CHAPTER 5

Illness Syndromes: High Disability

Our stability is but balance, and wisdom lies in
masterful administration of the unforeseen.
—*Robert Bridges: Testament of Beauty*

Part 1. Regulators of Homeostasis—Behind Illness Syndromes

The illness syndromes which are predominantly incapacitating, like the illness syndromes which account for major mortality in the United States, are intimately bound with the victim's coefficient of homeostatic elasticity. They differ, however, in that they appear to be more localized or circumscribed. They are more readily ascribed to adventitious agents, temporary indiscretion or a peculiar susceptibility.

Among the incapacitating illnesses most frequently encountered are the rheumatic diseases, particularly arthritis, and gastrointestinal and respiratory diseases. When these illnesses become chronic or recurrent they are readily associated with neurosis. Rheumatism and nervous stomach run in families and often become "the favorite illness" of one or another side of the family. But with these illnesses also susceptibility is based on or involves a disturbance of body chemistry and of channels of affective discharge.

Along with a reorientation in the understanding of physiological compensatory mechanisms, some progress has been made in understanding the specific physiological expressions of affect. It is known that physiological expressions of any given affect may occur without the corresponding emotional and mental experiences, that is, without individual awareness of their affective significance. It is the humoral state of the organism which determines to a major degree the way in which the person perceives or reacts to external stimuli. Omission of an impulsive response to stimulus, whether determined by external circumstances or,

as in the psychoneuroses, by internal inhibitions, necessarily interferes with the chemistry of the processes of excitation and gratification.

It has become clear that an understanding of diseases, cause unknown, as well as of immunity to diseases in which a known external noxious agent is involved, depends on knowledge of the homeostatic regulators of metabolism, especially of the neuro humoral system and its relationship to the central nervous system and the musculo skeletal system. Here also lies the hope of understanding the processes of growth and senescence. Life expectancy has been increased through the conquest of disease, but until Benjamin Franklin's prediction has been fulfilled and that most stubborn of all diseases, old age, has been conquered, there remains a point beyond which healthy functioning cannot be maintained.

Knowledge has increased more rapidly in the field of regulators of homeostasis than in any other field of medicine. There have been a few recent studies in which anxiety has been specified as an accompaniment of stress response and correlated with biochemical and physiological studies, but, as Basowitz et al.[38] note, the prestress personality structure on which stress is imposed is too often ignored. At higher levels of anxiety there is no longer the ability for effective action, and behavior breaks down. All aspects of psychological and physiological functioning are modified. The body has many adequate mechanisms for self-regulation, but the cost of such regulation to the total organism is too often overlooked. With increasing, and even more, with chronic stress, immediate adjustment often leads to impairment of some bodily function or functions as the organism's resources are diverted and absorbed more and more in defensive processes.

Although many illness syndromes, including the syndromes of mental disease, are chronic defenses against anxiety, anxiety need not result in illness. It may stimulate the organism to mobilize its resources toward a higher level of functioning, of learning and of adjustment. An enthusiastic, unfrightened response to change and to the unknown is among the outstanding characteristics of the long-lived,[151] and the illness history of centenarians is remarkably free from the diseases of organs and organ systems to be discussed in this chapter. Behind the syndromes of illness lie disturbances of the homeostatic regulators.

METABOLIC AND ENDOCRINE DISORDERS *

Physicians who were reluctant to call an unexplained illness imaginary tended to blame the glands. When the endocrinologist was unable to

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shed light on the problem there was still nothing to hold accountable but the patient's mind or heredity, or possibly allergy.

Gradually humoral mechanisms were recognized as the translators of the tempo of the nervous system into the tempo of metabolism and *vice versa*, just as chemoreceptors translate nerve impulses into substances analogous to those generated by and activating the endocrines. But it is only recently that the endocrine system has been recognized as the "chemical coordinator of the individual" which "includes more than the conventional system of ductless glands."[644a] It is now known that the interrelationship of the nervous and endocrine systems revolves around a physiologic attribute which is common to both the elaboration and secretion of hormones. The hypothalamus secretes an antidiuretic hormone which bypasses the pituitary-adrenal axis. In addition, it probably secretes another humoral agent which acts directly on the adrenal. This will be discussed in more detail later.

Of considerable interest has been the recent observation that the stimulus for aldosterone secretion may well lie in the posterior diencephalon as well as portions of the pineal. The significance of this realization can best be appreciated by reviewing the concept of harmful mineralocorticoid effects and understanding that aldosterone represents the prototype of such "damaging" corticoids. In addition, recent work by Venning et al.[653a] shows that aldosterone levels can be markedly increased in situations of emotional stress and tension. Farrel's report[181a] at the 1958 Laurentian Hormone Conference presented evidence of the isolation of a potent neurohumoral aldosterone stimulus center located in the diencephalon. This suggests a potential pathway for the liberation of so-called "harmful" corticoids during stress.

An analogous situation exists with respect to the mechanism of liberation of ACTH, and Clayton et al.[104] have recently isolated a hypothalamus neurohumor which can be shown to stimulate the production and release of ACTH in in vitro and in vivo systems. In addition to these hypothalamic influences on hypophyseal and adrenal secretion of hormones, one must bear in mind the homeostatic impact of the regulators of endocrine activity. Thus liberation of ACTH from the pituitary occurs also as a result of decreased plasma steroid levels secondary to increased peripheral utilization or accelerated hepatic detoxification. It is quite conceivable that certain forms of stress, particularly exercise and muscular tension, could activate the pituitary-adrenal axis by virtue of increased peripheral utilization and resultant hypocorticoidemia, rather than directly stimulating hypothalamic-hypophyseal pathways. Another possible mechanism might well be the liberation of catechol amines from the adrenal medulla or the release of noxious tissue factors such as histamine which might stimulate ACTH release. In all of this,

however, it is immediately apparent that a delicate system of checks and balances exists within the neuroendocrine apparatus which serves to preserve the constancy of the *milieu intérieur*.

Currently, attention is being directed to the role of the mineral-ocorticoids as part of this system. For example, constriction of the vena cava above the liver or pressure around the carotid with a cuff about the neck promptly results in a rise of aldosterone levels. If the carotid sinus nerve is sectioned, then this anticipated rise does not occur. On the other hand, section of the vagi does not interfere with the expected elevation, but following removal of the constriction the elevated aldosterone levels do not return to normal as occurs in the control animals. There is abundant evidence, then, to suggest the presence of excitatory and inhibitory factors in the reflex neural control of secretion of this important hormone, which plays a major role in the daily economy of salt and water.

The role of the central nervous system in the regulation of affective states and visceral function has long been recognized, but the modus operandi of its mediation via endocrine and autonomic pathways has been subjected only recently to objective observation and testing. Comparative anatomists and the neurophysiologists are mapping out the connections of the hypothalamus with higher centers. The two major connections of the posterior hypothalamus go to the limbic system, the "great limbic lobe" of Broca. This is paleocortex or old cortex which has been recognized only recently as having an integrative function in the regulation of emotional and visceral states.

The posterior hypothalamus is intricately connected with the amygdala. Stimulation of this area with implanted electrodes gives a prompt increase in plasma hydroxycorticoids. The second main connection is to the hippocampus, and stimulation via electrodes planted here fails to bring about a similar response. The result is instead a prolonged depression of compound F (hydroxycorticoid) secretion and the prevention of the anticipated rise seen with amygdaloid stimulation. Here again is evidence of reflex neural excitatory and inhibitory effects in a concerted effort to preserve homeostasis.

Furthermore, it becomes apparent that this system, which Paul McClean called the "visceral brain," can mediate two different patterns of response to stress. It is conceivable that adaptational disorders could arise in a setting of either increased or diminished neuroendocrine capacity for coordinated response. Of still greater importance is the fact that lesions in this limbic system result in profound changes in behavior. Whether or not such affective disorders and endocrine alterations are a result of the same basic process or whether one mediates the other cannot be determined at the present time, however.

Finally, in this cursory review of neuroendocrine relationships, justice could not be done to the adrenal medulla which synergizes the activities of the sympathetic nervous system. At the same time as it activates certain endocrine pathways, it may, in certain instances, communicate alterations in the external environment. The metabolic activities of the adrenal medulla are not to be ignored; for example, the role of epinephrine in the release of hepatic sugar.

The interplay between external environment and the endocrine system has received considerable study. After describing differences between wild and domesticated rats from the point of view of anatomy, physiology and behavior, Richter[514] calls particular attention to the marked atrophy of the adrenal glands "during domestication." He suggests that "man may have undergone parallel changes during his transition from a wild to a controlled, protected environment. As he has become more civilized his adrenals may have become less efficient, thus accounting at the present day for the high incidence of diseases that respond so remarkably to treatment with cortisone and ACTH."

The dominance of this system in the nonspecific factor in all diseases is known. Compensation is sometimes approximated following the dysfunction of one organ system by the overactivity of one other or others. Similarly, the loss of the sympathetic division of the autonomic nervous system in certain animals may be compensated by overactivity of the humoral mechanisms. Papez[483] demonstrated that bilaterally sympathectomized male and female dogs were able to live relatively normal lives and produce normal pups for over a year following the operation although autopsy revealed that no nervous regeneration had taken place.

Even if the dysfunction of one element in the system has been compensated so that the individual appears to be in perfect health, his adaptive capacity may be reduced to such a point that the imbalance caused by the next insult will be magnified, perhaps beyond the point of tolerance. Early experiments indicated that an animal highly adapted to one stressor agent (e.g., cold) loses much of its resistance and adaptability to other stressors (e.g., drugs). This phenomenon was called "crossed sensitization"[574] and ascribed to a "consumption of adaptation energy," necessitated by exposure to the first stressor agent.

During the past ten years, much has been learned about the equilibrating forces in blood chemistry, bioelectric potentials, possibilities of manipulating the humoral mechanisms, and the psychic as well as somatic factors which determine the balance of the *milieu intérieur* in relation to the *milieu extérieur*.[52] Commenting on the nervous system and the endocrines as regulators of body chemistry having countereffects which work as negative feed-back regulators, Williams[674] writes: "In some instances, the nervous system can stimulate the target gland directly,

and at times the impulses go directly to the body cells. Moreover, many of the adjustments can take place without the aid of the nervous system, the influences being exerted by certain hormones or the products of metabolism on the pituitary target glands or the general body cells themselves." Friedgood[206] notes:

> Until recent years, it was the practice to limit the use of the word *hormone* to the internal secretions of the endocrine glands, and to include among the latter only those ductless, secretory epithelial organs that elaborate chemically specialized substances of high biologic specificity. However, such distinctions are now considered untenable in view of what has been learned about the internal secretions of neurons, neuroendocrine cells, and highly differentiated endocrine epithelia from the standpoint of their ontogenetic physiologic and biochemical interconnections, their chemostructural relations, and their contribution as a coordinated group of substances to the integration and homeostasis of the organism's metabolic economy.

He concludes that environmental stress and its biologic repercussions in neuroendocrine function and enzyme metabolism constitute one of the most challenging problems with which the endocrinologist is confronted. The close compensatory relationship of the endocrine system and the autonomic nervous system involves the concentration of inorganic salts in blood and lymph, their effect on acid base equilibrium and the several biologic potentials intrinsic to all organ systems and to every cell. The neurohumoral system in its inclusive definition appears to supersede all other organ systems in its rheostatic control of biologic equilibrium. It brings about an adjustment that tends to integrate the component parts of the organism, which is analogous to the role ascribed to the ego in personality. What has been called the psyche of each living cell with its immediate contact with humoral mechanisms may aid or interfere in the integrative functioning.

The combined effect of nervous and endocrine stimulation may alter the function of any and all organ systems and they themselves are directly involved in situations of stress and anxiety. Physicians, then, have not been wrong in suspecting "the glands," but until recently there has been little knowledge of what Walter Bauer[41] called "the astonishing ability of cortisone and ACTH apparently to turn diseases on and off at will. This does mark the opening of a new era in medicine."

The understanding of the participation of the adrenal cortex in a variety of endocrine and non-endocrine disorders has been based on observation of the effects of cortisone and related steroids in various diseased states and the detection of abnormal adrenal function by conventional laboratory technics. While the observation that cortisone and its congeners are beneficial in diverse illness syndromes is of interest, this in itself does not permit one to conclude that the adrenal is basically

at fault in any of these situations. The fact that aspirin reduces the temperature in rheumatic fever or rheumatoid arthritis as well as in some infections should not lead one to conclude that there is a deficiency of salicylic acid in these states. Similarly, the nonspecific antiphlogistic (anti-inflammatory) effects of steroids may represent a pharmacologic rather than a physiologic phenomenon.

On the other hand, even with present crude technics it has been possible to obtain evidence of abnormal adrenal function in many clinical disorders markedly alleviated by steroid therapy. It is probable that better understanding of the pathogenesis of many of these disorders will clarify the role that adrenal function plays in their etiology or aggravation.

There are many factors which determine the present concept of adrenal function. While it is assumed that steroid levels in the plasma represent the functional activity of the adrenal cortex at a given moment, it is obvious that such values merely are indicative of the balance between adrenal output and the organism's homeostatic needs. The adrenal may respond exaggeratedly to any of a number of stimuli, but concomitant increased requirements for steroids may exist in the periphery. In such an instance the body's response to the increased demand may or may not be reflected in the sampling of blood or urinary corticoids.

The role of detoxification systems in the metabolism of physiologically active steroids deserves serious study. Well over 30 steroids have been identified in adrenal venous effluent or adrenal substances and the metabolic significance of many of these compounds is quite uncertain. It is difficult to determine what makes a steroid a hormone.

Today only three steroids are recognized as being true hormones of physiologic significance. They are cortisol (hydrocortisone, compound F), aldosterone, and corticosterone (compound B). The metabolic significance of the latter compound is not clear. Physiologically it possesses both mineralocorticoid properties similar to aldosterone and glucocorticoid propensities similar to hydrocortisone. The fact that it appears to be ineffective in both spheres has made physicians take it lightly. However, powerful synthetic compounds with marked glucoid (cortisone) and mineralocorticoid (desoxycorticosterone) effects can be found in adrenal tissue only in small quantities or on rare occasions, and their participation in daily function is quite obscure. The many other substances identified have varying impacts on physiological responses in the parameters mentioned above as well as in certain other specific and inadequately studied areas of biochemical androgenic and estrogenic activity. It is not known whether they are functionally significant compounds or merely represent inert precursors or inactive degradation

products. There remains the possibility that they are artifacts of extraction and identification.

Stress can exert its effects via influences on hepatic function. It is quite conceivable that the liver, with its tremendous capacity for enzymatic alteration of the cyclopentanoperhydrophenanthrene nucleus, may be a major factor in determining the functional status of adrenal activity since the competition for certain degradation systems, such as glucuronide conjugation, by other substances in the liver might easily affect the level of plasma steroids without mediation through the adrenal cortex. In patients with liver disease the rate of disappearance of intravenous hydrocortisone is inversely proportional to the degree of hepatic damage as measured by the bromsulphthalein test.[87a] Tetrahydrocortisone, the inert metabolic end product, disappears at an entirely independent rate, however, in the same type of experiment. There is definite morphologic evidence of hepatic damage during the alarm reaction in rats exposed to a variety of stressors (formaline, cold, spinal cord transection), together with marked reduction in hepatic function, as measured by the bromsulphthalein test.[574, 408a]

Of even more interest are recent experiments concerning the levels of free plasma 17-hydroxycorticoid concentration in adrenalectomized dogs, in which the possibility of pituitary-adrenal activation may be excluded.[607a] In this experiment, the dogs were maintained on hydrocortisone infusion at a constant rate and were exposed to immobilization, anesthesia and surgery. The plasma level of corticoids was significantly higher in the anesthetized and operated animals, compared with those who were immobilized. This suggests that surgical trauma can activate some mechanism which may delay the disappearance of free 17-hydroxycorticoid from the circulation. It seems quite likely that hypercorticoidemia may be a reflection of impaired hepatic detoxification. Furthermore, other studies suggest that the eventual level of corticoids in the blood following trauma may be greatly influenced by alterations in liver function.[644b]

In other words, stressful situations may act to produce a state of increased adrenal activity, without stimulation of the adrenal, by acting directly on the liver. Thus, the abnormal values of plasma and urinary steroids seen in severe hypo- and hyperthyroidism have been shown to result from hepatic rather than pituitary-adrenal alterations.

Methods for evaluation of adrenal function are at present crude and nonspecific, although criteria for more accurate estimation are being established. The conventional estimation of adrenal function depends upon evaluation of such tests as the 17-ketosteroids, the 17-hydroxycorticoids and the 17-ketogenic steroids in the urine.

More recently, measurement of specific steroids in the plasma and

alterations in all of these indices following the administration of ACTH have been made possible by the development of more refined technics. It must be remembered that most of these tests are of nonspecific colorimetric reactions which appear to indicate only the presence of a ketone or hydroxal grouping on certain parts of the steroid nucleus.

Perhaps these reactions are a reflection of the impact of significant glucocorticoid or androgenic compounds. It remains to be determined whether or not they actually measure these compounds.

They give clues as to whether certain aspects of adrenal function may be increased or decreased, but they give little information about qualitative abnormalities of adrenal function. Recent studies suggest that adrenal dysfunction rather than hyper- or hypofunction must be evaluated in order to estimate the adrenal-adaptive response to stress.

Quality rather than quantity of adrenal output may be a factor, and the usual criteria do not permit detection of qualitative abnormalities. This will be illustrated further in the section on obesity.

Thus, qualitative abnormalities of adrenal function may be as important as gross quantitative changes but evaluation of the qualitative and quantitative aspects of the changes can be made only by a physician who understands the illness syndrome from which the patient complains. More refined chromatographic technics may provide clinicians with a better sense of security in diagnosis, but without knowledge of his patient they may mislead him too.

Operational analysis of the organism-environment equilibrium in a field of stress indicates that the personality configuration plays a role in determining success or failure in adaptation. Over- or underactivity or pathology of any part of this system is in direct relationship with the duration of stress and the ego's capacity to apprehend it through pain and anxiety and cope with it. There is considerable literature, as yet inconclusive, about the relationship of personality configuration and ego defenses and over- or underactivity of one or another of the ductless glands. For example, pituitary-adrenal exhaustion may suggest clinically hypofunction of the thyroid, but administration of thyroid hormones in the attempt to restore normal function may cause severe adrenal insufficiency due to the sudden demand of the tissues for increased amounts of steroids. Evaluation of many laboratory tests, including the sedimentation rate, basal metabolic rate, cholesterol/esters, glucose tolerance, radioiodine uptake, protein bound iodine, urinary 17-ketosteroids, urinary 17-hydroxycorticoid, and ACTH response may all give clues, although a perceptive history and physical examination are of primary importance. At present, precision in this field is impossible because too little is known about how one can transform the language of ego failure as a regulator to that of rheostatic defect in humoral mechanisms and *vice versa*.

It has been pointed out by Wittkower,[678] Mirsky[441] and others that dysfunction of one or another ductless gland may predispose to illness under one or another type of stress, just as Silverman[586] demonstrated greater susceptibility to black out in pilots of the anger-in type with disturbed adrenalin-noradrenalin balance. Again, this undoubtedly represents a clinical example of the phenomenon of crossed sensitivity. Continued exposure to one stressor confers greater resistance to that stressor as the organism adapts but with resultant increased susceptibility to other stressful situations. This is undoubtedly mediated via adrenal cortical and medullary alterations. References to the relevant literature are given in the bibliography, but as yet too little is known to warrant discussion here.

In spite of the missing bits of concrete knowledge, however, the dominant role played by the endocrine system in maintaining homeostasis is recognized. The complexity of its role has been indicated. Elkinton and Danowski[174] describe it as follows:

> A basic characteristic of any self-regulating mechanism is oscillation of performance . . . when negative feedback just cancels the error of performance. (a) The oscillation of the system about a mean is steady, i.e., a steady state is maintained. When the feed-back signal leads to diminishing error of performance (b) the oscillations are damped and the steadiness of the system is increased. When the opposite is true and the oscillations are amplified (c) the system is becoming less steady. Such a process unchecked in a biological system is the antithesis of homeostasis and leads to death.

This statement is in accord with but adds something to the concept of homeostasis described earlier in the words of Cannon and Selye. The authors go on to illustrate their point with an example which makes it amply clear why the relationship of humoral mechanisms and the central nervous system has been so difficult to grasp. They write:

> In the example of water balance as a self-regulating physiological mechanism the servomechanisms are complex. The output of water in excess of electrolyte controlled by the antidiuretic hormone in the kidney, produces a rise in extracellular electrolyte concentration. The rise in this concentration feeds back to the osmoreceptors in the hypothalamus to stimulate the production of an antidiuretic hormone (ADH), in the supraoptico-hypophyseal system, and so the error in output of water tends to be corrected. At the same time this system is linked to regulation of intake through thirst. Hypertonicity of extracellular fluid with resultant cellular dehydration stimulates thirst and increased intake of water as well as the production of ADH. Thus both intake and output are regulated to minimize error in water content of the body. However, water turnover is conditioned by solute, especially sodium, intake and output. Here the whole chain of regulatory processes cannot be so readily described because, as indicated in the preceding section, much remains to be learned. But solute intake is certainly related to appetite and it is not surprising that the centers

for control of appetite apparently are located in the hypothalamus in close proximity to those for thirst and antidiuretic hormone production. It is tempting to consider the possibility of describing all these linked servomechanisms in the organism in terms of control of energy exchange with the environment.

Thus the total body content of solids and fluids is maintained in the healthy adult at a constant level with oscillation about a mean.

As has been indicated, recent observations suggest a diencephalic control of aldosterone secretion. The relationship of increased intravascular volume to aldosterone secretion is well known, and the determining influence of this compound in the regulation of salt and water excretion all indicate a fantastically complicated set of neurohumoral checks and balances in the body's daily economy. Again the tools necessary for a careful dissection of the *modus operandi* of this system are not available.

Neurologists and psychiatrists also have been thinking in terms of homeostasis and feedback. For example, Blum and Wolf,[67] the latter a specialist in electronics, refer to various sub-systems of psychic apparatus including the sensory sub-system which reports reality, the motor sub-system, the tissue-need sub-system and the affective sub-system, as all making demands on the energy of the organism considered as an open system.

In general, patients in whom endocrine dysfunction is suspected should have the benefit of a careful endocrinological study and a thorough psychiatric examination along the lines suggested in Chapters 2, 3, and 6. The role played by metabolic and endocrine dysfunction is discussed further in the sections devoted to obesity, diabetes, and hemic and lymphatic disorders. The significance of qualitative adrenal dysfunction and the complexity of neuroendocrine homeostasis is beginning to be understood and needs careful evaluation.

Obesity

From the point of view of contribution to mortality and morbidity rates, none of the syndromes to be discussed in this chapter is more important than obesity. Furthermore, with the possible exception of diseases of the skin, to many of which it appears to be a contributing factor, there is probably none about which so little is known.

Because it is only rarely that endocrine disorders can be convincingly related to obesity, its discussion in this chapter is more out of deference to tradition than to fact. Obesity, however, multiplies a potentiality for mortality in all of the three major killers. The obese person has nearly twice as much chance of dying of coronary disease or cerebral hemorrhage as does the person of normal weight, and in the age group 35-44 diastolic hypertension is three times as frequent.[33]

In a careful study of a group of Army officers it was found that sustained hypertension developed more than twice as frequently in the obese as it did in those of normal weight.[370a] Electrocardiographic abnormalities have been noted to exist in 15 per cent of men who were more than 25 per cent overweight as compared with 8.5 per cent of those of normal weight and 2 per cent of those of underweight.[583b] There is a definite impression that obesity plays an important role in the fatal outcome of cancer and it is known that carcinoma of the uterus is more frequent among obese than among normal women.[282a]

Obesity greatly increases the risk of operation and anesthesia. It is associated with a higher incidence of embolic phenomena.[30a] Osteoarthritis, especially in the weight-bearing joints, is appreciably more frequent in the obese[181b] as is gallbladder disease.[144a] Contrary to a popular belief that some degree of overweight is desirable in younger individuals, statistics indicate that the mortality ratio for overweight men was highest in the 20 to 29 age group, and for all ages was approximately 150 per cent of that expected in both sexes.[431a] Obesity quadruples mortality from diabetes and more than doubles mortality in cirrhosis of the liver and appendicitis. Finally, nine out of ten persons who develop diabetes after the age of 40 are obese, and it has been stated[167] that the mother of an infant with a birth weight over ten pounds may be expected to develop diabetes.

The propensity of infants overweight at birth to develop diabetes is well known.[126] Barr[33] writes:

> Obesity predisposes to diabetes, increases the tendency toward hypertension, favors the development of atherosclerosis and contributes to heart failure. It increases the instance of gall stones, causes shortness of breath on exertion, intolerance to heat and excessive sweating. It leads to maceration, intertrigo, eczema and furunculosis. It favors the development of postural emphysema, flat feet, hernia and osteoarthritis.

Although many practicing physicians place arthritis and gastrointestinal disorders above obesity from the point of view of frequency of occurrence in office practice, this is probably because many potential patients, and among them can be counted a not inconsiderable portion of physicians themselves, fail to recognize the seriousness of this illness syndrome. After all, the obese represent one-fifth of our total population, a very considerable minority.

In discussing obesity as a health hazard, Daughady[126] failed to mention the importance of obesity as a contributing factor to personality disturbances and neurotic and psychotic disorders. Perhaps this is because he introduces his section on treatment with a statement that, “This discussion will be limited to the 95 or more per cent of patients

whose obesity is due to environmental or emotional factors." From this statement, put together with Barr's[33] tables which indicate that obesity more than doubles mortality and disability from the major causes of death and incapacity in this country, one can conclude that the role played by "nervous and mental disease" has been understated in the picture given in the mortality and morbidity tables in this country.

In discussing clinical evaluation of the obese patient, Daughady emphasizes history and personality profile. He stresses correlation of onset and course with significant events in the patient's life, noting that severe obesity beginning in childhood suggests deep emotional disturbance, whereas obesity past middle age may indicate merely the persistence of eating patterns established at a more active period of life. He calls particular attention to the need for thorough investigation of obesity beginning at the time of puberty, marriage, childbearing, or menopause. In this he is in accord with other writers who have found obesity beginning at such times to be particularly high in malignant potential.

In discussing the familial incidence of obesity, Daughady notes: "The inheritance of eating habits may be a social rather than a genetic inheritance." The great majority of physicians and scientists who have devoted special attention to obesity insist that this illness syndrome is peculiarly resistant to treatment unless its significance to the patient is emphatically appreciated. This subject has been well discussed by Hilde Bruch.[88] But the tendency persists to call the obese well-nourished, husky or healthy. They usually are good company because, like the clowns and jesters of another era, they have learned early to make their disability entertaining to those around them.

Nevertheless, Mr. Pickwick notwithstanding, this illness should not be laughed off. Burwell et al.[94] have recently called attention to a syndrome characterized by extreme obesity, polycythemia, cyanosis and cardiopulmonary failure. Because somnolence suggestive of Mr. Wardle's boy, Joe, is a frequent accompaniment of this syndrome, they called it a Pickwickian Syndrome. In one patient with a weight loss of 40 pounds the total vital capacity increased from 1.6 to 4.2 liters and alveolar ventilation from 2.7 to 4.4. The oxygen saturation of arterial blood rose from 80 to 98 per cent. In another patient, weight loss of 36 pounds led to a fall in hemoglobin from 18.6 to 12.9.

In another study of patients with the syndrome of cardiopulmonary failure associated with obesity[97a] none of the common causes of heart failure could be demonstrated and vital capacity was markedly reduced without any suggestion of emphysema. The patients scarcely moved their chest walls with deep respiration, probably due to the tremendously heavy fat pads which immobilized the rib cage. Furthermore, the breathing (almost entirely abdominal) was inefficient as shown by the tendency

to hypercapnia. Severe alveolar hyperventilation lowered alveolar oxygen tension and arterial blood oxyhemoglobin saturation. This in turn resulted in polycythemia and increased blood volume so that the heart was required to pump more blood against an increased pulmonary artery pressure with a less efficient oxygen supply. Under such conditions, right sided heart failure is not surprising. Furthermore, the amount of work necessary to keep the carbon dioxide pressure normal may be too great so that the carbon dioxide level increases and symptoms of neurosis result. It is stated in conclusion of the study that the clinician must be increasingly aware of these harmful effects of obesity on the cardiopulmonary, hematologic and central nervous systems.

Perhaps only poets have been aware of the deep unhappiness or malignant depression covered by the clumsy body and the often seductive charm of the clown. Many such people were once children for whom the only way of gaining freedom for growth seemed to be to get bigger, just bigger from the point of view of space occupied. It was a way of forcing parents to allow them to desert the child's rocker for a chair that placed them on a level with those around them. Unable to gain recognition as persons in their own right they could at least gain recognition through weight and bulk. Some of these people were children under such stress and anxiety that more or less constant intake of food was necessary to maintain a normal blood sugar level, and some of them were compelled to eat frequently for reassurance when nobody cared. But thus, through their own efforts, they could survive. For many children, compelled to eat for this reason, lying and stealing with accompanying secrecy and guilt become a necessity. Children under these pressures often appear undisciplined and stubborn, but this is only a surface manifestation of a dangerous regressive and self-destructive illness. No diet and no disciplinary measures can help these patients to compensate. No citing of Shakespeare, "Leave gourmandizing. Know that the grave doth gape for them thrice wider than for other men," can startle them out of their fatefully determined course. It can have just the opposite effect. Attempts to frighten the obese into pursuing a course less destructive to themselves at best, can result in temporary spurts of dieting causing quick losing and quick regaining of weight. This can cause even greater damage to the patient than he has suffered hitherto.

Writing for the "nonpsychiatric physician," Strauss[620] points out that identification of a conflict is only a first step in a solution. Special psychotherapeutic technics may be required to identify the resistance and enable the patient to utilize his understanding constructively. Brosin[85] discusses the same subject with illustrative case studies.

The experience of most obesity clinics is that the majority of patients

do not continue treatment, "contact cannot be maintained," which probably means that contact never was really established. Others continue to gain weight while dutifully reporting for treatment. Many accomplish this after the pattern of the woman who, carefully questioned about adherence to her diet, stated conscientiously that she had eaten each meal exactly as prescribed, and to the question, "Nothing else?" answered, "No, I'm telling you the truth, nothing at all but my ordinary meals!"

It is well known that water may be retained concomitantly with the loss of body fat. Elkinton and Danowski,[174] after a careful study of defective water metabolism, called attention to the fact that the body's immediate response to the threat of starvation, as experienced by persons lost in a desert, is to retain water. The authors suggest that this is a part of the body's mechanism of self-preservation and that it may be called into play in any individual who fears imminent death through starvation. This suggestion is based on a psychosomatic study of a series of patients under stress characterized by this emotional conflict or overt fear.

Despite this unanimous agreement about the dangers of overweight the problem of weight reduction should be approached with caution. Obesity can be associated with states of emotional adjustment ranging from what might be thought of as essentially normal to psychotic reaction patterns dependent on it. It is perhaps fortunate that this illness syndrome does not yield readily to treatment.

For safe and successful weight reduction the patient must be relieved first of his need for the extra pounds. In order to accomplish this their meaning for him must be understood. This may be protection in a hostile environment or against a specific threat such as unwanted marriage or athletic competition. It may signify a substitute pregnancy or it may provide an easy alibi for failure in social relationships or business. In some cultural groups it is admired as indicative of social position or affluence or represents an identification with some highly regarded relative. Because the roots of this illness syndrome extend deep into the structure of the regulating mechanism of the organism the direct approach is not only rarely effective but also rarely advisable. Often it is contraindicated.

Frequently one finds the obese treating his body as if it were only partly his or even as if it did not belong to him at all. He joins others in making fun of it or insulting it. This feeling seems to have developed in early life when his parents assumed so much responsibility for what he should be fed, how he should be clothed, bathed and function that the child not only did not learn how to take care of himself but ap-

peared to caricature their efforts. Hence the physician who uses their approach in his prescription of diet and exercise not infrequently comes to feel that he too is being made a fool of.

Foods are often selected for reasons other than hunger or nutrition. They may represent security, prestige, reward, or other personal values. A better understanding of specific patterns of food usage may lead to curative treatment of an underlying psychological disturbance. The exhibitionist, compelled to attract the attention of others, may participate in public gorging contests, consuming large amounts of pie, watermelon or clams. The snob may find little palatability in exotic cheeses, but the show-off capabilities attached to the term "imported" more than compensate for the expense and unsavory characteristics of many such prestige foods. The frustrated or self-pitying individual may seek boxes of chocolates. In periods of stress, the intake of so-called security foods such as milk and milk products is unconsciously increased, and extra strength, courage, youth, and potency are often sought by the competitive individual in his search for "health foods." Subconscious attitudes toward husband and children may be expressed in the way food is prepared and served.

Rennie thinks that in many cases obesity serves a specific function in a total psychoneurotic disturbance.[510] Richardson[512] suggested that for these patients reduction by diet often represents a threat of death or suicide. It is of some interest that in Barr's tables[33] death by suicide is one of the few causes of death toward which obesity seems not to be a contributing factor. Actually the suicide rate among the obese is lower than in the average population. This is another reason for caution in using the direct approach in weight reduction.

Nicholson[468] has published the results of treatment of 93 obese patients by different methods:

1. In a group of 38 patients a detailed inquiry was made as to their developmental history, social and sexual adjustments, economic status, relationship to their family and friends, and other factors which might have had influence on their personalities. An attempt was made at superficial psychotherapy such as reassurance and interpretation. No calculated diet was given, though an explanation of energy exchange and caloric values of common foods was given. Care was taken to explain the phenomenon of water retention in order to anticipate the periods during which no weight loss would occur. A food diary was kept for three days prior to each clinic visit. No medication was given. In this group 26 instances were judged successful on the basis of weight loss of 5 kg. or more for one year with no relapse.

2. A second group of 35 patients was placed on an 800 calorie diet

which was explained by the dietician. No medication was given and no psychotherapy was attempted. There were 26 failures in this group, judged on the same basis as in the first group.

3. Ten patients were given 5 mg. of amphetamine sulfate three times daily. No diet was given and no psychotherapy attempted. All patients showed a weight loss the first four weeks and then gradually regained to the initial weight. In six patients the dose of amphetamine was gradually increased to 10 mg. three times a day without additional effect.

4. Ten patients received thyroid substance in sufficient dosage to produce symptoms. No appreciable weight loss occurred until diet was instituted. The aid of a psychiatrist was obtained for the more severe emotional problems. In one of these instances, with severe anxiety attacks relieved by eating, a weight gain of 22 kg. was reduced by 17 kg. in the period under treatment and was maintained up to three years.

Such studies suggest that there are "obesities" rather than "obesity." They emphasize the practical value of attention to other aspects of treatment than the diet or appetite depressants.

It has been said that for every patient who worries himself thin, nine worry themselves fat. But the way the latter accomplish this is not always obvious. Nevertheless there is a personality relationship between the patient who develops anorexia nervosa as a defense and the patient who renders himself too fat to breathe or move. Courting death by some means other than starvation or obesity appears to be in part a defense against death and in part a substitute for suicide or the acting out of the suicidal drive.

Up to the present the attempts that have been made to describe the personality of the obese patient have been lacking in definition. These patients appear to have an addiction to food for the relief of anxiety which is very similar to the addiction to drugs or alcohol. This, like other addictions, follows the pattern of repetition compulsion and occurs in patients who, according to the new classification, would be said to be suffering from sociopathic personality disturbance. These reactions are often indications of severe underlying personality disorders. Grinker[258] suggests that "eating becomes the means of binding the anxiety which comes from oral frustration since love and affection are equated with food." But many symptoms have served to fill this role.

Wulff[696], thinks of obesity as a symptom of a neurosis springing from a fight against pregenitally oriented sexuality. In fat periods, the body feeling is a repetition of the way the girl felt shortly before the onset of menstruation. The menstrual flow usually brings a feeling of relief with the feeling content, "Now I am slim again and will be a good girl and not eat too much." Alternating feelings of ugliness and beauty connected with these cycles show that exhibitionistic conflicts also are basic to

this syndrome. A small percentage of the obese may suffer from damage to the homeostatic regulators, occasioned before they were born as a result of infectious diseases or some other reaction to stress during intrauterine life.

In severe cases eating remains the only interest connecting the person with reality and Wulff finds this type of food addiction to be closely related to manic-depressive disturbances or psychosis. Hamburger[270] finds that the psychodynamics of persons addicted to food or alcohol are similar and expresses the opinion that overeating is a response to nonspecific emotional tensions, a substitute gratification in intolerable life situations and a symptom of underlying emotional illness, especially depression or hysteria. This appraisal has the merit of being closer to the physiological pattern of disturbed metabolism which rarely of itself causes illness but rather renders the patient an easy victim of diverse illness syndromes.

According to a Gallup poll taken in 1951,[219] 92 per cent of all those who tried to lose weight through dieting failed. Nicholson and others[468] recommend diet plus anorexogenic drugs but find that these drugs without supervision and psychotherapy give no success. Kaplan[319] confirms the opinion that "treatment of the underlying psychodynamic cause of hyperphagia is the key to the management of obesity." He feels that this is the job of the general physician except in cases in which the psychological conflict (for which this defense is needed) is too deep. He notes that treatment of these patients is time consuming and often threatening to the doctor because of the emotional demands made on him by the patient and the frequent therapeutic failures. For many patients overeating becomes a habit which tends to persist after the motivating anxiety has been relieved.

Clarification of the relationship between endocrines and obesity depends on the development of more adequate methods for measurement of adrenal function. Again the tendency has been to focus on quantity or quality, dysfunction rather than hyper- or hypofunction.

A not uncommon situation that confronts the general practitioner is the obese female with amenorrhea who occasionally is hirsute and may, in addition, show evidences of mild diabetes or hypertension. She may look as if she "ought to have some glandular problem" but a careful check-up may reveal only slight alterations. Usually the 17-ketosteroids and 17-hydroxycorticoids are normal as is the response to ACTH. Such women represent a very frustrating group of patients. Usually they are a little tense or neurotic and the tendency is to write off their trouble as normal variation or hereditary influence. Occasionally, if there are associated headaches and if some thickening of the inner table can be detected in skull films, such a patient may be labeled an example of the

Stewart-Morel-Morgagni Syndrome, hyperostosis frontalis interna.

Actually, if one pays attention to quality of adrenal function, then in some cases very definite abnormalities can be found in many of these patients. The abnormality revolves around a compound known as pregnanetriol. This is a steroid which is normally hardly detectable in urine unless ACTH is given, and then only in minute amounts. It represents a metabolite of 17-hydroxyprogesterone, an intermediate compound in the manufacture of hydrocortisone by the adrenal. In the adrenogenital syndrome there is a partial block in the synthesis of hydrocortisone just beyond the level of 17-hydroxyprogesterone and large amounts of 17-ketosteroids and pregnanetriol can be found. However, in many of these obese hairy women with oligomenorrhea, one finds definitely elevated pregnanetriol levels, although not as high as in the adrenogenital syndrome. If these patients are stressed or given ACTH, the levels rise even higher. These patients do not have the adrenogenital syndrome, however. They have normal 17-ketosteroids and 17-hydroxycorticoids and normal responses to ACTH using these excretion products as guides.

In a sense, perhaps, they represent a *forme fruste* of this disorder, in that they apparently have a partial defect in 21-hydroxylation. It is postulated that because of this relative failure in making hydrocortisone there is an increased stimulus for ACTH production which restores the deficient amount of hydrocortisone at the expense of making more pregnanetriol. Consequently, if one administers small amounts of a potent glucocorticoid which will inhibit pituitary ACTH function, the vicious cycle is stopped, and in practice judicious steroid therapy of this nature is frequently very rewarding.

The lesson to be learned is that recognition of this problem hinges on the detection and measurement of pregnanetriol. It just happens that pregnanetriol has neither a ketone grouping nor a dihydroxyacetone linkage, as measured by Zimmerman and Portes-Silbes technics. Thus, these patients would be labeled as having normal adrenal function by our conventional criteria.

Adrenal steroids have been found to be effective in certain other types of obesity in conjunction with dietary restriction. This appears to be so in the group of patients with familial lipodystrophy and in those females with a distribution of fat confined mainly to the lower abdomen, hips, and thighs, due to presumed ovarian dysfunction.[226a] It is claimed that the administration of cortisone and the newer synthetic steroids results in redistribution or relocation of fat and that weight disappears from all over the body.

These observations do not indicate that the adrenal is involved in the pathogenesis of this or other types of obesity, but it would not be surprising if further refinements in the detection of adrenal dysfunction did

reveal subtle abnormalities. It has already been determined that the production of 17-hydroxycorticoids is related to obesity. For every pound of body weight, approximately .05 mg. of hydrocortisone is excreted daily.

Practical Suggestions

For convenience in estimating the relative severity of the patient's conflicts as a basis for choice of therapy, Hamburger[270] divides the obese into four categories:

1. Overeating as a response to nonspecific emotional tensions.
2. Overeating as a substitute gratification in intolerable life situations.
3. Overeating as a symptom of an underlying emotional illness, especially depressions and hysteria.
4. Overeating as an addiction to food.

He has found that patients who use the first two mechanisms are comparatively amenable to the medical therapy used by most physicians in their total care of the patient. The third class, however, are best referred to a psychiatrist unless the physician seeks consultation with a psychiatrist on the nature of treatment. The fourth group who use food as addicts use drugs, generally require intensive psychiatric treatment. Where there are indications of uncontrolled behavior under stress, these patients may need hospitalization. The depressive component of their illness is a constant threat and a few will attempt suicide in the more severe phases of their treatment.

When psychiatric help is needed, Kaplan[319] recommends that dietary supervision by a general physician be continued but no modification made without consultation with a psychiatrist. Stunkard, Brosin and Grace[622] discuss this question also and make suggestions as to the type of patient who will be almost certain to need treatment by a psychiatrist. The latter also discussed the night-eating syndrome.

Group therapy has been recommended by Kotkov[339] and by Conrad,[117] but the consensus is that if this method is chosen, individual therapy should be instituted or continued at the same time. In judging the value of the amphetamines, it would be desirable to know more about their mode of action. Goodman and Gilman[238] believe that their appetite-depressant action is due to a not fully understood direct central cortical effect.

In all types of obesity, as Hilde Bruch[88] has stated, weight loss should be considered the "final step in the treatment program which needs careful individual planning." The syndrome of obesity is an inappropriate adaptive response which may involve metabolic and neuroendocrine dysfunction. It may serve to mask underlying manic-depressive disturbances or psychosis.

Diabetes

Practically every clinical condition is associated with disturbances in the smooth shifts of metabolic rate and direction of which the body is capable. Physiologic functions are manifestations of the molecular changes that are metabolism. Disease in one aspect is a constellation of disturbances of finely integrated chemical mechanisms. Ludwig Monné[449] notes that in biology "structure and function are like matter and energy in physics, merely two different aspects of the same thing."

Diabetes mellitus involves a chain of metabolic phenomena all initiated by disturbances of rates at which glucose is added to the blood and at which it is utilized in the tissues.[14] It represents the breakdown of mechanisms of correlation and adaptation in which the whole organism is involved. Sherry[583] indicates that although the hormonal imbalance may be temporarily corrected by injection of one of the hormones, "the abnormality may have been produced by a disturbance in any or all of the hormones involved." Frank Engel notes[14] a "state of disequilibrium results until a new level of adjustment is achieved. The new level, however, leaves the organism deprived of some degrees of ability to make the metabolic adjustments that are essential to health or to life." The diabetic is more or less deprived of the ability to accomplish "the smooth shifts in metabolism to meet the demands of the moment and maintain homeostasis."

In view of these facts, one might expect to find similarities between the obese patient and the patient with diabetes. Actually, similarities do exist because nine out of ten diabetics have a previous history of obesity, but the personality constellation of the patients who progress from obesity to diabetes is much more clearly defined. They are readily distinguished from those who develop hypertension instead, although in a small percentage of cases one finds these two illness syndromes existing side by side. Brody[83] observed a tendency to shift from mental suffering to organic illness or a coexistence of both in some patients. Two illness syndromes may appear to bar the shift to mental disorder. Dunbar[149] called attention to the frequency with which psychotic tendencies are observed in patients suffering from this degenerative disease and to the fact that in the 20 per cent of diabetics who differed somewhat from the psychodynamic picture characteristic of the majority, this illness was found in combination with hypertensive cardiovascular disease and the accident syndrome which usually antedated the onset of diabetes. It was not unusual for these patients to manifest other illness syndromes also, such as coronary or rheumatic disease. In regard to mental disorder, the illness picture was multi-symptomatic with schizophrenic, manic-depressive or hysterical reactions. In spite of the multiplicity of symptoms often found

in diabetics, Menninger,[427] Bruch,[89] Dunbar,[162] Rosen and Lidz,[532] Benedek,[46] and others have felt justified in speaking of a "diabetic personality reaction"[427] or a personality configuration peculiarly susceptible to the development of diabetes. Bruch calls obesity a way of life and diabetes a determinant of a way of life. Benedek attempted a study of the psychologic concomitants of a derangement of physiological homeostasis in these patients and found the trauma of diabetes to be deeper than that in association with any other disease studied. "Food is representative of the mother, security, life itself, and for the diabetic it becomes dangerous."

Some persons find a lack of definition in the diabetic's personality, but this very lack of definition which usually antedates the development of the disease, is characteristic of diabetics. Joslin[316] commented that "Diabetics are thought-provoking. No sooner is one goal of treatment achieved than new vistas open up to higher levels."

Since a test for the possible presence of diabetes is now part of every routine physical examination, it may be thought that the prediabetic personality is of little interest. Nevertheless, indications of susceptibility to this illness syndrome are sufficiently obvious to render the institution of preventive measures both feasible and effective.

The passive component in the personality of the diabetic has caught the attention of most observers. Raychaudhury,[503] commenting on the relative susceptibility of Asiatic Indians to diabetes—as opposed to other rice eating peoples—notes the role of suffering in their society and indicates that this susceptibility may be due to their more "masochistically inclined make-up." He calls attention, too, to the greater susceptibility of women to the disease and suggests that it may have the same cause. The vacillating nature of the diabetic and his dependent leanings in combination result in a recurring incompletion of tasks important to the patient. The concomitant annoyance which can find no outlet because of realization that it is his own doing or, more important, repression of anger and hostile feelings due to overdependence on others, may, as Raychaudhury indicates, "throw an excess of glucose in the blood stream" causing "the sugar-regulating mechanism of the body . . . to do extra work to oxidize or utilize that glucose." Thus the development under increased stress of diabetes mellitus may be favored by gradual exhaustion of the regulating mechanism.

The disease can serve to satisfy the patient's wish to regress into a state of blissful dependency as well as to satisfy a need for punishment which is provided by both the disease itself and the method of its treatment. Furthermore, all the patient's feelings of inadequacy, his vacillation and dependency can be blamed on the disease.

Patients with diabetes have found their major difficulty in areas of

adjustment involving the assumption of responsibility. This difficulty is manifest in childhood. It is increased by their inability to attain a mature sexual adjustment. They seem unable to develop a strong reaction against dependent needs and tend to assert such impulse as they may have toward independence in words, rather than action. They vacillate between what they consider male and female attributes and drift to a state where sexual interest is more or less completely denied and oral and anal traits come into prominence as defining their character and behavior. Their indecisiveness has subjected them to a life of wear and tear where their only satisfaction lies in eating and suffering.

Profile and Configuration. There is a high incidence of diabetes in the *family history* of the diabetic (about 35 per cent). Cardiovascular disease and "nervousness" are present in the families of most of the rest. There is an overemphasis on food within the family and also generally inconsistent treatment by the mother.

According to *personal data*, at least one parent lives well into the patient's adult life. A constant struggle with parents usually continues throughout life. There is a marked tendency, especially among males, to remain unmarried and both males and females are inclined to have few children. Divorce is rare, although separations from the marital partner are frequent.

Their *health and accident* records are exceptionally good prior to onset of illness. After this the accident record is relatively high. The women have histories of pelvic disorders. In their *general adjustment* they achieve a high level of *education* but display a tendency toward nervous breakdown in college. At *work* they have a disinclination to assume responsibility or take initiative in important matters. Their *incomes* are lower than their education would suggest even before the onset of illness. Their *social relations* are marked by anxiety. Although superficially agreeable they are self-conscious and aloof. *Sexual adjustment*, too, is marked by anxiety and inadequacy with a homosexual trend often present.

Their *characteristic behavior pattern* may be exemplarized by an inability to follow any consistent course of action, vacillation and indecisiveness. They talk to win sympathy, focusing attention on suffering.

Among *neurotic traits* in childhood one finds temper tantrums, phobias and nightmares; in adult life, nervousness, depression and suspicion, with a tendency to paranoid ideas.

Their *addictions and interests* include a preoccupation with innumerable odd jobs diverting energy from major career. In general, they avoid competitive sports and display little interest in religion except where awareness of homosexuality has led to religious experimentation. There is a marked indulgence in food and, at times, alcohol and cigarettes.

A long period of wear and tear, including conflicts with family and

spouse, overwork and homosexual difficulties, is typical of the *life situation immediately prior to onset of illness*. A dietary indiscretion often triggers the onset. They react to illness with depression and with alternating feelings of relief at being no longer responsible for shortcomings.

Situations involving responsibility and confusion of their sexual roles are their *areas of focal conflict*.

THE SILVER CORD IN A DIABETIC HISTORY

A 50 year old unmarried man was admitted to the hospital for the first time with symptoms of increasing fatigability, weakness, loss of 23 pounds in two to three months, and polydipsia and polyuria of two months' duration. Blood sugar was 400 mg. per cent on admission. There was no diabetes on either side of patient's *family*.

A study of his *personal data* showed patient to have been born in Philadelphia, a normal delivery. He was an only child. He had lived with his mother all of his life. She was living and well at time of his admission to the hospital. His father died of pneumonia just prior to the patient's adolescence. His *previous health* had been excellent with the exception of typhoid fever, which he had at the age of 12. His *personal injury* record revealed that several weeks prior to admission patient slipped in the bathroom and fell against the tub hurting his spine.

Educationally, the patient completed grammar school and high school and wanted to study medicine. After one year in college, however, he was told that his astigmatism was so severe that he should give up his schooling. (There seems to have been no basis for this since he has had no further difficulty with his eyes and his vision was good at the time of admission.) *Vocationally* speaking, his income was always relatively good. After leaving college he went on the stage for five years. Then he taught dancing, experimented with the hotel business and became a traveling salesman. *Socially*, the patient preferred not to see too much of people, got along better with men than with women. He had always lived with his mother and was still living with her at the time of admission as previously noted.

The patient stated that be "had forgotten all about *sex* years ago." He never married because be never knew any married people that were happy, besides which he and his mother were like brother and sister "Although she is 25 years older than I am, I get as much kick out of dancing with her as with any girl. She's really the only one I like to dance with." The patient disliked and had an almost complete amnesia for his father and was devoted to his mother.

The patient described his *adjustment to life* in these terms: "I believe in getting the most money and the most fun with the least trouble. I have always managed to get jobs that were easy. For a while I couldn't make up my mind whether I ought to go out with girls to be like other people; then I decided it wasn't worth the trouble. It's hard for me to make decisions but the way my life has been I haven't had to make any."

All early *neurotic traits* were denied. The patient could remember only that

his mother said that he used to cry out in his sleep as a child. His *addictions* consisted of being a moderate coffee drinker, smoking, and drinking somewhat to excess. He had no interest in religion.

There had been financial worries terminating in the loss of his job when the company with which he was working closed its offices. After seeking in vain for employment, he finally lost his $17,000 house just prior to the development of the first diabetic symptoms. These he blamed at first on his teeth, eight of which he had had extracted, and then on worry about having to "drive his mother out of house and home." It was a great blow to his pride that he and she had to become just ordinary boarders. The day before admission he came back to New York from a sales trip to see his dentist, "had a breakfast of griddle cakes and a pitcher of syrup and felt so tired that I consulted a doctor who found that my urine was full of sugar."

The patient accepted his illness philosophically, saying that with the loss of his house he had lost all he had to love and that after all he was better off than some because he had a mother to look after him.

Area of Focal Conflict and Characteristic Reaction. Throughout his life this patient had sought jobs involving little responsibility. He said of his father: "He was the great so and so but where does that get you? My system is better. Get your pay with as little responsibility as possible; then you have no worries. That's another reason I didn't marry. A wife is always a responsibility and if you have children it makes it worse. Living with Mother's fine. She had a little money of her own and is a much better housekeeper than any girl I've seen. When it comes to having fun give me Mother or the boys."

It is interesting that this patient had no conscious conflict about his sexual adjustment but, as he put it, "had just forgotten about sex because it gets you into trouble." Although his impulses followed the homosexual pattern there were no overt experiences after his early manhood, and incidentally he lacked the interest in religion characteristic of these patients when they become worried about their sexuality.

Additional case histories are given by Lowe,[385] Grinker and Robbins,[258] and Bruch.[88] After reading diabetics' histories, one cannot avoid the impression that they have more characteristics in common prior to the onset of diabetes than one would expect with a picture confused by the disease itself. Friedgood[206] states, "The nature and extent of the influence which socio-environmental factors and stresses exercise over this vital aspect of the body economy is being vigorously debated."

The doubt appears to rise in part from the complexity of the homeostatic mechanisms responsible for regulation and control of carbohydrate metabolism. These include the integrative function of "the higher cerebral centers, the diencephalon, the sympathetico-adreno-medullary system, and a galaxy of endocrine glands and other organs such as liver and kidney." Furthermore, as Mirsky[442] and his co-workers have pointed out, these mechanisms may be disturbed in one of two rather definite ways, one which results in insulin insufficiency and another in which vascular

damage takes place at an accelerated rate. "Using impairment of vibratory acuity as an index of aging, the diabetic responds as if he were twenty years older than the non-diabetic of the same age."

The fact that there is a little evidence of adrenal dysfunction in diabetes may mean that as yet adrenal function cannot be adequately assessed. Furthermore, variations in glycemic agents suggest that there may be several different types of diabetes.

In experimentally pancreatectomized animals the vascular complications of diabetes (retinopathy and intercapillary glomerulosclerosis) are not seen until cortisone is administered. In the rabbit such presumably "specific" pathologic hallmarks can be produced by cortisone alone. Vitamin B_{12} excretion differs in diabetics with retinopathy as opposed to those without it, but the administration of cortisone in the uncomplicated diabetic produces the diabetic with retinopathy.[43a] In addition, steroid excretion in some patients with retinopathy seem to demonstrate adrenal hyperfunctions.[583a] Other studies suggest diminished adrenal reserve in diabetics undergoing surgery.[188a] These observations suggest a basic endocrine abnormality and have contributed to increased interest in hypophysectomy and adrenalectomy in the treatment of diabetic retinopathy. The answer will not be forthcoming until we have a better appreciation of quality, not quantity, of adrenal function and improve our methods of measurement of patterns of adrenal dysfunction.

Two patterns have been observed also in the mental disorders toward which diabetics tend; the one, more manic, the other, more schizophrenic. Grinker[258] discusses this illness in a "thirty-three year old woman with an obsessive-compulsive character neurosis and another woman of thirty-eight with a long-standing chronic depression." Although much that has been said about diabetics could be said about any sick person, many who have worked with diabetics stress the depth of the disturbance and the severity of its impact on the integrating functions of body and ego.

Homeostatic regulation for the newborn depends completely on the mother, and this dependency continues to a lessening degree for several years. If what Bruch called mother-child symbiosis is seriously threatened and then followed by an inconsistent overemphasis of bodily nutrition, the normal patterns of growth and ego development may be sufficiently shattered to become reorganized in several somewhat different appearing forms.

Practical Suggestions

This experience of inconsistency about food and nutrition constitutes one of the major obstacles to therapy. These patients rebel against a restricted diet. They rarely do well on a free diet and almost any attitude suspected in the physician arouses hostility and guilt. This psychic turmoil may be somewhat checked by hysterical or compulsive reactions,

but underneath this behavior there lurks the fear of imminent dissolution and the fear of suicide. The diabetic is less well protected against this fear and his impulse to self-destruction than is the obese person who stops short of this, the most severe of metabolic disturbances, and simply remains more vulnerable to a diversity of other stressors.

Hinkle and Wolf[287] showed that emotional tension can induce ketosis even though the diabetic does adhere to his regimen. They found that a traumatic interview can cause an elevation of blood ketones which occurs more rapidly in the presence of severe diabetes. On the basis of the work of Rosen and Lidz[532] and others it appears that the diabetic who willfully abandons his regimen does so in a panic; driven by the need to escape, be seeks the shelter of the hospital in preference to suicide.

The problem may be summarized as follows:[625a]

> . . . basic human attributes (are) on the one side the urge to become an independent entity, and on the other the inherent quest for symbolic orientation, for establishing relations with the environment in a novel fashion. This development in which symbolization functions in a setting of structural and functional modifications cannot proceed smoothly, however, without proper integration with the organism's biologically integrative and interrelating propensities. It is here within the relationship between symbolic functions and basic organismic processes that the postulated malfunction seems to have occurred.
>
> Man's self-limitation and relative severance from the outer and partly self-made world embodies the danger of isolation. Inadequate relatedness means anxiety, and implies the threat of annihilation.

The diabetic lives under this threat of annihilation. He has made continuous use of the short circuit into the viscera in order to maintain his self-respect in subservience to his ego ideal which is, in essence, ego alien.

During the last ten years, with the increased experience and understanding of endocrinology and the application of psychoanalytically oriented technics to psychosomatic problems, the outlook of the medical specialist has changed. The close association between disorders of the humoral mechanisms and mental disorders is coming to be recognized, and it has been suggested that the specialist in this field should have special training in psychiatry also, just as the psychiatrist needs a thorough understanding of the basic metabolic processes. Lacking this, teamwork is the best solution. Anything more than supportive psychotherapy is likely to bring about apparent or actual psychotic episodes in these patients.

At best, with so many unknowns in this field, the physician must often rely on hunch. Hunches are to be distinguished from the bedside manner. Reliance on hunch, nevertheless, is to be preferred to reliance on the drug ads that pour into every physician's office. A physician capable of

watching carefully may find a moment in which a tranquilizer or change in the hormonal balance is desirable. But when a drug or hormone has been given to a patient careful watching is more than ever necessary. For the psychoanalyst this is inevitable, but the endocrinologist, irrespective of the number of appointments that can be arranged, should have the feeling that be has his hand more or less continuously on the patient's pulse. Within hours or days the patient may have had a dangerously exaggerated reaction to the drug or hormone administered. Experience indicates that patients with neurotic symptoms or with intense conscious or unconscious anxiety are more likely than others to react paradoxically to any form of chemotherapy. If the anxiety is unconscious and not clearly revealed in behavior, the endocrinologist may be caught off guard. Even with the average patient, if a month has elapsed between appointments, the physician may have lost important clues because the patient will have forgotten his body response to the increasing or decreasing dosage that had been prescribed.

This is particularly important with patients suffering from hypo- or hyperfunction of the adrenal cortex. As Elkinton and Danowski noted,[174] "until several years ago the all-or-none attitude prevailed, i.e. either the patient had classical Addison's disease or the adrenal cortex was perfectly normal." Today, fortunately, fewer patients are kept on thyroid without having been tested to ascertain whether or not their main trouble may or may not be adrenocortical dysfunction.

The last ten years have placed new tools in the hands of every medical specialist. It is now known that the varying degrees of hypo- or hyperfunction of the adrenal cortex play a role in the development and course of all psychosomatic syndromes.

Hemic and Lymphatic Disorders

Changes in blood chemistry are known to occur in response to changes in the endocrine system and are used as an indication of its state of balance and healthy functioning. They occur also in response to diverse stressors and constitute an integral part of the general adaptation syndrome. Changes in cell count and sedimentation rate may occur in states of fright and in mental disorders. Their significance is a focus of contemporary research. Although observations have been made concerning patterns of adaptation to anxiety characteristic of patients with leukemia, Hodgkin's disease and other disturbances of the hemic and lymphatic systems, there is too little known to justify their discussion here.

In the few studies available of reticuloendothelial disease, the consensus is that the disturbance of homeostasis has produced an intricate injury to the organism in a pattern somewhat like that produced by a shot-

gun. Greene and his associates,[253] for example, report that "patients with lymphoma or leukemia are manifesting a syndrome with various types of dysfunction including depressive responses, *and* anxiety reaction, *and* hysterical manifestations, *and* vegetative neurotic responses, *and* the characteristic somatic changes observed in the blood and other tissues." These authors, like others who have stated this problem, stress separation from a key object or goal with ensuing depression as a determining factor.

R. B. Benedict[49] noted that in the recent literature little attention had been paid to the possible existence of emotional factors in idiopathic thrombocytopenic purpura. She, too, stresses loss or threatened alienation of a key figure as playing a predominate role in certain blood dyscrasias. She noted, however, that only one of the fifteen patients studied appeared well adjusted. The others had well-defined psychiatric diagnoses, the majority characterized by obsessive-compulsive traits and the minority by anxiety and hysterical reactions. Feeling that her observations suggested a relationship between emotional trauma and bleeding and hemolysis in these diseases, she makes the following suggestion concerning the mechanism whereby one could lead to the other:

> It seems likely that in the hemolytic anemias psychic difficulties can act as stressful stimulus which precipitates crises by activation of the pituitary adrenocortical axis, since experience has shown that other stressful stimuli often precede crises, and since Kass and his co-workers were able to induce crises in Sickle Cell Anemia by the administration of adrenocorticotropin.

Board[69] and his associates studied blood levels of adrenocortical and thyroid hormones in acutely disturbed patients as compared with a group of normal controls. He concluded that the more severe the disturbance, the higher the level of 17 OH and PBI. He found little difference between what he called the psychosis group and the psychotic depressive group.

Such studies suggest that, like other disorders of the endocrine and metabolic systems, hemic and lymphatic disorders are associated with profound personality disorders of a very regressive and degenerative type. This subject has been discussed earlier as it relates to neoplasms.

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