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THE ENDOCRINE RESPONSES TO PROTEIN CALORIE MALNUTRITION

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INTRODUCTION

The syndrome of protein-calorie malnutrition (PCM) in the human entails nutritional deficiencies of not only protein and calories, but also of minerals and vitamins in varying degrees. These deficiencies result in a number of metabolic changes, which include a large variety of hormonal alterations

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related to the major changes of fuel homeostasis in the malnourished state. Increased or decreased circulating levels of a variety of hormones have been reported in the human. Conflicting data in the literature are presumably due to variations in the degree of malnutrition in individual patients, the timing at which studies are carried out, possibly the different etiologies of the malnutrition, and the association of complicating factors such as infection. Despite the relatively uncontrolled study situations in the human, animal models of PCM, which are much purer in their specific deficiency, have produced surprisingly similar hormonal changes. The abnormalities of circulating hormone levels are due to alterations in their secretion rates, clearance rates, and binding proteins. In addition, changes in hormone receptors at the tissue level are likely, but this has not been well studied. These modifications of the endocrine system probably represent adaptation of the organism to the altered nutritional status, although in some instances they may be nonspecific consequences of severe nutritional insults. It should be stressed that hormonal abnormalities associated with fasting or acute starvation are often different from those of chronic PCM. These different forms of malnutrition may represent a spectrum of duration, severity, and diet composition resulting in a continuum of functional endocrine changes. These factors are also likely to affect the rate of recovery from endocrine dysfunction or of adaptation during nutritional rehabilitation. Conversely, the rate of hormonal recovery may affect the rate of nutritional recovery.

Most studies of PCM have been carried out in underdeveloped countries. The increasing recognition of the high incidence of undernutrition in hospitalized patients makes the understanding of the consequences of malnutrition clinically relevant, especially with the utilization of enteral and parenteral nutrition. To be both safe and effective, therapy with hypercaloric nutrients requires that the organism be able to produce adaptive hormonal alterations.

This review includes current descriptions of the hormonal milieu in PCM and anorexia nervosa in the human with some reference to the literature relating to starvation and experimental animal models.

GROWTH HORMONE

"Pseudo-hypophysectomy" (with drecreased growth hormone secretion) was long thought to be the cause of growth failure in PCM, based on biological features of the pituitary gland (150), decreased growth of the epiphyseal end plates (96), and reduced pituitary bioassayable growth hormone (200). It was even suggested that growth hormone therapy was necessary to achieve normal growth during recovery from PCM (145). It therefore came as a surprise when the majority of authors reported high immunoassayable growth hormone levels in children with PCM (81, 141, 158, 159, 163, 164); these levels return to normal with nutritional therapy. The few reports of low levels of growth

hormone in malnourished children with poor response to stimulation may come from studies of different patient populations or studies done at different stages in the illness, with testing having been delayed after admission to the hospital (16, 75, 76). Basal growth hormone levels are more likely to be normal in children at the marasmic end of the spectrum of PCM than in children with classical kwashiorkor (110). Although low nonstimulatable growth hormone secretion has been reported in both adults (60, 119) and children (72, 102) with anorexia nervosa, most reports show elevated basal serum growth hormone levels that response normally to a variety of stimuli (86, 119, 132, 190). Levels are higher in individuals with a poor caloric intake but do not compare with actual weight deficit (42). As is the case in children with PCM, these abnormal growth hormone responses return to normal with weight gain. Basal growth hormone levels are markedly elevated in most systemic diseases associated with severe wasting or caloric deprivation (139). Even acute experimental caloric deprivation in man results in a striking increase in serum growth hormone levels (138). In children with cystic fibrosis with resultant malnutrition, basal levels of growth hormone are high; but there is no further increase in response to acute hypoglycemia (85), as is reported in some cases of PCM. Similar high basal levels with growth hormone unresponsiveness have been demonstrated in children with emotional deprivation dwarfism (117). The concept that this syndrome may be associated with malnutrition is controversial. By contrast, low growth hormone levels without response to stimulation are also reported in these patients (175).

The elevated growth hormone levels do not correlate with fasting blood sugars (165, 218) nor do they suppress normally during glucose tolerance testing in most studies, and may even show paradoxical increases (50, 164, 202). Paradoxical elevations of circulating growth hormone occur in response to thyrotropin release hormone (TRH) stimulation of the pituitary gland (78, 169). Postabsorptive values and suppressibility return toward normal, frequently within a few days of therapy, with a protein-containing diet but not a protein-free diet (165). This improvement is far more consistent when the nutrients are given as oral milk or amino acids than when equal amounts of protein are given intravenously (23, 27, 141). Although basal growth hormone levels correlate inversely with serum albumin levels on admission (27, 110), correction of the hypoalbuminemia with intravenous albumin infusion does not result in diminished growth hormone values or return of suppressibility. This contrasts with the improvement seen after oral milk feeding (23, 27). In addition, no correlation exists between serum growth hormone and albumin after a few days of any form of therapy or in patients with hypoalbuminemia due to the nephrotic syndrome (23, 166). Therefore, hypoalbuminemia per se cannot be a cause of growth hormone elevation and may merely be a marker of the severity of the malnutrition. The same can be said for the branched chain amino acids and arginine, which also show an inverse correlation with basal

growth hormone levels prior to therapy but not after albumin or amino acid infusions or milk feeding (166). A notable exception is the inverse correlation between basal serum growth hormone and alanine values, which persists during all therapeutic manipulations (166).

The increased growth hormone secretion during PCM may result from a homeostatic attempt to utilize the meager amounts of amino acids available for protein synthesis with a dramatic decrease of growth hormone when adequate amino acids are supplied with milk feeding, which changes intracellular rather than circulating levels. The striking and persistent inverse correlation with serum alanine levels introduces the possibility of a feedback relationship between growth hormone and carbohydrate metabolism, the increased growth hormone secretion being a compensatory effect secondary to poor gluconeogenesis caused by the lack of alanine, its major precursor (66). This relationship apparently also exists in short-term starvation (3). However, neither 30-min nor 12-hr intravenous infusions of alanine decreases circulating growth hormone levels or alters their suppressibility to glucose in children with PCM (28). Basal glucose levels and glucose tolerance show no correlation with serum alanine levels prior to therapy or after alanine loading, giving no support to an important role for serum alanine levels in the carbohydrate homeostasis of PCM (30).

The elevated circulating growth hormone levels of PCM have been shown to reflect increased secretion rather than impaired clearance of the hormone by the demonstration of a normal half-life of growth hormone during somatostatin infusion (170). At present, the most feasible explanation for increased growth hormone secretion is a feedback relationship between growth hormone and the low somatomedin levels demonstrated in PCM.

Studies of the effects of constant parenteral or enteral feeding on growth hormone secretion during therapy of malnutrition are very sparse. In infants, parenteral nutrition with a high-fat formula resulted in lower plasma growth hormone levels than with one that was fat free, presumably owing to the inhibitory action of fat on growth hormone secretion (9). In adults, growth hormone levels during a period of weight gain are normal, probably reflecting a balance between the stimulatory effects of amino acid and suppressive effects of glucose infusions. However, the responses to stimulation were not studied (46, 71). During constant enteral nutrition in six children with undefined nutritional status, sleep-related growth hormone peaks were normal and not inhibited (65).

SOMATOMEDIN

Low serum somatomedin levels have been demonstrated in PCM by chick pelvis and pork rib bioassays and by radioimmunoassays (84, 98, 194, 211,

214). Such a relationship between low somatomedin and high growth hormone levels is also seen in other conditions such as Laron dwarfism, renal failure, and cirrhosis (162). The mechanism in PCM is not clear, but may be due to the inability of the liver to synthesize the somatomedin molecule as part of a general failure of protein synthesis. This is suggested by a correlation between serum somatomedin and albumin levels (84, 144). It is also possible that the anterior pituitary secretes an abnormal, biologically inactive growth hormone molecule or that there are alterations in growth hormone receptors. Decreased plasma insulin levels or an inhibitory action of increased cortisol may play a role (194). The fact that somatomedin C levels determined by radioimmunoassay are as low as those measured by bioassay (214) suggests that the lack of a growth effect on the epiphiseal cartilage is not due only to the presence of circulating somatomedin inhibitors, as has been suggested (98, 211). Refeeding results in a steady increase of somatomedin values concomitant with the fall in basal growth hormone levels (84) and the values are normal at the time that most patients exhibit clinical recovery.

In children and adolescents with anorexia nervosa, bioassayable plasma somatomedin activity also decreases in the face of elevated growth hormone levels. There is a significant negative correlation between weight deficit and plasma somatomedin activity (179). In one patient, prolonged growth hormone therapy did not increase plasma somatomedin, suggesting that the production of an inactive growth hormone is unlikely (179).

In one group of cystic fibrosis patients, somatomedin activity measured by bioassay was low (121). However, it was reported to be normal by radioreceptor assay in another group of patients who exhibited normal basal growth hormone levels (182) but poor growth and other features of malnutrition.

In experimental fasting, radioimmunoassayable somatomedin declines acutely after 5 days. There is a rapid recovery with refeeding, which apparently requires an optimal intake of protein as well as a minimum quantity of calories. Changes in somatomedin C correlate with those of nitrogen balance (209).

In experimentally starved rats there is also decreased bioassayable somatomedin activity with an inability of exogenous growth hormone to raise serum somatomedin C (161, 162). Also in growing rats an optimal intake of both protein and energy is needed to maintain somatomedin C (176).

HYPOTHALAMO-PITUITARY-THYROID AXIS

There is little agreement concerning the status of thyroid stimulating hormone (TSH) secretion from the pituitary in malnutrition. The elevated basal TSH levels with an exaggerated response to stimulation by thyrotropin releasing hormone (TRH) in patients with PCM and hypoalbuminemia, which is readily

reversible by exogenous T_3 administration, suggests an element of thyroid unresponsiveness (137, 167). However, normal and even decreased TSH levels have been reported, mainly in marasmus (72, 82, 92, 105, 124).

In anorexia nervosa, basal TSH levels and their response to TRH stimulation have been reported to be normal in both adults and children (42, 120, 148). However, a delayed peak response suggestive of hypothalamic dysfunction is often seen (8, 78, 143, 183, 218). Acute fasting and starvation in man causes a decreased TSH response to TRH (220), a situation very different from that seen in PCM and anorexia nervosa. This blunted response is not seen in rodents (89, 113). In more prolonged fasting there is essentially no change in the TSH response to TRH, despite a low circulating T_3 concentration (174). It is interesting that with calorie deficits, TSH response to TRH also remains normal (225). In patients with cystic fibrosis both normal and increased TSH responses to TRH are reported (12, 186). Possibly the variation reported could be explained by differences in the nutritional status of the patients studied, although no such correlation was attempted.

THE THYROID GLAND AND PERIPHERAL THYROXINE METABOLISM

The early studies of thyroid function in PCM are difficult to interpret. Low basal metabolic rate was initially thought to be a sign of hypothroidism but may have been related to variations in body size or surface area (77, 146, 147, 158). Decreased levels of protein-bound iodine (77), butanol extractable iodine (15), and thyroxine (T_4) (77, 82) may be primarily due to decreased synthesis of the thyroxine carrier proteins (82, 103, 104). This seems to be confirmed by the report of normal or even high plasma levels of free T_4 in kwashiorkor, but normal or low levels are found in marasmus (80, 82, 124, 158). Measurement of thyroid iodine^{131} uptake did not clarify the situation, although in retrospect, findings of normal uptake in kwashiorkor (80) and reduced or normal uptake in marasmus (15) seem to correlate with the free thyroxine levels. More recently, the biologically active thyroid hormone, triiodothyronine (T_3), has been shown to be decreased in children (105) as well as adults with PCM (55). These low T_3 levels do not increase normally after exogenous TSH stimulation (30). The coexistence of low T_3 and high reverse T_3 (rT_3) levels in adults with PCM (55) is presumably also present in children. This suggests that the decreased circulating T_3 is not due to diminished hormone production at the thyroid level alone, but rather is an adaptive alteration of the peripheral metabolism of T_4, directing the deiodination pathway of T_4 to rT_3 (the inactive isomer of T_3).

Similar alteration in thyroid hormone metabolism has been well documented in adult starvation and anorexia nervosa (44, 210). Apparent clinical hypothyroidism with normal or decreased BMR, iodine I^{131} uptake, and serum PBI is

well known in anorexia nervosa (59, 112, 126, 143). Later techniques have shown low serum T_4 and T_3 levels (143, 148, 210) but normal free T_4 (210). By contrast, as is seen in PCM and acute starvation, serum rT_3 and $3,3'T_2$ are increased, again reflecting preferential peripheral metabolism of T_4 to an inactive isomer (44, 69, 210). In these patients TRH induces a normal TSH and T_3 increment, suggesting that there is no functional damage to the thyroid gland itself (210). One would thus assume that patients with anorexia are euthyroid and their hypometabolic state is an adaptational protective phenomenon.

These results are similar to those in patients with a variety of chronic illnesses (56), including cystic fibrosis (186) and experimental starvation (210, 225). Fasting is associated with a decreased T_3 production rate; both normal and decreased metabolic clearance rates (MCR) have been described (225). The typical increase of rT_3 is primarily due to a decrease in its MCR and cannot all be attributed to increased production from T_4. There is conflicting data in man as to whether these changes in peripheral thyroid metabolism are related to total calorie deficits or mainly to the carbohydrate content of the diet (45, 153, 199, 225).

In pure protein deficiency in rats, levels of circulating thyroid hormones differ greatly. Both T_4 and T_3 levels increase (73, 154, 193, 208) in association with abnormally low MCR of T_3, but normal production rates. This suggests decreased tissue uptake of T_3 because of altered receptors or binding proteins (154). In another study the elevated T_3 levels in protein malnourished rats were thought to be associated with increased thyroid hormone binding with normal or decreased free T_3 (193). By contrast, in starved rats serum T_3 and T_4 as well as nuclear T_3 are reduced (154).

It is not clear how these experimental data relate to human PCM. However, it is clear that in man, the major effect of malnutrition on thyroid function appears to be at the peripheral level. In PCM the hypothalamo-pituitary-thyroid axis is often normal. The delayed TSH response to TRH frequently seen may reflect either hypothalamic or mild thyroid tissue dysfunction.

HYPOTHALAMO-PITUITARY-GONADAL AXIS

Delayed puberty is well known in malnourished children (63, 160). Adults with malnutrition or with anorexia nervosa have amenorrhea or testicular failure. These effects are probably due to alterations of both the hypothalamo-pituitary axis and the gonads caused by the nutritional insult. The apparently conflicting data in the literature regarding gonadotropin release may reflect differing degrees of malnutrition or unequal dysfunctional effects on the hypothalamus relative to the gonads. The data reviewed below support both of these hypotheses and suggest that changes seen in anorexia nervosa may well fit into the spectrum of those observed in other forms of undernutrition.

In both very young and older children with severe PCM, basal LH and FSH levels are reported to be normal (155, 168) or decreased (53). In an excellent cross-sectional study of mild malnutrition in boys, basal FSH levels were lower and LH levels were higher than those in age-matched controls, but both were identical to those in weight-matched controls (160). This was interpreted to represent a delayed onset in the pubertal gonadotropin changes. Pubertal changes did occur with attainment of weight, height, and lean body mass similar to those in normal boys, supporting the possible importance of the attainment of a critical lean body mass rather than body fat for normal gonadotropin function (67, 160).

Very young children with severe PCM have exhibited poor responses of LH to LHRH stimulation; the reduction of FSH release was less consistent (168). This suggests a pituitary-hypothalamic disorder. By contrast, in adult men with PCM and low circulating plasma testosterone levels, mean plasma LH was significantly increased and fell during refeeding (197). These raised LH levels suggest a primary testicular defect that apparently persisted after clinical recovery, the LH levels remaining abnormally high despite normal plasma testosterone values. Plasma FSH was also elevated in the malnourished male but dropped to levels similar to those in race-matched controls with refeeding. However, a number of individuals in this study initially had low plasma LH and FSH levels despite the low circulating gonadal steroids. In the former situation one would suspect that the major functional damage was to the gonads while in the latter there was also, as in the children, a hypothalamo-pituitary disorder. Again these differences may relate to the degree of malnutrition, though this was not evaluated.

In adults and children with anorexia nervosa both situations occur. There is usually a decrease in urinary gonadotropin excretion as well as in basal serum levels of LH and FSH and in their response to LHRH and clomiphene (19, 42, 60, 112, 133, 157, 188, 189, 206, 218). Typically, the gonadotropin secretion reverts to prepubertal patterns of LH:FSH ratio, response to stimulation and to sleep (38, 171, 188). In some patients a delayed LH peak response to LHRH is described in which the quantitative increment and area under the curve are normal despite low absolute levels (218). It is postulated that these cases involve a normal releasable pool of LH and FSH, but a decreased endogenous stimulation of the pituitary gland. The report in one study of exaggerated LH and FSH responses to LHRH suggests a normally functional hypothalamic-pituitary axis with primary gonadal failure (20), as is described in adult PCM. However, part of the reason for the high circulating LH levels may be the decreased metabolic clearance rate of this hormone (54).

The concept that a hypothalamic defect causes low LH and FSH responses is supported by the return of pituitary responsiveness after 3–5 days of LHRH therapy (7, 229) and the induction of follicular maturation after 4 weeks of

LHRH injections 3 times daily (152). Particularly striking is the maturation of LH and FSH response to LHRH induced by low-dose intravenous pulses of LHRH every 2 hr for 5 days, the initial increment being seen after 36 hr. The changing pattern is similar to that seen over years in normal puberty (134).

Weight gain in anorectics is also associated with increasing plasma levels of gonadotropins and reversal of the impaired pituitary responsiveness to standard stimulation. However, decreased responses are reported to persist as ideal body weight is approached in some cases (42,218). In the majority of cases the LH and FSH responses to LHRH and the LH sleep profiles change from an infantile to a pubertal and then to an adult pattern with recovery of normal height and weight proportions (171). Frequently the low pituitary hormonal responses become exaggerated when followed longitudinally during weight gain, suggesting later recovery of the gonads than of the hypothalamus (20, 106, 188).

Unlike the situation with growth hormone, there is a strong correlation between basal and stimulated LH levels and the degree of weight loss and actual body weight during recovery; LH levels do not correlate with caloric intake (20, 42). This correlation is also seen in women with "simple" weight loss resulting from causes other than anorexia nervosa (217), in infertile women with a wide range of weights (115), and in prepubertal boys (160). This supports in part the Frisch hypothesis that body mass or body composition is related to menarche and the development of secondary amenorrhea (67). Decreases in relative body weight from that of adults to that seen in prepubertal children during undernutrition are associated with reversals of LH patterns similar to those in the prepubertal state (68). However, lean body mass, or relative weight for height, seems more important than a fat index or an absolute critical weight (160). In children with cystic fibrosis and malnutrition who have low normal basal LH and FSH levels, menarche did not correlate with the body fat index, but its relationship with lean body mass or expected weight was not examined (149). In a larger study in cystic fibrosis, basal LH and FSH values were lower than those of age-matched controls with associated delayed pubertal changes (180).

Few experimental data exist on the effects of malnutrition on gonadotropins. Fasting in obese humans decreased FSH but not LH responses to LHRH in one study (114) but caused no change in another (204). Protein deficient weanling rats exhibit poor LH and FSH rises after LHRH administration, but these responses are abnormally high when the malnourished rats are castrated (74). This led the authors to postulate the presence of an inhibitory gonadal feedback effect on the pituitary during malnutrition—i.e. a third mechanism for gonadal failure.

Irrespective of changes in the hypothalamus and pituitary, there is abundant evidence for primary gonadal damage during malnutrition. Thus raised gonadotropin levels resulting from the absence of normal feedback inhibition of

testosterone or estrogens would be expected. In adult men with PCM, mean plasma levels of total and unbound testosterone are significantly decreased with recovery after refeeding (197). Plasma estradiol in these men is low and increases during refeeding. A relatively high free-estradiol concentration was measured in the one patient who developed gynecomastia during refeeding. Stimulation of the Leydig cells with 3 days of human chorionic gonadotropin (HCG) injections produced a subnormal testosterone response both in the malnourished and refed states (197). In fact the testosterone increments were actually smaller after refeeding, a phenomenon that may be related to a more rapid metabolic clearance rate. The persistently subnormal testosterone responses to HCG together with elevation of LH levels in the refed state show a delay in the recovery of Leydig cell function. Although zinc deficiency has been implicated in hypogonadism with mild malnutrition (57), in these patients plasma zinc levels were normal, with no significant increase during refeeding.

In anorexia nervosa plasma urinary levels of estradiol (206, 218) and testosterone (17, 18) are low, and their improvement lags behind that of the pituitary gonadotropins (70, 188). This would account for the raised LH secretory patterns referred to above. Thus in both PCM and anorexia the end organ of the hypothalamo-pituitary-gonadal axis seems to be the most severely affected. This effect of malnutrition is not easily considered part of adaptation; it seems rather to be an end result.

PROLACTIN

Studies of prolactin responses to TRH provide the most impressive evidence for suggesting that changes in hypothalamo-pituitary function in PCM may be adaptive. Prolactin levels in children and adults with PCM are low, with decreased responses after TRH stimulation (29, 137). During the same tests, TSH responses are normal or exaggerated—i.e. a dichotomy in the responses of two pituitary hormones to the same stimulus. In one study, children with kwashiorkor had higher levels of prolactin than did marasmics (53). The functional significance of altered prolactin levels in PCM is unknown but has been postulated to correlate with changes in total body water.

In anorexia nervosa, results of studies on prolactin secretion vary greatly and in some cases may be influenced by a variety of psychotropic drugs. Basal prolactin levels and their response to stimulation with TRH and chlorpromazine are reported to be normal in most series (19, 91, 106, 217, 218). Raised basal levels of prolactin have also been reported (93, 136, 187, 191, 206) and are thought by some to result in decreased gonadotropin secretion and thus amenorrhea. The increase of prolactin response to TRH during refeeding in one study was interpreted as a return from low pretreatment levels (106) reminiscent of the situation both in PCM and in acute experimental starvation (219). Because

dopamine exerts an inhibitory control over prolactin secretion from the pituitary gland, raised prolactin levels would support the view that patients with anorexia nervosa have depleted dopaminergic activity in the brain (135). Low prolactin levels would support the opposing theory of increased dopaminergic activity, which has also been suggested. These mechanisms are difficult to prove because the CNS dopamine activity cannot be measured by peripheral blood or urinary changes.

A paradoxical prolactin response to LHRH, which was found during refeeding in one study, suggests a generalized pituitary abnormality also resulting in the growth hormone increment after TRH administration, as mentioned above (21).

These unexplained results and their variability underscore the complexity of the effects of malnutrition. However, it seems unlikely that they are a direct cause of the amenorrhea.

PITUITARY-ADRENAL AXIS

Basing their conclusions on the histological appearance of adrenocortical atrophy at autopsy and rather low urinary levels of 17-hydroxysteriods (52, 129, 207), early workers in the field of PCM thought that malnourished patients had hypoadrenalism. Again, different results were reported in marasmus, with urinary 17-hydroxysteroids being normal or even increased (52, 151). These low urinary steroid levels were found in the face of elevated plasma cortisol levels (2, 4, 108, 127), with abnormal diurnal variation (4, 32), despite cortisol secretion rates lower than those in size-matched controls (4, 32). These data, the elevated plasma free cortisol levels found in children (122) and adults (196), and low normal urinary free cortisol (32) suggest decreased clearance rates of cortisol. A prolonged half-life of cortisol has been shown in PCM (4), as well as reduced metabolic clearance rates (196). This may in part account for the increased free cortisol levels in addition to decreased steroid binding protein levels (122, 184). Incomplete suppression of serum cortisol levels with dexamethasone suggests hypersecretion of ACTH similar to that of growth hormone (4, 196). In adults, this is apparently confirmed by normal serum ACTH levels that are not suppressed by the elevated circulating plasma cortisol levels (196). There is normal adrenal reserve in most patients, as assessed by their cortisol response to exogenous ACTH stimulation (4, 108, 196), though slightly lower responses are reported in kwashiorkor than marasmus (108) and vice versa (212). In one study ACTH produced no further increase in the very high plasma cortisol levels (215). Testing with metapyrone and pyromen revealed normal stimulation of the pituitary-adrenal axis (177, 196).

The elevated levels of plasma free cortisol presumably have active tissue receptor sites, thus explaining the "moon facies" classically seen in many

patients. This increased circulating cortisol, maintained by continued ACTH secretion, is thought to be an adaptive phenomenon. Its stimuli may be generalized stress (156), hypoglycemia (4), or restricted food intake per se (110). The catabolic action of corticosteroids is hypothesized to provide the required amino acids for organs with a high protein turnover at the expense of muscle mass (110). Jaya Rao suggests that adrenocortical activity is lower in kwashiorkor than in marasmus; this would reflect a breakdown of adaptation, with insufficient amino acid substrate from muscle, decreased protein synthesis, and hypoalbuminemia. This interesting hypothesis is supported by the increase in serum albumin in protein deficient rats after cortisone injections (128). However, this theory would not explain the hypoalbuminemia in cases of kwashiorkor with very high plasma free cortisol levels or with total cortisol equal to that measured in marasmus (155). The apparent differences in circulating levels of total cortisol and its response to stimulation in kwashiorkor and marasmus may merely reflect differences in the cortisol binding proteins.

In anorexia nervosa, elevated circulating morning and mean 24-hr plasma cortisol levels, with either normal or abnormal diurnal rhythms, are also well documented (33, 39, 62, 70, 101, 119, 132, 223, 224). Again urinary 17-hydroxycorticoid excretion is low or normal (34, 224), suggesting decreased clearance rates of steroids; but urinary free cortisol values were higher than those of controls (39, 223). As in PCM, cortisol half-life is prolonged and is associated with a decreased metabolic clearance rate (39). Cortisol production rate, however, is normal (39, 223), as are the responses to ACTH and metapyrone stimulation (224). Plasma cortisol levels correlate with plasma T_4, probably because both are affected by circulating binding proteins (41). It is thought that the low T_3 in these patients affect cortisol degradation, and treatment with T_3 decreases the half-life of cortisol (39). Surprisingly, the cortisol binding capacity of corticosteroid binding protein is normal, but its affinity constant is lower than in controls (39, 51). There is a significant correlation between cortisol binding capacity and the binding protein levels (51), with apparently impaired feedback inhibition of ACTH by endogenous and exogenous steroids (62). The reason for this is not clear. Plasma cortisol levels do not correlate with calorie intake, weight loss, or duration of amenorrhea, as do levels of growth hormone and LH (41). They return to normal after therapy.

In the emotional deprivation syndrome of childhood, both low and normal urinary 17-hydroxycorticoids are reported (116, 175); but high plasma cortisol levels and cortisol secretion rates are similar to those found in PCM (116).

In experimental animals (pigs and monkeys) with protein malnutrition, plasma cortisol levels are also high, with abolition of the diurnal rhythm. Cortisol values are related to blood sugar levels and hypoproteinemia (11, 64); they respond to hypoglycemia (11).

ADRENAL CORTEX

Little is known about the alterations of adrenal enzyme activity in PCM. In anorexia the mean tetrahydrocortisol/tetrahydrocortisone ratio is higher than in controls (39). There is also evidence of depressed 5-alpha-reductase activity (40), both abnormalities being found also in hypothyroidism and both being corrected by T_3 administration. Increased dehydroepiandrosterone and testosterone concentrations in extremely severe anorexia probably have an unexplained adrenal origin (13); however, most authors find normal testosterone levels (51).

Alterations of aldosterone secretion would be expected in PCM associated with the known alterations of total body water, edema, and total body potassium deficits (5). As was the case with urinary 17-hydroxycorticoids, urinary levels of aldosterone are reported to be low, probably due to diminshed glomerular filtration rates (130, 195). However, more recent methodology reveals that children with edema have elevated plasma aldosterone levels but a normal aldosterone secretion rate. By contrast, those with marasmus have normal plasma levels and an increased secretion rate (31). The significance of these studies is not clear; the small numbers studied and the alterations of aldosterone binding proteins (122) make them difficult to interpret. Increased plasma renin bioactivity in both kwashiorkor and marasmus could be associated with high aldosterone secretion (118, 213), again adaptive phenomena.

CATECHOLAMINES

Theoretically, malnutrition of any type, whether acute or chronic, represents a stress situation to the organism. It would therefore not be surprising to find increased catecholamine secretion in PCM. However, existing data conflict. Increased urinary epinephrine:norepinephrine ratios in kwashiorkor with low urinary dopamine are reported (99, 159). Metanephrine in the urine is decreased in a few marasmic children (36), and decreased adrenalin compared to noradrenaline has been found (178). However, Graham suggests that urinary catecholamine excretion is normal in PCM unless there is coexisting infection (83). In adult anorexia nervosa, plasma levels of norepinephrine are diminished with decreased urinary excretion of catecholamine metabolites (87). Plasma levels have not been measured in children with PCM, and, as with cortisol, many present a different picture from that of urinary excretion of catecholamines. Alterations of catecholamine production as well as the norepinephrine:epinephrine ratio may be part of an adaptive mechanism that maintains homeostasis during malnutrition (79). Suppression of the sympathetic nervous system would decrease metabolic rate and conserve calories, as occurs during experimental fasting (120).

THE POSTERIOR PITUITARY: ANTIDIURETIC HORMONE (ADH)

A number of authors have suggested that the edema of PCM may be related to increases in antidiuretic hormone. This is supported by the report of elevated bioassayable plasma and urinary levels of ADH in children with kwashiorkor and more normal values in those with marasmus (201). Presumably, the stimulus to ADH secretion is the decreased plasma volume associated with hypoalbuminemia and is an adaptive phenomenon. Confirmation of these results by radioimmunoassay of ADH is not available.

Studies of water conservation and ADH secretion in anorexia nervosa are minimal (218).

THE ENDOCRINE PANCREAS

Insulin

Considerable debate concerning the status of insulin secretion in children with PCM arose after the characteristic abnormalities of carbohydrate metabolism were described (10, 35, 90, 95, 192). Workers initially tried to reconcile the classically decreased glucose tolerance with the frequently reported hypoglycemia—attempting to explain both situations by invoking alterations of insulin secretion and/or sensitivity. Impaired glucose tolerance in children in Uganda 5–10 years after an acute episode of kwashiorkor was interpreted as evidence for permanent insulin deficit caused by damage to the pancreatic islet cells (58). The high protein turnover of the pancreas (227) was thought to make it particularly vulnerable to protein depletion, resulting in the well-documented acinar atrophy (61, 207) associated with impaired exocrine pancreatic function (14). However, the histological effect of protein deficiency on the pancreatic islets is far less clear as decreased granulation and atrophied (94, 172, 173, 203), hypertrophied (47, 61), and normal islets (48, 216) have been reported. Use of more recent techniques in the protein deprived rat revealed normal islet histology under the light microscope, but the total islet volume was reduced. Electronmicroscopic studies in these rats failed to demonstrate alpha and beta cell damage (226). These discrepancies are presumably related to variations in the severity of PCM, differences between experimental animals and man, and the use of different staining methods.

Using an indirect technique, Bowie (37) concluded that insulin resistance, rather than insulin deficiency, seemed likely because exogenous insulin failed to increase the glucose disappearance rate after a glucose load in PCM. However, Aballi (1) reported increased insulin sensitivity when insulin alone was injected.

Since the advent of radioimmunoassay for the measurement of circulating insulin levels, the consensus is that basal serum insulin levels are low or normal

in both children and adults with PCM and subnormal responses to oral and intravenous glucose (10, 22, 76, 90, 107, 109, 140). Diminished insulin responses are also found after other stimuli such as arginine (55, 81, 198, 200), mixed amino acids (141), and glucagon (142). In some cases, the insulin secretion after glucose stimulation can be augmented by the addition of intravenous glucagon, suggesting impaired release mechanisms rather than deficient synthesis (22). This is confirmed by the inspection of the patterns of insulin release after glucose stimulation in those children in whom insulin release does occur.

Delayed or low insulin responses after oral glucose with prompt normal release after intravenous glucose suggest a disturbance of the gut beta-cytotrophic mechanism (24). Further evidence for the deficiency and later recovery of an "incretin" factor is provided by the low insulin:glucose ratios after oral compared to intravenous glucose loads, the ratio increases significantly in response to oral glucose after nutritional rehabilitation (24). Another factor apparently affecting the early insulin release in response to oral glucose and the peak responses to intravenous glucose is the total body potassium deficit that usually accompanies PCM (26, 131). Insulin secretion correlates with total body potassium measurements and improves markedly within a few days of therapy with oral potassium (26, 131). The effects of chromium deficiency in the glucose intolerance of PCM are poorly understood, and no clear data on insulin levels exist (49, 88, 100). A certain proportion of children with PCM demonstrate a sustained and exaggerated insulin response to glucose in the face of glucose intolerance, suggesting resistance to the action of insulin (24). This is not due to an abnormal insulin molecule as assessed by column chromatography (25). There is an increase in a number of circulating factors in PCM known to be associated with insulin resistance, such as growth hormone (164), cortisol (122), and free fatty acids (123). Insulin degradation and clearance rates are apparently normal in the experimental animal with PCM, but there are no confirmatory studies in man. Also, no data exist on the status of insulin receptors in PCM in childhood. Increased receptor number has been reported in anorexia nervosa (222) and cystic fibrosis (125).

Because glucose intolerance has been noted to persist ten years after recovery from PCM (58), it has been suggested that insulinopenia may be permanent. In some patients recovery of normal insulin secretion is rapid, occurring within days of the onset of therapy, while in other children, particularly those with severe wasting, it may take months for normal insulin responses to stimulation to return (22, 27). However, normal levels are eventually found in all of these patients (22), which has not been the case in studies of shorter duration (107). A group of children ten years after PCM also had normal insulin responses (22). It has been suggested that there is an augmentation of insulin release above normal associated with increased energy intake and catch-up

growth during recovery from PCM (181). Some patients exhibit decreased insulin secretion during recovery, suggesting exhaustion of their B-cell reserve (22).

Glucagon

There are few studies of the alpha cell of islets in PCM. Normal basal levels of plasma glucagon with low insulin levels have been reported in malnourished rats (6). Lower glucagon levels were found in single blood samples from hypoglycemic children with PCM than in normoglycemic children with PCM (43). In preliminary studies using a glucagon antiserum that cross-reacted with both gut and pancreatic glucagon we noted in four of five children decreased levels of glucagon-like activity in response to arginine. Activity increased after recovery from PCM (30). Normal glucagon responses to arginine have been found in older children with anorexia nervosa (190).

Parenteral nutrition requires the ability of the pancreas to secrete insulin in order to metabolize the usually large glucose and amino acid load. This may not be possible in the severely malnourished state when insulin deficiency and insulin resistance occur. This situation could result in hyperglycemia and hyperosmolarity. There are few data in patients with severe PCM to document this, however. In 6 severely ill patients with some degree of malnutrition, frequent sampling over the first 6 hr showed a prompt increase of serum insulin to fairly high levels with the initiation of parenteral nutrition and a subsequent drop over the next few days, presumably as peripheral resistance decreased (185). Other studies in patients with varying degrees of PCM also reveal appropriate insulin levels on the first day of therapy with normoglycemia (46, 111). It is interesting that plasma glucagon is often high and is not suppressed by the high glucose load (46, 111), but levels are lower than during a high fat infusion in both adults and children (9, 111). Further studies with frequent blood sampling at the onset of parenteral nutrition are needed to assess whether some patients with PCM—e.g. those with burns and injury (97, 228) —would benefit from exogenous insulin administration during parenteral nutrition.

Somatostatin

No published data exist regarding this gastrointestinal hormone in PCM in man. Starvation in rats increases extractable pancreatic and intestinal somatostatin (205, 221). This again may represent a homeostatic mechanism, as somatostatin is known to suppress insulin secretion.

CONCLUSION

PCM results in both increases and decreases of a number of circulating hormones. Because levels change in both directions, one is tempted to assume that they are part of an adaptational mechanism. The similarity of the hormonal milieu in anorexia nervosa to that of PCM suggests that the endocrine changes are due to the malnutrition rather than a primary hypothalamic disorder.

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