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Introduction

The evaluation of psychopathology in patients with endocrine disorders poses problems for the psychiatrist, especially in determining what specific relation the endocrine disease has to the psychiatric abnormalities. In such disorders, there are many nonspecific factors which can affect mental functioning. Obviously, the mental status of the patient needs to be interpreted in the light of his premorbid functioning. Beyond that, it should be noted that endocrine disease is often a severe stress involving loss of functions, feelings of illness, and changes in appearance, as well as sometimes posing a threat to life itself; the vulnerable personality may well decompensate under these conditions.

Furthermore, endocrine diseases have widespread biochemical and physiological consequences, and it is often difficult to determine whether the mental changes noted are due to direct hormonal influences on the brain, or to associated disturbances in electrolyte metabolism, blood sugar, renal function, and so forth. Unfortunately, much of the literature is obscure on these important points. Furthermore, systematic psychiatric assessments have not been reported as frequently as one would like. For example, a

description of a patient as being "agitated, confused, and delusional," leaves it unclear as to whether one is dealing with an organic mental syndrome or another type of psychotic reaction. In addition, because of the great difficulty of assembling nonbiased series and adequate control groups, precise data about the incidence of mental dysfunction specifically due to endocrine diseases are hard to gather. Elucidation of some of these issues is provided by observation of patients receiving hormone therapy, although here too consideration must be given to the mental effects of the medical illness being treated. It is with these limitations in mind, then, that this summary of the current status of knowledge about psychiatric disturbances in endocrine disorders is presented.

For a full medical discussion of the endocrine disorders, as well as a summary of related mental disturbances, the reader is referred to Williams' *Textbook of Endocrinology.* For a recent comprehensive survey of the psychiatric aspects of endocrine disease, with an extensive bibliography, see Smith et al.

Adrenal Disorders

Cushings Syndrome

Cushing's syndrome is produced by excessive secretion of corticosteroids from the adrenal cortex. In about 70 percent of cases, the adrenocortical hyperplasia is secondary to hypersecretion of ACTH (adrenocorticotropic hormone) from the anterior pituitary, either because of a tumor or a hypothalamic neuroendocrine disturbance. In these latter cases, then, both ACTH and cortisol are secreted excessively. In the remainder of cases, there is a secreting tumor of the adrenal cortex, with secondary suppression of ACTH. Because of the effects of cortisol on intermediary metabolism and electrolyte regulation, the illness is usually associated with hyperglycemia, truncal and facial obesity, osteoporosis, muscle wasting and weakness, and hypertension. Hypersecretion of adrenal androgens may lead to hirsutism and intensification of libido in women (the latter probably related, in part, to local effects on the clitoris).

The occurrence of significant mental disturbance in Cushing's syndrome has been noted since Cushing's original paper—indeed, one of his cases was found in a mental hospital. For reasons noted before, the precise incidence of significant psychopathology in Cushing's syndrome is hard to determine, but it is quite high, perhaps up to half the cases, and the range of psychological disturbances which occur is unusually wide. Rough estimates from the

literature (reviewed by Smith et al.) suggest that about 15 percent of untreated cases become frankly psychotic, with another 35 percent experiencing a significant mental disturbance of other types. The literature, does not, however, distinguish between the aberrations seen in primary pituitary from those seen in primary adrenocortical Cushing's syndrome.

Depression (beyond the fatigue typical of the disease) is the most commonly occurring symptom ranging from a moderately depressed mood and overreactions to distressing life events, to severe depressive illness with delusions. Suicidal attempts occur in about 10 percent of cases. Elation is also occasionally observed, at times closely mimicking naturally appearing manic psychoses, with grandiosity, mental and physical overactivity, sleeplessness and inappropriate behavior. Irritability, anxiety, insomnia, difficulty with concentration, and spells of agitation often occur. Paranoid states, sometimes with hallucinations, are not uncommon. Patients may also experience periods of amnesia, episodes of confusion, and outbursts of temper. The mental changes may be quite fluctuant, with, for example, periods of elation, depression, irritability, and lucidity rapidly succeeding each other. Organic mental syndromes are sometimes seen, but they are more likely to be associated with the medical complications of Cushing's syndrome, e.g., severe hypertension with encephalopathy or congestive heart failure, uncontrolled diabetes, and electrolyte disturbances.

Prolonged corticosteroid therapy can induce somatic changes like those seen in Cushing's syndrome. Early psychiatric reports describe psychological responses to ACTH and cortisone, which were very similar to the wide range of mental disturbance seen in endogenous Cushing's syndrome, although not as common. (See references 12, 26, 38, 61, 66, 74, and 76.) At present, potent steroid analogues, like prednisone, have generally replaced ACTH and cortisone in medical practice, but the types of psychiatric complications appear to be the same, although some clinicians have the impression that depression was more common with ACTH therapy. Depression is much less commonly associated with steroid treatment than with endogenous Cushing's syndrome and elation seems much more common. True organic mental syndromes (in the absence of medical complications) probably are not common, and the confusional states appear to be primarily experiences of depersonalization and unreality, with perceptual distortions.

Even with small doses of prednisone, mild changes of mood are frequent, especially elation. Occasionally, patients accustomed to the mild elation associated with steroid treatment become depressed after steroid withdrawal. From our review of recent medical literature, major psychiatric disturbances appear to be more likely in dose ranges above 20 mg. of prednisone a day. But beyond that, a clear relation of psychiatric risk to dose has not been established. The same dose may be well tolerated on one occasion and not on another. Sometimes it is hard to separate the

psychological effects of the illness being treated from the drug effects themselves, especially in steroid treatment of disseminated lupus erythematosus with CNS (central nervous system) involvement.

As noted before, some of the psychological disturbances in Cushing's syndrome can be attributed to associated metabolic, cardiovascular, and electrolyte complications; some of the depression, for example, may be associated with hypokalemia. However, there appears little doubt that much of the psychopathology is due to the effects of ACTH and corticosteroids on the brain, although the mechanisms remain unclear. Corticosteroids have important effects on intracellular sodium content, and on the excitability of neural tissue, with alteration of the EEG (electroencephalogram) and lowering of seizure thresholds. Both ACTH and corticosteroids exert influences on the enzymes involved in the metabolism of catecholamines and serotonin, biogenic amines which have been implicated in naturally occurring affective disorders. Interesting effects of hyperadrenal-corticism on sensory thresholds in taste, hearing and smell have been noted in patients with Cushing's disease. Cortisol also increases the reuptake of norepinephrine by rat-brain tissue. Maas has recently reviewed the literature on the effects of corticosteroids and ACTH on catecholamines and electrolytes, and suggests a mechanism by which these effects may mediate depressive states when the hormones are hypersecreted. In hypophysectomized animals, corticosteroids prolong the extinction of learned avoidance behavior, while the opposite is

true of ACTH.

This experimental demonstration that ACTH alone has significant psychological effects which differ from those of corticosteroids may have important implications for understanding the differences in the psychological concomitants of Cushing's syndrome, Addison's disease, ACTH therapy, and corticosteroid therapy. It is possible, for example, that excess ACTH itself exerts primarily a depressing effect on mood, while excess corticosteroids may tend to produce mostly elation. This would account for the higher frequency of depression in pituitary Cushing's disease compared to steroid therapy, and the preponderance of depressive symptomatology in primary adrenal Addison's disease (see below) in which ACTH is hypersecreted. It is unfortunate that the older literature did not systematically and clearly differentiate the psychiatric complications of ACTH therapy from that of corticosteroid therapy; if ACTH is "depressogenic," one would expect more depressions with ACTH therapy. Similarly, the literature generally does not distinguish between the psychological concomitants of primary hypothalamo-pituitary from primary adrenal Cushing's syndrome; one might expect a higher incidence of depression in the former, if ACTH is "depressogenic." It also should be considered that in all three forms of Cushing's syndrome—hypothalamic, pituitary, and adrenal—a variety of corticosteroids are hypersecreted, while in exogenous steroid therapy, a single synthetic steroid is administered. It may be that certain corticosteroids differ in their euphoric

or depressive effects, and such differences may account for the differences in psychological responses to exogenous and endogenous steroids. These could be useful areas for future clinical investigation.

The treatment of choice for the psychiatric disturbances associated with Cushing's disease or corticosteroid therapy is to correct the disease or to reduce or temporarily discontinue the hormone medication. When the surgery must be delayed, or the medication continued for pressing medical reasons, however, the problem of controlling the psychiatric state by other means arises. We know of no definitive studies of the effectiveness of phenothiazines or antidepressants in such situations. Our own experience suggests that psychotropic drugs are often palliative, but rarely induce complete remission of the mental symptoms, as long as the hyperadrenalcorticism continues.

It should also be noted that certain naturally occurring psychotic states, particularly acute schizophrenia with emotional turmoil and severe depressive illnesses, are associated with excessive secretion of cortisol, probably due to hyperactivity of the hypothalamic neuroendocrine cells controlling the secretion of ACTH. Such patients never show the physical stigmata of Cushing's syndrome, but it remains a possibility that the increased ACTH and cortisol secretion may have a secondary effect on CNS function, perhaps aggravating the existing psychopathology.

Addison's Disease (Hyposecretion of Cortisol)

While acute failure of the adrenal cortex is a medical emergency, chronic adrenocortical insufficiency may lead to symptoms which are more subtle. The main clinical features include weakness and fatigue increasing as the day progresses; pigmentation of the skin; hypotension with associated dizzy spells and fainting; hypoglycemia with associated periods of headache; sweating; hunger; and gastrointestinal disturbances, including anorexia, weight loss, and diarrhoea. In primary adrenocortical failure, there is a secondary hypersecretion of ACTH in the absence of feedback inhibition by cortisol.

The mental symptoms are now seen as an "integral part of the disease syndrome." Apathy and negativism are present in most cases, with depression and irritability occurring in substantial numbers (although one German report describes euphoria as a common complication). Delusions occur in a small but significant percentage. Disorientation, confusion, delirium, and convulsions are features of severely advanced Addison's disease. As in Cushing's syndrome, the symptoms may fluctuate in intensity and gradually alter in type.

There are several possible mechanisms for the psychiatric disturbances. Profound debilitation and weakness certainly play a role in the depression of many patients. The hypoglycemia (which, in the absence of cortisol, does not

have to be great) may also contribute to the confusion and irritability, as may the decreased cerebral blood flow associated with marked hypotension. Correction of the electrolyte disturbances only partially alleviates some of the psychic disturbances. Because of the similarity of many psychic symptoms to those of hypercalcemia, it is worth noting that Addison's disease is on rare occasions associated with elevated serum calcium levels. Pre-renal azotemia may also play a role.

Not all of the psychiatric abnormalities can be directly related to the severity of these metabolic complications, however, and there are significant effects of both cortisol deficiency and of ACTH excess on the brain. These include the previously mentioned effects on excitability of brain tissue, on intracellular electrolytes, and on the metabolism of biogenic amines. The paradox that depression is a common feature both of Cushing's and Addison's disease could possibly be related to the fact that in both conditions ACTH can be hypersecreted. With appropriate corticosteroid therapy (which also suppresses the excessive ACTH secretion) the physical and mental disturbances are nearly always reversed.

Adrenogenital Syndrome

In the adult, androgen-secreting tumors of the adrenal cortex produce pronounced virilizing effects in the female, with intensification of libido and

associated psychological responses to the change in physical appearance.

It is in the virilized female infant, however, that the most enduring effects on the psyche may be noted. An adrenogenital syndrome at birth may be the result of inborn enzymatic defects in the synthesis of cortisol, or may be secondary to the use of androgenic progestins in the treatment of the pregnant mother to forestall impending abortion. Since there are frequently marked effects on secondary sex characteristics, especially in the female, the infant may be assigned to the wrong sex. The evidence, well reviewed by Money, raises the possibility that gender identity is greatly influenced, perhaps fixed, by the nature of the sex assignment and associated social and psychological upbringing in early childhood, and that after gender identity is formed, it is unwise to reassign the child to his "correct" chromosomal sex.

Of further interest is the evidence that even transient fetal androgenization may have effects on the developing brain of the female, leading to enduring psychological traits in childhood and adolescence. Such effects were first noted in fetally androgenized female monkeys, who after birth were significantly more aggressive in play and in other social situations than their nonandrogenized female cohorts. There is some preliminary evidence that there are analogous effects of fetal androgenization in human females, who have been reported to be more tomboyish in interests and behavior in childhood. More controversial are preliminary data, suggesting

that fetal exposure to androgens may be associated with a significant increase in intelligence; artifacts in the sampling of the population may account for these latter results.

Klinefelter's Syndrome

This genetic disorder (XXY) of males is associated with hypogonadism and decreased testosterone secretion. At puberty, testosterone secretion does not increase, with resultant eunuchoid appearance and impotence.

For many years, an apparent increase in psychopathology in these patients has been reported, well reviewed by Swanson and Stipes. The available evidence (not conclusive) suggests that the average IQ of these patients is less than would normally be expected, and that the incidence of a variety of psychotic states is increased. The most common psychiatric disturbances, however, are severe character disorders of several types, especially schizoid withdrawal and antisocial psychopathy. It is not clear to what extent the psychopathology is due to the patient's psychological response to his sexual disorder; however, the physical disability does not become clinically manifest until puberty, and most psychological theories of psychosis and severe character disorders predicate traumata in *early* childhood. If indeed in such patients the IQ is lower and the incidence of psychosis and severe character disturbance is higher, one must consider the possibility of associated genetically determined mental aberrations, or of effects of testosterone deficiency on the developing brain.

Testosterone replacement therapy in the adult appears to be of little value in the treatment of either the impotence or the mental disturbance,

although it may possibly be of value in the child or adolescent.

Thyroid Disorders

Hyperthyroidism

Excessive secretion of thyroid hormone may be due to tumors of the thyroid gland, or to excessive stimulation of the thyroid by extrathyroid agents. Graves's disease is an example of the latter and, in its clinically fully manifest form, is characterized by thyrotoxicosis, goitre, and exophthalmus. The disease is much more common in women. Recent evidence relates Graves's disease to the presence of an immunological blood factor of extrapituitary origin, of which long-acting thyroid stimulator (LATS), 35 may be an example.

The chief symptoms of thyrotoxicosis include an increase in metabolic rate, with excessive heat production, and associated heat intolerance and sweating; an increase in cardiac rate and output; weight loss despite increased appetite and caloric intake; muscular weakness and easy fatigability.

Mental symptoms are practically always present, with nervousness, emotional lability, and hyperkinesia characteristic of most patients. To quote Ingbar and Woeber, "The nervousness of the thyrotoxic patients is not that of the patient who is chronically anxious, but rather is characterized by restlessness, shortness of attention span, and a need to be moving around and

doing, despite a feeling of fatigue." Other clinicians have noted that the warm dry hands of the nervous hyperthyroid patient distinguish her from the anxiety neurotic, whose hands tend to be cold and clammy. Crying spells, irritability, and excessive startle reactions are also typical. (In older patients, the muscular weakness may be so great as to preclude hyperkinesia, leading to a predominantly apathetic picture.) Paranoid trends and suspiciousness occasionally are present. Nevertheless, more severe psychiatric illness in chronic hyperthyroidism is rare, except in the psychosis prone person.

The so-called thyroid "crisis" or "storm" is rarely seen since the advent of modern antithyroid therapy. This fulminating attack of hyperthyroidism is usually characterized by extreme hyperpyrexia, anxiety, and tachycardia; delirium, coma, and even death may ensue. It may be precipitated by an episode of anxiety, especially presurgically.

The mental symptoms of hyperthyroidism are evidently related to the direct effect of thyroid hormones on the brain, and the symptoms can be partially reproduced in normal subjects by the administration of thyroid hormone, but the mechanism is not clear. Thyroid hormone increases the sensitivity of neuroreceptors to catecholamines, decreases monoamine oxidase activity, and decreases the turnover rate of norepeinephrine; these actions may play a role in the mental states associated with thyrotoxicosis.

Recent investigations have raised questions about once prevalent theories that Graves's disease is likely to be precipitated by emotional stress, especially object-loss, or that it is more likely to occur in patients with specific personality types characterized by premature assumption of responsibility and a martyrlike suppression of dependency wishes. Retrospective evaluations, always difficult, have not reliably replicated these psychological formulations. A prospective study has shown increased activity of subclinical, but radiologically demonstrable, thyroid "hot spots" in association with nonspecific life stress; the relation of these subclinical "hot spots" to the etiology of Graves's disease is unknown, however, and whether they even have a role in the pathogenesis of toxic nodular goitre is not established. The role of psychological factors in the etiology of hyperthyroidism remains, then, an open question.

Hypothyroidism

Hypothyroidism in the adult is commonly caused by surgery or radioactive-iodine therapy. The spontaneous form is usually secondary to atrophy of thyroid tissue, probably due to an autoimmune thyroiditis. The spontaneous disease usually has an insidious onset, and the changes may not be noticed by the patient until the disease is far advanced. With the deficiency of thyroid hormone the metabolic rate is markedly reduced, and nearly all hypothyroid patients experience cold intolerance, decreased sweating, and

generalized weakness and lethargy. In addition, speech is slowed, eyes and face become puffy, and the skin coarse and dry.

Mental symptoms are very common. Thinking is slowed in the great majority, and memory is impaired in about two-thirds of the cases. Depressed mood is typical although clinical depressive illness probably is not. Psychological testing confirms the impression that the majority of myxedematous patients suffer from at least a mild organic mental syndrome. The psychoses which have been reported ("myxedema madness") occur in a small percentage of patients and appear to be mostly more dramatic and severe organic mental syndromes, with the typical symptoms of confusion, memory loss, and agitation, and occasionally paranoid ideas, delusions and hallucinations.

Unfortunately, while appropriate thyroid- hormone-replacement therapy reverses most of the clinical stigmata of myxedema, the organic mental deficit does not always fully remit, especially in cases of long standing hypothyroidism. In cretinism the prognosis is especially poor, with the degree of permanent intelligence loss roughly correlated with the duration of the untreated illness.

Parathyroid Disorders

Hyperparathyroidism

Parathyroid hormone promotes the absorption of calcium from the gastrointestinal tract, the resorption of calcium from bone, and the excretion of phosphate from the kidney, all of which actions increase the concentration of circulating calcium ion. Chronic hypersecretion of the hormone, due to tumor or neoplasia of the parathyroid gland, produces clinical symptoms related to the disturbances in bone metabolism and the effect of hypercalcemia on various organ systems: skeletal pains, anorexia, nausea, constipation, muscular weakness, polyuria, renal calculi with renal colic, and cardiac irregularities.

Mental symptoms are present in at least half the cases, the most common being lassitude and depressive mood, with loss of interest and anhedonia. A minority of patients develop organic mental syndromes, with memory impairment, confusion, paranoid ideas, and hallucinations. In an outstanding study of fifty-four cases, Petersen showed that the severity of mental symptomatology increases with the blood calcium level, with organic brain syndromes occurring primarily at concentrations of about 14-16 mg. percent and above. Parathyroid hormone itself appears to have no mental effects, since lowering blood calcium by dialysis (which does not affect parathyroid hormone itself) immediately reverses the mental disturbances,

and patients with hypercalcemia due to other causes show similar mental aberrations.

Calcium ion plays a significant role in altering permeability and excitability of the nerve membrane, and also promotes the discharge and depletion of norepinephrine and its biosynthetic enzyme, dopamine beta hydroxylase, from nerve granules. It is not unlikely that these actions play some role in the mental aberrations noted in hypercalcemia.

Hypoparathyroidism

Hypoparathyroidism is most commonly secondary to damage or surgical removal of the thyroid gland. About 200 cases of idiopathic hypoparathyroidism had been reported in the literature by 1962. In both conditions symptoms develop which are closely related to the lowered blood calcium concentration characteristic of the illness. Seventy per cent of cases present manifestations of tetany, such as numbness, tingling, and cramps in the extremities, leading to carpopedal spasm. In milder forms of the illness, the patient complains of fatigue, weakness, and tingling sensations.

Mental symptoms are common. In an extensive review, collecting data from 258 papers, Denko and Kaelbling attempted to classify the psychiatric disturbances occurring in patients with both idiopathic and surgical hypoparathyroidism. Because the disease is rare, and cases have generally

been reported by nonpsychiatrists, a clear picture of the psychiatric symptomatology is difficult to form. In idiopathic hypoparathyroidism, about one- third of the cases appeared to suffer intellectual deterioration, in many instances reaching levels of mental retardation. At least a third also showed symptoms of organic mental syndromes of various types, with some patients experiencing both intellectual deficit and organic mental syndromes. There also appear to be additional psychiatric disturbances which are hard to classify, described as “nervousness,” “emotionality,” etc. In idiopathic hypoparathyroidism, treatment of the endocrine disorder often leaves the individual with intellectual deficit. In surgical hypoparathyroidism organic mental syndromes also occur but intellectual deficit is seen less frequently. A variety of other psychotic states are noted, but their vague descriptions leave it unclear as to whether these are also organic mental syndromes or psychoses of other types. Treatment of the endocrine disorder in surgical hypoparathyroid cases (by Vitamin D) generally leads to complete remission of symptoms.

Pancreatic Disorders

Diabetes

Diabetes in its usual form is believed to involve a genetic predisposition and an evolution which goes through several stages before the manifest clinical illness appears. Initially, the central disturbance may be a defect in the metabolic action of insulin; during this latent period insulin may actually be hypersecreted. In the later stages, when the disease is manifest, insulin secretion is deficient, and the clinical symptoms are secondary to this disturbance. As sugar fails to be metabolized, blood sugar rises and is excreted in the urine, with secondary polyuria and polydipsia. Proteins and fats are metabolized in excess, with associated weight loss, ketosis, ketonuria, and potassium loss. Susceptibility to infection is increased, especially in the skin and genital tract. The patient feels chronically weak and fatigued and may complain of mental dullness and depression.

The mental symptoms become especially prominent in severe untreated diabetic acidosis, which is associated with somnolence, difficulty in thinking, confusion, obtundation, and eventually, coma and death.

The mechanism of the mental dysfunction in diabetic acidosis is partially understood. The deficiency of insulin per se is not responsible, since the brain does not require insulin to metabolize glucose, and although the

patient is severely dehydrated, cerebral blood flow is not decreased. However, as shown in the classic study by Kety et al, cerebral oxygen consumption is substantially reduced, the decrement correlated closely with degree of stupor and also with the extent of ketosis. In all likelihood, certain of the blood-borne ketones act like ether anesthetics on the CNS.

Physiological stress such as infection, fever, and obesity may precipitate the onset of clinical diabetes, as well as exacerbate the established disease. There is some evidence that emotional stresses may play a similar role. For example, in a study of adult diabetics on a metabolic ward, emotional stresses were shown to be associated with temporary increases in metabolic indices of diabetes. The pathophysiological mediating mechanisms have not yet been demonstrated. One possible pathway is the hypersecretion of cortisol and adrenalin associated with severe emotional distress, since increases in both cortisol and adrenalin secretion antagonize the action of insulin. In support of the role of adrenalin, one study indicates that beta adrenergic blocking agents can be helpful in stabilizing the medical management of brittle juvenile diabetics, who show increased FFA (free fatty acids) and ketonuria during stress interviews. It also may be relevant that nondiabetic patients who develop depressive illnesses are noted to have a relative insulin resistance, which reverts after recovery.

Although it is beyond the scope of this discussion, it should be noted

that severe diabetes poses a major burden on the psychological adaptative mechanisms of many patients, particularly juvenile and adolescent diabetics who must rigorously control diet and insulin dosage at a time when there is a great need not to feel different from their peers. Other patients may improperly manage their regimens in the context of periods of depression, struggles with significant objects, needs for secondary gain, and so forth. The fear of developing major medical complications from chronic diabetes also may shadow the outlook of many patients. The need for psychological sensitivity and understanding on the part of family members and primary physicians is accordingly great.

Hyperinsulinism

Hyperinsulinism spontaneously occurs with insulin-secreting islet-cell tumors of the pancreas, and more rarely, with insulin-secreting extrapancreatic tumors. In patients with adrenocortical insufficiency, the normal secretion of insulin is functionally excessive, giving rise to the symptoms of hypoglycemia. There is also a group of patients who appear to secrete excessive insulin postprandially with a drop to unusually low concentrations of blood sugar two to four hours after meals. Most commonly, however, hyperinsulinism occurs in diabetic patients who take more than their metabolically required dose of insulin.

All of these states lead to hypoglycemia, and since brain metabolism is completely dependent on glucose, the primary symptoms of hypoglycemia are due to CNS glucose starvation, similar in its effects to cerebral anoxia. Indeed, the degree of depression of CNS oxygen utilization in hypoglycemia has been shown to be closely correlated with the CNS symptomatology. As would be expected, preexisting brain damage or cerebrovascular insufficiency significantly increases the sensitivity to the effects of hypoglycemia. The initial effects are due to cortical depression and a concomitant release of epinephrine from the adrenal medulla. The cortical symptoms include headaches, faintness, confusion, restlessness, somnolence, hunger, irritability, and visual disturbances. Adrenergic symptoms include anxiety, tremor, perspiration, tingling of the fingers and around the mouth, tachycardia, and pallor.

In patients with insulinomas or massive insulin overdose, progressive CNS depression may occur: the patient loses consciousness, and often manifests sucking, grasping, and grimacing movements, along with twitching and clonic spasms. Further CNS depression leads to the neurological signs associated with the involvement of deeper brain structures, such as Babinski signs, inconjugate ocular deviation, tonic and extensor spasms, and so forth. Death may ensue.

Administration of glucose promptly reverses the acute symptomatology.

However, those patients who suffer repeated or extended periods of severe hypoglycemia frequently suffer some degree of irreversible brain damage. The pathological and mental changes are similar to those seen after chronic CNS anoxia.

Menstrual Disorders

Premenstrual Tension

Several systematic studies have confirmed what clinicians and women have long believed, that the menstrual cycle is frequently associated with definite changes in mental state, significant enough in some women to be termed a premenstrual syndrome. Psychological assessments of large samples of women reveal that, for the groups as a whole, negative affects begin to increase about a week before menstruation, reaching a peak on the day of menstruation, and then falling after the menstrual phase, reaching a minimum during the middle portion of the cycle. One study also indicates that positive pleasant feelings follow an inverse pattern, reaching a peak in midcycle. The premenstrual feelings noted by the women included irritability, hostility, depressed mood, emotional overreactions to trivial incidents, crying spells, anxiety and tension, and mood swings. In addition, many women note difficulties with concentration, forgetfulness, and judgment. Behavioral changes, such as lowered school or work performance and withdrawal from social activities, also occur. Other features of the premenstrual period are fatigue, bodily aches, particularly headaches and backaches, as well as water retention with uncomfortable feelings of distention. Moos has noted that the psychological symptoms can be grouped in several categories (negative affects, concentration disturbances, behavioral changes, and pain) of varying

prominence in different women, sometimes occurring together and sometimes not.

What is of further significance to the psychiatrist is the evidence that psychopathological disturbances of many types can be intensified during the premenstrual and early menstrual phases. One study, for example, suggests that preexisting neurotic traits become more prominent in the premenstrual period. Others have noted that the incidence of suicide and hospitalization for acute psychiatric illness is disproportionately great during this phase.

The pathophysiological mechanisms underlying the various premenstrual syndromes are becoming clearer. While water retention accounts for the bloating, swelling, and painful distention troublesome to many women, it is not closely correlated with the onset and disappearance of many of the psychological symptoms, and diuretic medication is not particularly effective in relieving the purely psychological symptoms.

On the other hand, there is a growing body of circumstantial evidence that progesterone, which is increasingly secreted in the premenstrual phase, may play a primary role in the psychological symptomatology. Regimens of combination-type oral contraceptives, which contain fixed doses of progestogens and estrogens, are associated with a greater incidence of those mental symptoms typically seen in the premenstrual syndromes, but also, as

might be expected, the fixed dose of progestogens throughout the cycle appears to eliminate the psychological fluctuations seen during the normal cycle. On the other hand, the oral contraceptive regimens which administer only estrogens until the final five days of the cycle, at which point progestogen is added (sequential type), are associated with fewer emotional complications, although a premenstrual increase in symptomatology is once again apparent.

A possible mechanism for the apparent mental effects of progesterone is an influence on monoamine oxidase activity (MAO). Grant and Pryse-Davies reported that increased uterine MAO activity normally occurs in the premenstrual (progesterone) phase. Contraceptive agents which contain strongly progestational compounds markedly increase uterine MAO activity much earlier in the cycle, while agents that are primarily estrogenic in action tend to inhibit uterine MAO activity. The incidence of depressive symptomatology in their study roughly correlated with the effects of contraceptives on MAO activity. If brain MAO is similarly affected, it is possible that increased catabolism of biogenic amines may be involved in the psychological symptoms, since such a neurochemical disturbance has been proposed to occur in clinical depression.

These theories remain unsupported, however, and there are some defects. The synthetic progestogens in oral contraceptives differ in several

ways from endogenous progesterone, and in some respects, resemble androgens in their biological activity. Furthermore, a clear hormonal difference between women with premenstrual tension and those without has yet to be demonstrated. Finally, for some women with premenstrual tension, progesterone administration appears to be helpful.

Functional Amenorrhea

It has long been recognized that under conditions of emotional stress women frequently fail to menstruate for one or two months. As an extreme example, a high incidence of amenhorrea was reported in women on imprisonment in concentration camps during World War II, even before starvation became a factor. Similar observations have been made in less grim settings, however, for example among adolescent girls adjusting to boarding school, summer camp, etc.

The mechanism appears to be a failure of ovulation, associated with an absence of the usual midcycle burst of LH (luteinizing hormone) secretion by the pituitary. Presumably, emotional stress in some way inhibits the hypothalamic neuroendocrine cells producing LH releasing factor.

In anorexia nervosa, amenhorrea also typically occurs, not necessarily associated with malnutrition.

There is also a group of women who fail to ovulate for long periods of time in the absence of any demonstrable endocrine or gynecological abnormality, other than the absence of the surge of secretion of LH (luteinizing hormone) and related hormones at midcycle. In the past the diagnosis of “functional” amenorrhea was made by exclusion of obvious anatomical or endocrine pathology. Recently it has been possible to re-establish ovulation by the use of such agents as clomiphene. There are very few systematic psychological studies reported on such women, however, to support the idea, once widespread, that the disturbance is primarily psychogenic. The existing psychiatric case reports suggest in certain women the prominence of conflicts over masculine and feminine strivings, and also around separation-dependency issues with their mothers. It should be noted, however, that these are common conflicts in women, while chronic functional amenorrhea is relatively rare.

Failure-to-Grow Syndrome

Among children who fail to grow normally, a subgroup has been identified in which psychosocial issues appear to play a significant role. Frequently there is evidence of parental neglect, with associated behavioral disturbances of many types in the children, including the syndrome of anaclitic depression. Endocrine studies on the children have demonstrated a failure to release growth hormone in response to the usual stimuli, such as insulin-induced hypoglycemia. The disturbance appears likely to be in the hypothalamus, involving the neural influences which normally control secretion of growth hormone releasing factor or inhibiting factor from the median eminence neuroendocrine cells. What is especially striking is that after a period of emotionally supportive hospital care, behavior, growth, and growth hormone secretion all frequently return to normal. Since growth hormone secretion appears to be closely related to the metabolism of brain catecholamines, and since these neurotransmitters also mediate mood, it is possible that emotional deprivation alters growth hormone secretion via these neurochemical mechanisms. In this respect, it is interesting to note that depressive illness in adults is frequently associated with an inhibition of growth hormone release.

Concluding Remarks

A review of the psychiatric disturbances associated with the major endocrine disorders (excessive or deficient secretion of the adrenal cortex, thyroid, parathyroids, and pancreatic islet cells) reveals a wide variety of psychopathology. Certain mental symptoms appear to be especially common, however, such as fatigue, depression, diffuse anxiety, and organic mental syndromes. While the fully developed endocrine disease is usually quickly recognizable by the psychiatrist, the early stages can frequently pass unnoticed, leading to incorrect diagnoses and treatment. Since endocrine disease is probably as frequent a cause of psychiatric disturbance as brain tumor, it would seem appropriate for the psychiatrist to be as alert to the possibility of the former as the latter, particularly in the presence of the symptoms noted above. A definitive diagnosis requires a full endocrine workup, of course, but screening information could easily be obtained by a group of morning blood tests readily analyzed by any good commercial laboratory: a fasting blood sugar, protein-bound iodine, calcium, cortisol, sodium, and potassium. Such a battery of tests probably should be considered as often as an electroencephalogram in the evaluation of the patient presenting with psychiatric disturbance.

Finally, as has been indicated, the mechanisms by which hormonal disturbances lead to mental aberration are in many instances still unclear.

Further research in this area not only offers the potential for clarifying the pathophysiological effects of endocrine disease on the central nervous system, but may also illuminate significant neurochemical and neuro-physiological aspects of primary psychiatric disorders as well.

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Notes

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