual cycle (Yatham *et al.* 1989; O'Keane & Dinan, 1991). However, it has to be accepted that direct changes at the lactotroph cell or probably in dopaminergic systems may account for these effects: these issues require further investigation.

5-HT AND SEXUAL FUNCTION

Psychosexual immaturity and conflict about sexuality have been implicated in the development of anorexia nervosa (Janet, 1907; Waller *et al.* 1940; Beumont *et al.* 1981; Buvat-Herbaut *et al.* 1983). It is, therefore, interesting to note that 5-HT inhibits sexual behaviour in several species (Carter & Davis, 1977). Destruction of 5-HT pathways in the ventromedial hypothalamic nucleus with 5,6-dihydroxytryptamine increases lordosis behaviour in rats (Luine *et al.* 1983), and the threshold dose of oestrogen needed to elicit this behaviour is lowered (Luine *et al.* 1987). Both oestrogen priming and destruction of 5-HT neurons lead to an increase of dendritic spines on ventromedial hypothalamic neurons (Frankfurt & McEwen, 1991).

5-HT AND BEHAVIOURAL STYLE

In Cloninger's (1987) theoretical model of personality, harm avoidance, a form of behavioural inhibition, is considered to result from abnormal central 5-HT function. We have found subjects with anorexia to have elevated scores on this dimension (O'Dwyer *et al.* 1992). Anorexia nervosa is characterized by high levels of control and perfectionism (Casper *et al.* 1990), which contrast

markedly with the impulsive, aggressive and suicidal behaviours associated with low levels of 5-hydroxyindoleacetic acid (5-HIAA) in cerebrospinal fluid and blunted 5-HT neuroendocrine function (Traskamn *et al.* 1981; Linnoila *et al.* 1983; O'Keane 1992). In summary, 5-HT pathways could account for the behavioural inhibition and control observed in anorexia nervosa.

5-HT IN ANOREXIA NERVOSA

Interpretation of studies of the pathophysiology of anorexia nervosa is difficult as weight, nutritional and menstrual status are often confounding variables (i.e. some of the apparently discrepant findings in the literature arise because observed changes may be a result rather than a cause of the illness). Thus, although a theoretical model of anorexia nervosa would implicate increased hypothalamic release of 5-HT (Morley *et al.* 1986; Morley & Blundell, 1988), there are reports that in anorexia nervosa plasma tryptophan levels are reduced (Coppen *et al.* 1976; Johnston *et al.* 1984) as are CSF levels of 5-HIAA (Kaye *et al.* 1988*b*). Interestingly, however, long-term weight-restored anorexic subjects have elevated concentrations of CSF 5-HIAA compared with controls (Kaye *et al.* 1991). The same problems of data interpretation arise when the literature on endocrine responses is examined. McBride *et al.* (1991), using DL-fenfluramine, found reduced and delayed release of prolactin in women with eating disorders at low weight (i.e. these studies suggest that 5-HT mediated prolactin release is decreased in subjects with anorexia nervosa at low weight). Brewerton *et al.* (1990) have also shown that compared with normal controls, women with anorexia nervosa have reduced prolactin responses to both L-tryptophan and M-CPP, in an emaciated state. However, in addition, they have reported that these diminished responses persist after the achievement of goal weight. (It should be emphasized that goal weight is not necessarily normal weight.) On the other hand, Goodwin *et al.* (1989) found no abnormality in prolactin release in response to L-tryptophan in underweight patients with anorexia nervosa. Thus, overall, the clinical picture remains unclear.

CONCLUSION

It is reasonable to propose that the underlying abnormality in anorexia nervosa is related to an increase rather than a decrease in 5-HT mediated responses and that weight loss obscures this abnormality. A predisposition towards overactivity in 5-HT pathways could plausibly account for the clinical and epidemiological features of the condition. Furthermore, fluxes in oestrogen or other sex hormones may be necessary to reveal this vulnerability.

Further studies in which the confounding effects of weight nutritional and sex hormone status are controlled, as in patients following recovery, are needed to test this hypothesis.

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