American Handbook of Psychiatry

Promising Interactions Between Psychiatry and Medicine

Herbert Weiner
Sidney Hart

Promising Interactions Between Psychiatry and Medicine

Herbert Weiner and Sidney Hart

e-Book 2015 International Psychotherapy Institute

From *American Handbook of Psychiatry: Volume 6* edited by Silvano Arieti

Table of Contents

In fact, medicine has a very strong intellectual appeal to most physicians because of the deep understanding of disease processes that the great advances in biology have provided them. But the theory and practice of medicine encompass much more than an understanding of basic physiological, physicochemical, and biochemical mechanisms. For example, the prevention of illness is much more effective than its treatment. To prevent an illness requires a rather full account of its etiology and pathogenesis, as well as an understanding of the social, economic, psychological, and political factors that may play proximal or distal roles in its etiology. However, most of medicine and medical education is predicated on knowledge and teaching about disturbances in body physiology and biochemistry *after* the inception of the disease—e.g., the nature of disturbances in electrolyte and water metabolism in primary aldosteronism or in adrenal-cortical insufficiency, or the fall in cardiac output in some cases of congestive heart disease. Treatment is directed at these disturbances, and not at their etiologic and pathogenetic causes, or the general circumstances under which the illness occurred. No distinction is made between disease and illness, illness being the result of the interaction of disease and its host—the person.

In this chapter, we offer evidence that the base of medical theory and practice needs to be broadened, in part to achieve a biological foundation for it in which man is seen in continuous interaction with his environment. As the result of this interaction, devices in the brain that control and regulate bodily

Furthermore, the fact that antibiotics rapidly arrest the disease process and the knowledge that penicillin interferes with bacterial cell-wall formation by the inhibition of mucopeptides, satisfies the physician that he has a complete picture of the disease and its cure. But what if the patient refuses to leave his bed when all signs and symptoms of the pneumonia have disappeared? An understanding of the pathophysiology and pathology of pneumonia does not provide him with an understanding of the patient's behavior.

Such a banal, yet relatively common, occurrence in the practice of medicine highlights the current belief systems, and the conceptual issues that tend to permeate the practice of medicine.

These belief systems are the result of a longstanding tradition in Western life that holds that man is a machine, and that a full knowledge of man can only be furthered by an increasingly refined quantitative analysis of his complex machinery. Such an analysis requires that complex phenomena be reduced to increasingly simple elements, which can be analyzed by available scientific techniques.

This process of analysis has been highly successful for *simple systems,* but when we deal with *complex* phenomena such an analysis is not usually successful. It is, of course, entirely true that great scientific advances have

the particular attitudes that the practice of psychiatry generates in other medical men, psychiatry has, to a very large extent, remained outside the mainstream of medicine.

To specify: first, the central problem in the study of mind is the problem of consciousness. Its study continues to remain wholly outside the realm of science, despite the fact that Descartes was wrong and that it is a good bet, according to ethologists, that at least some of the higher mammals, in addition to man, must be capable of consciousness. Therefore, animals cannot merely be machines.

Secondly, many behavioral scientists believe that there are such serious limitations on the reliability and validity of observations about one's own and other people's minds, that the study of the mind is worthless. Behavioral scientists of this persuasion believe, in addition, that man is only a machine, a passive automaton controlled by his environment,[1] and that only behavior and its course can be quantified.

Such behavioral scientists are, therefore, very much of the same philosophic persuasion as those who have limited the scientific method only to quantitative measurement and simple elements. Unfortunately, the belief systems of the behaviorists (already described) lead them to speak of the "control" and shaping" of behavior by reward or reinforcement, or,

patient. If he is ultra-scientific, he sees himself as coldly objective and removed from the patient, who, in turn, feels himself rejected by the physician.

It is, however, not our purpose to write a polemic about the clay feet of physicians, but rather to point out that current belief systems in medicine have inevitable consequences for the behavior of the physician; furthermore, that such behavior may be stressful to the patient.

The study of stress in the past twenty years is, in actuality, highly relevant to the practice and theory of medicine. It has been brought to such a state of knowledge that it is possible to document today that stressful situations may have very important physiological consequences for the organism. The onset of disease may be one of the consequences of stress. To understand why a stress may lead to disturbed physiology and—even disease in one person and not another—one must have knowledge of a patient's genetic endowment and previous experiences.

We have chosen this topic to illustrate how psychiatry, as a behavioral science, can productively interact with medicine in contributing to an understanding of the etiology, pathogenesis, and pathophysiology of disease. Such an interaction can also influence patient care and may point to new directions in medical education.

which he is raised may also be of determining influence. The impact of these experiences on his mind, and their storage, "programs" him to react toward others and specific situations in his life in a manner similar to or identical with ways first learned in childhood. In respect to the practice of medicine, he may, as an adult, when ill, react to and interact with the physician in terms of his experiences as a child with his pediatrician, and with his parents when he was ill and what being ill meant to him when he was young.

Studies on Attachment and Loss

During childhood very strong attachments to others are also formed. Such bonds have been observed to occur in other mammals, and their importance to the well-being of the organism is highlighted when they are broken.

The breaking of a bond between human beings may have one of several consequences. The usual manner in which man psychologically reacts is with grief, which is then gradually dispelled by the process of mourning. On the other hand, he may react with depression and suicide, with helplessness or hopelessness, or even elation, or with behavior called schizophrenic, or he may "drown" his feelings in alcohol or "forget" with other drugs. Loss of another person may lead to the development of a wide variety of physiological effects and anatomic lesions: it is a setting in which peptic

Many of these persons had unresolved conflicts with respect to these events, which were rekindled by their present illness. In a later study, Adamson and Schmale noted that object loss and "giving-up" were associated with the development of severe psychiatric disturbance. Recently, Stein and Charles reported that almost half of the juvenile diabetics they studied in an adolescent clinic had a history of loss of one or both parents. This was in marked contrast to the experience of a group of matched controls, comprised primarily of adolescents with hematological disorders. As a result of their data Stein and Charles concluded that "diabetes occurs most frequently in that segment of the population in which there are special stresses and trauma in the form of a chaotic family life, separations, and early losses."

Young et al., studying the mortality among widowers, found that 213 of 4486 widowers, fifty-five years old and older, died within the first six months of the loss of their spouse, an increase of about 40 percent above that expected for married men of the same age. Kraus and Lilienfeld noted that the mortality rate of persons of both sexes, who had lost a spouse, was increased and that there was a mortality in excess of that expected in those under thirty-five years of age. Parkes in a study of patients admitted to a psychiatric hospital found that the number of patients whose illness followed the loss of a spouse was significantly greater than anticipated for people of that age and social group. Developing Schmale's work in the area of giving-up and its primary feelings of hopelessness and helplessness, Engel has hypothesized

from, family members and the precipitation of congestive heart failure. Kennedy and Bakst studied patients admitted for cardiac surgery to see if their preoperative psychological state would influence the morbidity and mortality of operation. They established six categories of psychological state:

1. Patients who evidenced strong but not psychotic denial of the operation and were strongly motivated to recover.

2. While manifestly cooperative and seemingly motivated, another group of patients had settled comfortably into dependency on others and the benefits of being disabled. Postoperatively they tended to experience little or no improvement in cardiac function.

3. Another group of patients was increasingly panicky as the day of surgery approached. They tended to exaggerate the risks of the procedures and were afraid of dying.

4. Patients who tended to have mixed feelings about surgery, in that they preferred to be ill rather than well.

5. Patients who had effectively given up all hope and perceived surgery as “sanctioned suicide” that the surgeon committed for them.

6. Patients with overt psychiatric illness who exaggerated their relatively minor physical illness into a major one.

The authors found that the postoperative morbidity and mortality were

depressed patient from the pain of loss and mourning. Studying six acutely depressed women in an inpatient setting, Sachar and his co-workers made longitudinal studies of urinary 17-OHCS levels and correlated these with observations of the patient's behavior. They postulated that if depressive symptoms actually protected the patient against the realization of loss, confronting her with the loss should provoke psychological "disequilibrium" and result in the rise in the excretion level of 17-OHCS. Indeed, this was what happened. Using more sophisticated techniques, Sachar and his colleagues conclude that ". . . adrenocortical activity in depressed patients is primarily related to dimensions of emotional arousal and psychotic disorganization rather than to depressive illness *per se"* or to schizophrenia. This conclusion applied to the observations of Schmale and Engel suggests that the emotional consequences of the loss—the "giving-up, given-up" complex—is the result of a failure of "coping" mechanisms, leading, on the one hand, to the psychological reactions described and, on the other hand, to physiological change, including physical illness. Since the perceived threat of stress results in the increased secretion of ACTH (adrenocorticotropic hormone) and cortisol, and since these hormones are known to have wide-ranging effects on a variety of systems and functions (electrolyte balance, glucose and fat metabolism, nitrogen excretion, the induction of the biosynthetic enzyme of epinephrine, immune mechanisms, and the electrical excitability of brain tissue, etc.) the possible effects of this form of stress on the onset of disease

have suffered severe burns, Hamburg noted that they tended, at first, to deny or minimize the nature and extent of the injury and its probable consequences, but that later a gradual transition occurred allowing them to accept the injury and their own rehabilitation. Eventually, such patients come to terms with the realities of their situation, their prospects for recovery, the potential limitations on their future lives: periods of depression and discouragement are regularly observed during this period. When permanent disability results, the coping process is aided by a sense of belonging to a "special" group. An opportunity for a badly burned patient to discuss with a physician his concerns about the injury and its consequences occasionally resulted in a dramatically improved outlook. In an effort to relieve their distress and difficulty, some patients are prepared to face certain facts and to make use of them in a way that they avoided previously . Thus, the seeking and' utilizing of information provided by another person may be useful to some patients as a means of coping with injury.

This was true of the parents of children dying from leukemia who were studied by Wolff et al. After an initial period of shock, disbelief, and depression on being told about their child's illness, these parents gradually came to accept it by inquiring about it. Their sense of responsibility for the illness could be dispelled by a frank discussion of its nature, by information about treatment and, finally, by advice and sympathy concerning the anticipated loss of their child.

side, one may conclude that an adaptation to a dangerous situation had occurred with a correlated lowering of steroid excretion levels, whereas in their comparison group of trainees, no such adaptation had taken place. It may, therefore, be that in an acutely stressful situation excretion levels are high, but that as psychological adaptation occurs they fall.

After the development of techniques for measuring cortisol production rates (rather than excretion levels), Katz et al. found that in a group of women anticipating breast biopsy the correlation of psychological-criteria measures similar to those employed by Wolff et al. worked better with production rate than with excretion levels. Women who showed the greatest emotional distress or experienced such unpleasant feelings as fear, dejection, despair, or apprehension tended to have relatively elevated hydrocortisone production rates, while those who were more hopeful or accepting showed relatively low rates.

Other forms of loss may be correlated with changes in body biochemistry by mechanisms still unknown. Kasl, Cobb, and Brooks reported a longitudinal study of changes in serum uric acid (SUA) and cholesterol levels in men undergoing job loss. The subjects were fifty-six married men, thirty-five to sixty years of age, who had held blue-collar jobs for a minimum of three years, and who were about to lose them because of a permanent plant shutdown. They were seen by public health nurses approximately three

exercises are considered to be among the most “rigorous . . . and stressful” training experiences in military life. The subjects were picked randomly from a UDT class and observed until they either successfully completed the course or withdrew. The behavioral data was obtained by means of clinical interviews and a psychological questionnaire prepared by Holmes and Rahe.

The investigators found statistically significant ($p < 0.025$) elevations in mean SUA level on mornings when the subjects were eagerly preparing to take on new, challenging and often physically complicated UDT activities. A significant fall in mean serum uric acid levels occurred on days of prolonged, tedious, and unpleasant physical activity, or when the schedule was unusually light. These fluctuations were more dramatic in the group of twenty men who successfully completed the course than in the twelve who did not. In general, SUA levels were higher and cholesterol levels lower in those who mastered the course most successfully. Serum cholesterol levels generally tended to fluctuate in the opposite direction from SUA levels. Illustrative of this pattern were the changes that occurred during the first week of training when the men were most enthusiastic, alert, and generally confident of their abilities to cope with the task at hand; at this time, group mean SUA level was at its highest (7.78 mg. percent) and cholesterol level near its lowest value. By the time the training course was almost over, the enthusiasm of the participants had waned considerably as the task had become mechanically routine but physically overwhelming. During this period, SUA levels fell to relatively low

anticipation of training situations that promised to be exceedingly demanding. Since, for many subjects, situations that were likely to evoke anxious anticipation alternated with those associated with enthusiastic optimism about the task, SUA and cortisol levels were frequently out of phase with each other, i.e., one would be falling while the other was rising, or vice versa.

This finding may be of importance in the light of a report in 1946 by Heilman that acute gouty arthritis had occurred in previously asymptomatic hyperuricemic subjects following the termination of a course of ACTH.

It had also been shown by Heilman that corticosteroids have, in addition to their anti-inflammatory action, the capacity to increase uric acid excretion by the kidneys. Thus, a precipitous decline in relatively elevated serum cortisol level could conceivably result in a rebound elevation (via the kidneys) in SUA level; this might then be associated with an attack of acute gouty arthritis.

Lest we be misunderstood, we are *not* saying that loss of another person by death or separation, or loss of a job is the only cause of illness or of physiological changes. We are saying that given a certain kind of genetic endowment (such an endowment probably plays a part in serious depressive illness, gout, peptic ulcer, etc.) *and* certain kinds of life experiences that

In these studies, in which young animals have been separated from their mothers, her offspring usually treated her disappearance as a complex experience that could be compensated for by surrogate mothering. In these experiments no attempt was made to analyze the individual effects on the infant of nutritional, olfactory, tactile, auditory, visual, or thermal stimuli after separation. The absence of such an analysis makes it impossible to determine whether changes in or deprivation of these simpler forms of stimulation do not produce the observed effects. Because prematurely separated young animals eat less and lose weight, their food intake is possibly the most critical, uncontrolled variable in these experiments. Deprivation of sensory inputs and litter size may also affect the development of young animals. Hofer, using rats, found that the critical variables that intervene in the effect of separation of fourteen-day old rat pups from their mothers are the mother's milk, and, in part, an unfamiliar environment. He is also the first investigator to study the *physiological* effect of separation: It produced a 40 percent drop in heart and respiratory rate during the first twelve to sixteen hours after separation. Hofer also showed that it is the absence of the mother's milk that produces the separation effect on these rats. Milk fed by stomach tube to fourteen-day old rats, left without food for sixteen hours after being separated from their mothers, transiently but fully reversed the decrease in heart rate that had occurred. The effect is rapid, produced by all three of the major chemical components of milk, and is related to the amount of milk given, but not to

So far we have emphasized work or loss as an important stress that may play a role in the inception of illness and in producing physiological changes. The knowledge derived from such studies has implications for medical care. For example, the doctor can act as a surrogate for a bereaved spouse or child. He can aid the grieving person in the process of mourning. He can support a bereaved person to ameliorate the psychophysiological consequences of loss. If he knows that a patient has suffered a loss, he will not label elevated levels of SUA, etc. as "idiopathic."

There are, however, many other stressful events that may occur in a patient's life. These include the ambiguity of not knowing the diagnosis and prognosis of his illness, the indifference of the physician, the anticipation of surgery, treatment by special technical procedures such as renal dialysis, and being put in intensive- or cardiac-care units.

Elsewhere in this *Handbook* (see Volume 4, Chapters 1 and 2) these topics are discussed at length.

Other Socioeconomic Variables in Disease and Illness

We have emphasized the role of separation or loss in human life as the prototype of the kind of social situation that may be correlated with behavioral and physiological changes. Separation may have its most profound effects early in a child's life and, again, in old age. As far as we know the

Work such as this suggests that the social structure of a community does play a role in averting disease. One may not casually conclude the obverse, however, For example, even under the most dire conditions such as those of a Nazi concentration camp, the incidence of peptic ulcer and bronchial asthma was said to be very low. Oppression and discrimination may play an additional and marked role in disease. The incidence of hypertension, and, in particular, its malignant phase, is much higher in American blacks than in whites or in African blacks.

Factors other than social ones may play a role in the etiology of essential hypertension. Unknown in New Guinea, it is a major cause of death in Japan; relationships between elevated blood pressure and the dietary content of salt have been sought to explain these observations which indicate an interaction of diet, culture, and disease.

Socioeconomic factors may play a role in the pathogenesis of disease. Overcrowding, economic hardship, job loss, and poor housing conditions, etc. may expose urban inhabitants to lead poisoning, rat bites, and rat-borne diseases, etc. The life in the city may prove stressful to those from rural areas, and vice versa. For some, success, marriage, or parenthood may prove a hardship and precipitate illness. An important variable is the rapidity with which political, social, or economic change occurs, even if this change appears to be personally salubrious or desirable: In our particular historical era, there

Hormonal Variables

Most physicians are not accustomed to the language of the behavioral sciences and they tend to dismiss the observations of behavioral scientists, psychiatrists, and medical sociologists as unreliable. There are, indeed, many methodological problems that await research in these areas. And observations made retrospectively on patients about the settings in which their illness began are often contaminated by such variables as the effects of hospitalization, and of the illness on the patient. However, when patients are selected at risk for, but prior to the onset of, an illness, the data becomes more convincing. When this is not possible, a test of hypotheses can be made on animal subjects.

We now present data to show that stress indeed has potent effects on physiological variables. From Mason we learn that there are, in all likelihood, neural and neuroendocrine mechanisms that regulate the orderly and sequential release of hormones in animals under stress. During and following a seventy-two-hour period when a monkey is actively engaged in avoiding shock, some hormone levels rapidly rise while levels of other hormones decline, and the change in levels of still others far outlast any avoidance session. For example, he has shown that urinary 17-hydroxycorticosteroid and epinephrine levels are elevated during an avoidance session. After the session, levels of the former decline slowly, and the latter rapidly.

changes in catecholamine levels are at first neuronally mediated, but later hormonal and neuronal mechanisms play a part in their elevation. We do not know what regulates the particular change in sex-hormone levels. One might ask if the stress of avoidance conditioning actually causes a decline of pituitary-trophic hormones or whether the suppression of sex-hormone levels is due to a decreased production in testis, ovary, or adrenal gland. If so, how does this come about?

The patterns of the release that Mason has studied are, with some likelihood, in part determined by hypothalamic and adrenal transducer cells. It remains to be determined by what neural circuits and mechanisms these cells are linked to mechanisms responsible for the emotional disturbance that is, in Mason's opinion, the critical intervening variable.

In the meantime, however, we have learned that these integrated patterns of hormone release are analyzable into separate components. For example, the biosynthesis of the catecholamines in the adrenal gland is under several separate mechanisms. These include long-term hormonal control by ACTH over three of the enzymes involved in the biosynthesis of the catecholamines, and short- and long-term neural control and regulation of the same enzymes.

That such separate mechanisms obtain is implicit in Mason's work. The

catecholamines. This pattern is analogous, if not homologous, with that described by Brod in man.

This work highlights the need to study much of the behavioral and physiological responses to stress in order to elicit an organized pattern of change. One may then align the pattern with known physiological fact. As exemplified, known patterns of physiological change can be produced by stimulating discrete brain sites—either by relay nuclei or axons that are part of complex neural circuits with different outflow channels.

In so doing, it becomes more apparent that the brain is capable of regulating a whole pattern of physiological change that is mediated by autonomic and hormonal outputs. However, the manner in which the brain does so is largely unknown.

What we are also beginning to realize is that the brain is capable of regulating, with exquisite precision, discrete physiologic change in one or another organ function. To a large degree we owe our awareness of this startling fact about the autonomic outflow to Miller and his pupil, DiCara. Heart rate, systolic blood pressure (independent of heart rate), peripheral vasomotor responses, gastrointestinal motility, and urine formation can be specifically modified in an expected direction by instrumental learning in the curarized rat. They have shown that only the rewarded response changes;

Early experiences modify both behavioral and physiological response tendencies. Presumably, therefore, during the course of the transduction of early experience by the brain, permanent changes are produced that modify later responses to stressful or other experiences.

We should like to review some evidence for this contention, and the even more impressive evidence that there are different physiologic mechanisms in the body that are responsible for bodily changes, depending on the duration of the stress.

Very acute stress, preparation for activity, and novel experiences is now known to be divided into anticipatory' and reactive phases that are associated with increases in systolic blood pressure, heart rate, and catecholamine and steroid excretion, etc. In all likelihood these changes are largely mediated neuronally. The mechanism underlying the increase in catecholamines, especially norepinephrine secretion (see Von Euler's Figure One) appears to be due to a sharp increase in norepinephrine synthesis from tyrosine but not Dopa, when an increase in sympathetic nerve activity occurs. However, no increase in tyrosine hydroxylase (TH) activity occurs, so that either no new enzyme is formed or formation is inhibited by norepinephrine.

The absence of change in TH content of tissue during acute stresses or stimulation stands in contrast to the change that is produced by sustained

but, in addition, it produces correlated changes in blood pressure and renal pathology.

Henry and his co-workers' results have been confirmed by the use of the restraint technic. Further evidence for the dually mediated changes in adrenal enzyme content has been obtained. Other work, using this method, begins to provide insight into some of the possible brain mechanisms mediating these changes.

Restraint of animals is also an excellent method for producing gastric ulcers and, therefore, for working out some of the mechanisms by which stress promotes an anatomic lesion.' Many of the experimental parameters and characteristics of the animals that promote or prevent the development of the gastric lesions have been worked out, and were ably reviewed recently by Ader.

But, one finding is of central importance because it attests to the importance of the interaction of an experience—in this case, restraint—with the state of the organism. Ader' found that his rats were significantly more likely to develop gastric ulcers when immobilized during the peak, rather than the trough, of the activity cycle.

Restraint—immobilization also has potent effects on the peripheral and central content of biogenic amines. Kvetnansky and Mikulaj have shown in

rise in TH levels in operated rats is neuronally dependent in the main, while the rise in PNMT and some of the rise in TH levels depends almost entirely on administered ACTH prior to stress.

On the other hand, serum dopamine--hydroxylase, which transforms dopamine into norepinephrine, was increased after one thirty-minute immobilization of rats, and continues to increase with daily immobilization for a week. The source of this increase is not, however, the adrenal gland but sympathetic nerves.

Immobilization stress of three hours also significantly accelerates the disappearance of radioactive norepinephrine from the heart and kidney. The question of how immobilization stress is centrally translated into these neuronally and hormonally dependent, peripheral changes is unanswered except for some very interesting work by the Welchs. They showed that restraint stress can cause a greater elevation of *brain* norepinephrine and serotonin in mice who previously had spent eight to twelve weeks in isolation when compared to litter mates housed in groups.

This elevation of brain amines occurs despite the fact that the isolated mice have slower, baseline turnover of brain biogenic amines than those housed with others.

This work has several important implications. The isolated mice were

basis for understanding individual differences in behavioral and physiological response tendencies to stress.

Further evidence for this statement can be found in Henry et ah's paper dealing with responses to the stress of social confrontation with members of the animal's own species in animals with different previous experiences.

They showed that the effects of mixing males from different boxes, of aggregating them in small boxes, of exposing mice to a cat for many months, and of producing territorial conflict in mixed males and females resulted in sustained elevations of systolic blood pressure, arteriosclerosis, and an interstitial nephritis; higher levels of systolic blood pressure were achieved by male rather than by female mice who also failed to reproduce under such conditions. If male mice were castrated minimal elevations in blood pressure occurred, while in those given reserpine minimal decrease in blood pressure resulted. Previous, that is, early experiences of living together attenuated the effects on blood pressure of experimentally induced aggregation and territorial conflict. On the other hand, isolation of animals from each other after weaning and to maturity exacerbated the effects of crowding on blood-pressure levels.

Recently Axelrod et al. and Henry et al. reported that the socially isolated mice showed a decreased activity of TH and PNMT activity in the

We still do not know very much about how early experiences interact with a schedule of maturational changes in the brain. There is evidence to suggest that permanent changes in behavior or of physiological function regulated by the brain can only be accomplished during “critical” periods of development. We know little about what such periods represent in terms of brain function. In fact, a major, unexplored area of neurobiology is the study of the interaction of experience with the biochemical and physiologic maturation of the brain. For example, there appears to be a maturational sequence for brain biogenic amines; Glowinski et al. showed that after the eleventh day of life, the rat rapidly develops the capacity to excrete norepinephrine and its metabolites with an efficiency approaching the adult. They also showed that the blood-brain barrier to norepinephrine is present at birth.

Endogenous levels of brain norepinephrine rise rapidly in the second week of the rat’s life, so that after twelve days they are only slightly lower than levels at twenty-four days and in adulthood, but are quite noticeably influenced by external factors such as nutrition.

In the future, one might study the effects of separating young animals at different ages on amine, RNA, DNA, amino acid, etc. levels. For example, separating rat pups from their mothers produces significant alterations in brain levels of free amino acids and acetyl cholinesterase in two days.

exclusively due to prenatal effects, since switching the litters of adrenalectomized and non-adrenalectomized mother rats had no effect on the differences in adrenal function in the offspring, despite the fact that adrenalectomized mothers lactate less. Thus, the effects of the maternal adrenalectomy on the offspring must have occurred *in utero.*

There is a large body of evidence on the effects of early life events on the adrenal-cortical response to stress. Levine et al. showed that rats handled as infants had a more marked adrenal-cortical response when exposed to cold in adulthood than did unmanipulated litter mates. This was also true" for rats exposed to a brief electric shock in adulthood after neonatal handling. They observed a significantly greater and more sustained increase in plasma corticoids as compared with unhandled controls, despite the fact that not only were the resting plasma levels of corticoids the same for both groups but the weights of the adrenal glands did not differ. When less drastic stresses were used, neonatally handled rats had a less marked adrenal-cortical response than control animals that had not been gentled. When exposed to an open-field trial for three minutes in adulthood, the handled rats showed some increase in plasma corticoids but significantly less than the control animals. To explain these seemingly inconsistent findings, Levine postulated that one of the major consequences of handling young rats “is to endow the organism with the capacity to make finer discriminations concerning relevant aspects of the environment. The animal then is able to make responses more

It has been postulated by two groups of investigators'' that the control of the endocrine system in the adult is partially accomplished by a feedback mechanism or "hormonostat." This mechanism would constantly "monitor" levels of plasma corticoids, compare these levels with a controlling "set point," and adjust ACTH secretion according to the plasma level. The crucial feature of this regulatory system requires that the "set point" not be fixed, but rather that it varies according to the metabolic demands placed upon the organism. Since the sensitivity of such a regulatory mechanism could be determined by a number of variables, among which are stressful early experiences during a critical period of development, it is possible that early experiences may allow for more graded and versatile responses. This could explain why stimulated rats showed a moderate increase in steroid output when placed in an open-field situation, and a large and rapid increase when subjected to electroshock. Unstimulated animals tended to react hormonally in a more stereotyped way, with large increases in hormone levels in response to change because of a more limited "hormonostatic" repertoire.

Sensory input to the brain, from handling, for example, may alter its maturation. (Obversely, sensory deprivation may impair levels of neurotransmitter substances in the brain.) In 1933, Langworthy observed that visual stimulation accelerates myelinization in the optic tracts of premature and term infants. Other workers' have shown that a flashing light in a cat's eye will increase the blood flow, temperature, and metabolism

gland. As a result of this work, new concepts about the relationship of the CNS to the endocrine system have developed. It is believed that the brain and the endocrine glands comprise a thoroughly integrated system that coordinates the organism's responses to alterations both in its external and internal environment. Under the influence of stressful stimuli, a sequence of events is believed to occur that terminates by the activation of hypothalamic "transducer" cells. These cells respond to neural input by the release of a putative, amine transmitter with the release of a polypeptide, similar to pitressin in structure. This polypeptide is called the corticotropin releasing factor (CRF). CRF reaches the anterior portion of the pituitary gland via the portal-venous system around the hypophysial stalk at the median eminence, and ACTH is released to stimulate the adrenal gland to produce cortisol. The degree to which the system is activated may depend upon the degree of stress and its duration. Despite the fact that a negative "feedback loop" exists between the adrenal cortex and the anterior pituitary, mediated by circulating levels of cortisol, persistent neural input will result in the continued release of CRF and ACTH despite elevated cortisol levels. Individual differences in animals in the nature and duration of the cortisol response to stress may be due to early experiences. Mason and Hamburg have observed individual differences in 17-OHCS excretion in man that are consistent over months and through several stressful experiences. These individual differences consisted of variation in the range of fluctuation of 17-OHCS

undifferentiated brain is “organized” by gonadal hormones during fetal and early neonatal life. Subsequently, several investigators have shown'' that the presence of androgens in small amounts during the first five days of life in female rats alters the regular cycle of gonadotrophin release to an aperiodic one. In the absence of any gonadal hormones, the gonadotrophins are secreted cyclically. Thus, the absence of androgens in the male rat in the first forty-eight hours of life results in the cyclic elaboration of gonadotrophins. In addition, the neonatal castration of a male rat drastically alters his sexual behavior. When injected with low doses of estrogens and progesterone’s as an adult, he exhibits the complete repertoire of female sexual behavior. Castration of adult males and similar treatment with estrogen and progesterone does not yield such results. It is apparent from these data that during a critical period in early development androgens acting on the brain are responsible for the acyclic secretion of gonadotrophins. They determine male sexual behavior in much the same way that they affect the development of male sexual morphology. It is evident, therefore, that sex hormones in early life play a major part in determining sexual behavior, morphology, and physiology. It is possible also, as Levine has pointed out, that the adrenal corticoids may have a profound effect upon the organization of the brain and may influence a number of functions associated with neuroendocrine regulation of ACTH.

Varying early experiences also influence immune responses. Friedman

throughout the preweaning period or during the third week only had a lower death rate than other groups of mice, including unshocked, control animals. Thus, the effects of early experiences of this kind upon resistance to Walker sarcoma depend upon the nature of the experience and the time during early life when it occurs.

Psychobiological Studies in Animals Relevant to the Etiology and Pathogenesis of Some Medical Illnesses

Observations of patients have led to the formulation of the role of psychological factors in the etiology and pathogenesis of disease. To test the validity of the hypotheses derived from such studies and to work out the mechanisms postulated, studies of animals have been used. Such studies have been successful where research in the clinic has been less than reliable. For one thing, animal studies have added scientific evidence to the claim that environmental stimuli and a wide range of experimental variables do, in fact, produce physiological or structural changes analogous or homologous to clinical disease. Secondly, the postulate that social stimuli may act via the nervous system to alter bodily functions has been strongly supported if not substantiated by such work.

To summarize the achievements of animal studies reviewed up to this point: much is now known about the kinds of behavioral, endocrine, and autonomic changes that conditioning techniques, restraint, or separation may

administration of drugs, brain stimulation, diet, restraint or immobilization, and conditioning techniques—used singly or in combination.

When restraint is used, the important parameters are the species and age of the experimental animal, the length of time he is immobilized, and the availability of food and water. The experimenter must also bear in mind that different experimental manipulations may produce gastric erosion in different parts of the stomach and may, therefore, be mediated by different physiological mechanisms that are still unidentified.

Another important experimental variable to be considered is that some animals are more susceptible to a particular manipulation than others. As is true of man, a high level of serum pepsinogen (on a statistical basis) may be assumed to constitute a biological indicator of an increased susceptibility to erosion in the glandular portion of the animal's stomach.

Ader's experiments with rats have particular relevance for our understanding of gastric and peptic ulcers. Specifically, Ader bred rats for susceptibility to gastric lesions on restraint. These animals had higher levels of serum pepsinogen prior to restraint: high serum pepsinogen levels were not, therefore, a response to restraint. In addition, these lesion-susceptible rats manifested some interesting behavioral characteristics. They were more reactive emotionally, and appeared to dominate non-susceptible animals with

"psychosomatic" research on humans in the mind of the critical reviewer, are dispelled by research on the production of ulcers in animals. A number of laboratory experiments and behavioral characteristics (such as activity cycles) do seem to combine with physical stimuli and genetically determined physiological factors to produce gastric ulcers. Moreover, despite the fact that the relationship of gastric ulceration in the rat to duodenal ulceration in man is unclear, duodenal ulceration was produced in monkeys in Brady's experiments.

One may also conclude from these studies that a number of different experimental conditions produce the same anatomical lesion, presumably through some common mechanism. The studies conducted by Levine and Senay are relevant in this connection. These investigators found that when rats were restrained in a cold climate, intragastric pH fell and ulcers appeared. However, an antacid protected against the production of ulcers under such environmental conditions. Presumably, then, these ulcers were caused by an increase in gastric acidity, which is believed to be mediated by histamine. Interestingly, Levine and Senay also demonstrated that restraint and cold increase the activity of histidine decarboxylase, which increase is positively correlated with the incidence and severity of stress ulcers. The inhibition of diamine oxidase (the enzyme which catabolizes histamine) has the same effect.

Stress of the kind used by Henry can set into motion a number of physiological changes. As we mentioned earlier, Thoenen, Mueller, and Axelrod' showed that a reflex increase of sympathetic nerve activity transsynaptically induced enzyme activity in the adrenal gland after from one to three days. However, others have also shown that social stimuli may increase levels of adrenocortical steroids, constrict renal vessels, and alter levels of brain norepinephrine.

In another area of investigation, salt was found to play a role in the pathogenesis of hypertension; the precise nature of this role has been hotly contested, however. To summarize these findings, various steroids produced experimental hypertension in animals only in the presence of salt. When hypertonic saline was the only source of fluid, hypertension was produced in a variety of animals. The chronic ingestion of too much salt produced hypertension in the rat, but it took time and even then hypertension was not found in all the animals of a particular strain.

In this connection Jaffe and his co-workers have reported that there are two genetic strains of rats. One is resistant and the other is sensitive to salt ingestion. Even a diet containing only 0.38 percent salt caused the rats in the sensitive group to have higher blood pressures (134 mm. Hg, mean) than the resistant ones (112 mm. Hg, mean). In fact, resistant rats on a diet of 8 percent salt showed no blood pressure increases, but the blood pressure of

sodium content of the arterial wall may be increased in such animals.

The fourth line of evidence implicating salt —and specifically the sodium ion—is proven by the fact that the amount of renin extractable from the kidneys of hypertensive rats was proportional to salt and water intake. As renin disappeared from the kidney, the rats showed an increased sensitivity to injected renin. In depleting the kidney of renin, salt probably acts through the medium of an increased plasma volume. Unfortunately, however, the increase of blood renin (and the decrease of kidney renin) in response to the increase in blood sodium does not parallel the increase in blood pressure.

The question of whether psychosocial stimuli elicit circulatory responses has been answered, in part, by the use of conditioning procedures. Experimentally induced general behavioral changes, such as fear, are particularly likely to evoke an increase in unconditioned responses in animals. Conditioned cardiovascular responses, including elevations of blood pressure, can be retained in animals for many years, even after the original and concomitant motor or salivary responses can no longer be elicited.

Direct brain stimulation can serve either as the conditional stimulus or the unconditional stimulus. Motor cortical area stimulation (as an unconditional stimulus) that does not produce movements leads to vasoconstriction or dilation; parietal stimulation leads only to constriction.

occurred. Pressor responses that had been neutral prior to training were observed in the presence of a variety of stimuli. Only one point has not been made in this report: we do not know whether the elevated pressures persisted after the avoidance performance had ceased. We have indicated that no single psychological or physiological variable can account for the pathogenesis of essential hypertension. This statement is further attested to by an interesting set of observations made by McCubbin. After very small doses of angiotensin (which had no immediate effect on blood pressure) had been infused into dogs for several days, their arterial pressure became elevated and labile. (Before the infusion the mean arterial pressure had been steady.) When the dogs were surrounded by normal laboratory activity, their blood pressures were labile and high. If the laboratory was quiet, even minor distractions caused marked further increases in blood pressure, due to abrupt increases in peripheral resistance. When these dogs were sensitized with an infusion of tyramine, which releases endogeneous stores of norepinephrine, further elevations of blood pressure were produced. Infusions of norepinephrine had no effect on blood pressure. These observations suggest that a systematic study could be carried out of the role of psychosocial stimuli in animals made hypertensive by small doses of infused angiotensin. Extrapolating from recent work on the pharmacological effects of angiotensin, it might be possible to test the hypothesis that angiotensin sensitizes the brain to sensory input as well as having effects on blood pressure through the

manipulated in the laboratory. In fact, the recent evidence of Miller and Mason raises the exciting possibility that we may be on the verge of a real breakthrough in understanding the pathogenesis and pathophysiology of hypertension. Moreover, by a combination of techniques, the answers to the three central questions delineated earlier might be sought in studies of animals. This possibility justifies the restatement of these questions: (1) Can renal blood flow be increased in one renal artery and decreased in the other by operant conditioning? If so, the content in each renal vein of renin and/or angiotensin II could be measured; (2) Can the distribution of blood flow within each kidney (measured by intra-arterial injections of Krypton and intravenous injections of Iodoantipyrine-I 131) be affected differently by different operant methods? And (3) If renal blood flow can be diminished by operant conditioning procedures, does hypertension ensue? Some of the mechanisms that mediate these events remain unknown.

Stressful Influences on Cardiac Rhythm and Their Mechanisms

Ectopic activity of the heart beat has been recorded in stressful situations and can be produced experimentally by stimulating either the vagus or the sympathetic cardiac nerves. When both are stimulated simultaneously, ventricular extrasystoles can be produced. Stimulation of the posterior hypothalamus can elicit a similar arrhythmia in cats under chloroform anesthesia. While stimulation of the posterior part of the lateral

hypothalamus and the mesencephalic reticular formation regularly causes a profound tachycardia as well as raising the blood pressure—both phenomena outlast the duration of the stimulus.

In all likelihood, the effects on rhythm of such brain stimulation are mediated both by the vagus and cardiac sympathetic nerves. Therefore, arrhythmias of various kinds can be produced in animals whose heart is intact by means of brain stimulation.

When the heart is damaged, as for instance by coronary artery ligation, ventricular fibrillation can be prevented only by total denervation of the heart. In the obverse experiment, ventricular fibrillation could be produced in some dogs by hypothalamic stimulation following coronary artery ligation.

Neither the exact mechanism of arrhythmia nor the pathways mediating the effects of brain stimulation leading to the vagus and cardiac nerves from hypothalamic centers have been fully worked out.

It is also of interest that heart rate and rhythm can be affected by psychological means. Heart-rate changes can be produced by instrumental learning in animals and man, and arrhythmias decreased by these means.

Thyroid Disease

In contrast to the large number of animal studies of gastric ulcers, few systematic studies have been done in the field of thyroid disease despite the relatively large number of available tests for thyroid function.

A rise in plasma protein-bound I consistently occurred in sheep exposed to barking dogs. The reverse effect on thyroid function was obtained when rats were exposed to the sight of a larger, fierce wild rat through a glass screen. Two explanations have been advanced for this response. Some authors believe that corticosteroids inhibited the release of I from the thyroid gland; others contend that secretion of the hypothalamic corticotrophin releasing factor resulted in the diminution of the thyrotropin releasing factor (TRF). The mediating role of TRF between social stimuli and enhanced thyroid function is a source of considerable controversy. However, Mason found that plasma-thyroid-hormone levels showed a slow but prolonged elevation concomitant with a three-day avoidance session in monkeys. This elevation of hormone levels began during the avoidance session, and lasted for two or three weeks after termination of the schedule. The finding that electric stimulation of the hypothalamus enhances thyroid function in several species of animals has been well documented, and various limbic-area structures have also been implicated in the regulation of thyroid function. Finally, norepinephrine and epinephrine are known to activate thyroid function, and are, of course, acutely responsive to psychosocial stimulation.

However, thyrotropin may not be an important factor in thyrotoxic disease because it is believed today that a long-acting thyroid stimulator (LATS) rather than thyrotropin, is the pathogenetic agent in Graves' disease. LATS is an immunoglobulin. Therefore, the logical question arises as to how the nervous system could contribute to its regulation; or, putting it another way, in addition to the exposure to an antigen, do other factors control antibody formation or contribute to the action of an antibody? At this point, one can only speculate that there may be genetic factors that influence antibody formation in thyroid disease, and that LATS may act on cyclic AMP (adenosine monophosphate) as the corticosteroids and catecholamines do, to promote the entrance of iodine into thyroid cells. In addition, it is known that adrenalectomy and the administration of thyroid hormone enhance antibody formation, and that the nervous system may regulate immune responses. For example, avoidance conditioning influenced immunological responses. At the same time, some evidence has been accumulated that indicates that midbrain and hypothalamic (tuberal) lesions could protect guinea pigs against anaphylactic shock. Anterior hypothalamic lesions were significantly more successful in protecting rats against anaphylaxis to ovalbumin than were posterior hypothalamic lesions. Anterior hypothalamic lesions lowered circulating antibodies to the same antigen in guinea pigs and made them less sensitive to toxic doses of histamine, possibly by modifying the physiological reactivity of the bronchiolar tree to the constrictive effects of histamine.

In summary, animal studies have provided rather reliable evidence on several scores: target-organ change and physiological responses occur that are relevant to the diseases under consideration in this paper. Furthermore, one may now conclude, on the basis of Mason's work in particular, that avoidance conditioning does indeed act through the CNS to produce changes in a series of hormones, including such critical ones as corticosteroids, catecholamines, aldosterone, plasma-thyroid hormone, growth hormone, plasma insulin, and sex hormones. Furthermore, these studies have given rise to generalizations that these hormonal changes are patterned and do not occur individually. Nor are these patterns of change unique to avoidance conditioning: they occur with novel stimuli as well.

Such patterns of change also occur in the autonomic system, as evidenced, for example, by the cardiovascular changes that precede and accompany exercise. Whereas these adjustments were once considered to be instigated exclusively by peripheral mechanisms, Rushmer has postulated that the onset of vasodilation and increased flow in muscle, heart rate and output, etc. at the start of exercise emanate from the nervous system as an autonomic concomitant to the muscular activity under volitional control.

In other words, concomitant patterns of cardiovascular and motor activities exist. These cardiovascular adjustments seem to be specific to a given behavioral activity; other adjustments probably occur with other

activities: For example, in preparing to fight another cat, cats showed bradycardia, a decreased cardiac output, and vasoconstriction in the iliac and mesenteric vessels. But when actually striking the other cat, the heart rate and cardiac output rose, the iliac bed dilated and the mesenteric bed constricted. In neither case was there a significant rise in blood pressure, however.

Clearly, these findings require further clarification. A contradiction appears in the work on the production of gastric ulcers in rats—Mason's work and the work mentioned above on cardiovascular changes. On the one hand, different psychosocial stimuli or situations were found to produce the same anatomical lesion or pattern of physiological change; on the other, they produced different changes. Immobilization restraint invariably produces lesions in the glandular portion of the rat's stomach, but conflict situations produced ruminal lesions in some rats, and glandular lesions in others.

Is this discrepancy a function of strain differences? Or can it be attributed to quantitative or situational factors, or differences in mediating physiological mechanisms? Only further research will provide the answers to such questions. Other interesting questions remain unanswered as well: At what thresholds do avoidance schedules produce the requisite changes, as measured by the animal's ability to escape, the predictability of his response, and the intensity and duration of stimuli?

Conclusion

We have attempted to demonstrate that many physiological parameters are influenced by environmental factors and that disease states may be produced by experimental manipulations of animals. There is increasing evidence from a review of the literature that many integrative physiologists are beginning to be aware of the fact that certain broad generalizations no longer hold. The autonomic nervous system is no longer viewed as mainly responsible for the maintenance of the "constancy" of the internal environment, or as separate from the endocrine system. (For a review of modern data and concept about the autonomic nervous system, see Volume 4, Chapters 22 and 23, of the *Handbook).* We regard the autonomic nervous system today as one of the three principal output systems of the brain that are involved in the mediation of the brain's responses to stimuli of environmental origin, including preparation for activity in response to an outside stimulus. These responses are imposed on continuous, ongoing, autonomic discharge, which varies according to the behavioral state of the organism. In the state of rapid eye movement sleep, for example, *variability* of heart and respiratory rates, blood pressure, etc. is much greater than in slow wave sleep or quiet wakefulness. In other words, autonomic discharge is phasic during this behavioral steady state.

The autonomic nervous system is both responsible for and under the

influence of hormonal output. The endocrine system, in turn, is the second major output system of the brain mediating environmental change. In fact, there is an increasing realization of the close interactions of hormonal and autonomic mechanisms.

The classical view of autonomic function was largely obtained by analytic experiments in which only a single input (such as blood-pressure change) was varied while inputs from many other afferent zones were either eliminated or held constant. Only when the organism is studied as a whole, in an integrative manner, does it become obvious that a change in one variable (such as carotid-sinus pressure) interacts with other inputs to the brain as well as giving rise to a multiplicity of effects such as decreased adrenal-catecholamine-antidiuretic-hormone production as well as cardiac-reflex slowing, decreased cardiac-sympathetic activity, and splanchnic-bed vasodilatation, etc. All these effects must be mediated by widely disparate circuits in the brain.

These advances in physiological data and concepts must be made available to the behavioral biologist while medicine must incorporate the contributions of behavioral biology. For example, it is generally recognized that genetic factors play some role in the etiology of essential hypertension, Graves' disease, and probably in peptic ulcer. But we have not yet determined how much of the etiologic variance can also be attributed to experiential (e.g.,

social, familial, and economic) factors. Methodologies have been developed that would allow the investigator to determine the relative contributions of genetic and experiential factors in the etiology of disease.

At present, in the case of hypertension, about one-third to one-quarter of the variance is ascribed to genetic factors. That familial factors may play a role is attested to by the fact that spouses tend to share similar blood-pressure levels in proportion to the duration of the marriage. Further, the parent-child correlation of pressures tends to be greatest in families in which spouse aggregation is demonstrated. But what could be the factors in the environment of family groupings capable of influencing their blood pressure? Some recent work suggests that if familial factors play a role in elevated blood pressure, they are established early in life. Only future research can determine the nature of these familial factors.

On the other hand, by extrapolating from the work done on animals by Ader and Mason (see von Euler's Figure i], one is led to the inevitable conclusion that these many diseases (such as hypertension and ulcers) are neither caused nor sustained by any single pathogenetic or pathophysiological factor. Rather, psychosocial stimuli, acting through the nervous system, activate a wide range of interrelated, integrated responses. In essence, the nature of the factors involved, the changes they undergo in the course of the disease, and their interrelationships attest to the fact that many

diseases are primarily diseases of physiological regulation. Similar statements have been made by Brooks, Harvey, Menguy, and Ryss and Ryss. In the past, clinical psychobiological research consisted primarily of psychoanalytic observations and single dependent variables studied by psychophysiologists. Psychophysiological results were then conceptualized in linear causal terms. For example, "anxiety" caused an increased heart rate.

It is not enough to state that many important diseases are diseases of regulation in which the nervous system participates. The specific nature of the disturbance in regulation must be specified: Admittedly, it is difficult to conceptualize such regulatory patterns. But control-theory models and models derived from molecular biology do exist.

For example, in molecular biology various kinds of regulatory devices are known: (1) In enzyme synthesis, enzymes may be formed ("induction") only in the presence of substrate. (2) Enzymes in a biosynthetic pathway may be repressed by an excess of the end product of the pathway ("feedback inhibition"). (Jacob and Monod have attributed these two types of regulation to a regulator gene. In the proper configuration, the product of the gene acts on another area to inhibit expression of one or more genes in an adjacent area. Other regulatory devices have been described as well.) (3) In enzyme activity, the initial enzyme in a biosynthetic pathway is usually the one inhibited. (4) There is usually more than one initial enzyme in a common

biosynthetic pathway. These act in conjunction and catalyze the same chemical reactions, but are subject to different feedback regulation. And (5) in protein synthesis, regulation is achieved at the rate at which the initial step in the synthesis of the protein chain occurs, and not at the rate of enzyme synthesis. Other forms of molecular regulatory activity, though carefully conceptualized, do not fit any of the five models mentioned above. And regulation of excitation at the synapse may also take different forms, most of which are well known.

These concepts have important implications for a theory of medicine, with particular emphasis on theories of etiology and pathogenesis of disease. At the same time, they may help to incorporate data that suggest that stressful experience plays a role in the etiology and pathogenesis of disease.

In turn, we would suggest that the information we have reviewed has implications for the practice of medicine and the education of students and physicians. Thus, it may be economically more expeditious and technically more feasible to isolate a patient completely from other human beings in an intensive-care unit, but the psychological effects of isolation, or the impact of a patient watching his own irregular or faltering heart beat on an oscilloscope, may be much more stressful than having him share a room with others with whom he can talk about his real and imaginary concerns.

We believe that the organismic and integrative approach to medicine and disease implied in this chapter can be translated into the teaching of students. Space does not permit a detailed plan for such a curriculum, which one of us has outlined elsewhere.

Bibliography

Abrahams, V. C., S. M. Hilton, and Sbrozyna. "Active Muscle Vasodilatation Produced by Stimulation of the Brainstem: Its Significance in the Defense Reaction," *J. Physiol.,* 154 (1960), 491-513.

Adams, D. B., G. Baccelli, G. Mancia et al. "Cardiovascular Changes during Preparation for Fighting Behavior in the Cat," *Nature,* 220 (1968), 1239-1240.

Adamson, J. D. and A. H. Schmale, Jr. "Object Loss, Giving Up and the Onset of Psychiatric Disease," *Psychosom. Med..,* 27 (1965), 557-576.

Ader, R. "Plasma Pepsinogen Level in Rat and Man," *Psychosom. Med.,* 25 (1963), 218-220.

----. "Gastric Erosions in the Rat: Effects of Immobilization at Different Points in the Activity Cycle," *Science,* 145 (1964), 406-407.

----. "Behavioral and Physiological Rhythms and the Development of Gastric Erosions in the Rat," *Psychosom. Med.,* 29 (1967), 345-353.

----. "Early Experiences Accelerate Maturation of the 24-Hour Adrenocortical Rhythm," *Science,* 163 (1969), 1225-1226.

Ader, R. and S. B. Friedman. "Differential Early Experiences and Susceptibility to Transplanted Tumor in the Rat," *J. Comp. Physiol. Psychol,* 59 (1965), 361-364.

Alousi, A. and N. Weiner. "The Regulation of Norepinephrine Synthesis in Sympathetic Nerves: Effect of Nerve Stimulation, Cocaine, and Catecholamine-Releasing Agents," *Proc.*

Natl. Acad. Sci. U.S.A., 56 (1966), 1491-1496.

Axelrod, J. "Brain Monoamines: Biosynthesis and Fate," *Neurosci. Res. Program Bull.,* 9 (1971), 188-196.

----. "Noradrenaline: Fate and Control of Its Biosynthesis," *Science,* 173 (1971), 598-606.

Axelrod, J., R. A. Mueller, J. P. Henry et al. "Changes in Enzymes Involved in the Biosynthesis and Metabolism of Noradrenaline and Adrenaline after Psychosocial Stimulation," *Nature,* 225 (1970), 1059-1060.

Bahnson, C. B. "Psychophysiological Complementarity in Malignancies: Past Work and Future Vistas," *Ann. N.Y. Acad. Sci.,* 164 (1969), 319-334.

Barraclough, C. A. "Production of Anovulatory, Sterile Rats by Single Injection of Testosterone Propionate," *Endocrinology,* 68 (1961), 62-67.

Bing, J., and N. Vinthen-Paulsen. "Effects of Severe Anoxia on the Kidneys of Normal and Dehydrated Mice," *Acta Physiol. Scand.,* 27 (1952), 337-349.

Bliss, E. L., C. J. Migeon, C. H. H. Branch et al. "Reaction of the Adrenal Cortex to Emotional Stress," *Psychosom. Med.,* 18 (1956), 56-76.

Bonfils, S., G. Liefooghe, G. Rossi et al. "L'Ulcère de constrainte du rat blanc," *Comp. Rend. Séances Soc. Biol. Filiales*, 151 (1957), 1149-1150.

Bourne, P. G., R. M. Rose, and J. W. Mason. "Urinary 17-OHCS Levels: Data on Seven Helicopter Ambulance Medics in Combat," *Arch. Gen. Psychiatry,* 17 (1967), 104-110.

Brady, J. V., R. W. Porter, D. G. Conrad et al. "Avoidance Behavior and the Development of Gastroduodenal Ulcers," *J. Exp. Anal. Behav.,* 1 (1958), 69-72.

Brod, J. "Essential Hypertension—Hemodynamic Observations with Bearing on its Pathogenesis," *Lancet,* 2 (1960), 773-783.

----. "Hemodynamics and Emotional Stress," *Bibl. Psychiatr.,* 144 (1970), 13-33.

Brod, J., V. Fencl, Z. Hejl et al. "Circulatory Changes Underlying Blood Pressure Elevation during Acute Emotional Stress (Mental Arithmetic) in Normotensive and Hypertensive Subjects," *Clin. Sci.,* 18 (1959), 269-279.

Brod, J., V. Fencl, Z. Hejl et al. "General and Regional Hemodynamic Pattern Underlying Essential Hypertension," *Clin. Sci.,* 23 (1962), 339-349.

Brodie, D. A., and H. M. Hanson. "A Study of the Factors Involved in the Production of Gastric Ulcers by the Restraint Technique," *Gastroenterology,* 38 (1960), 353-360.

Bronfenbrenner, U. "Early Deprivation in Mammals: A Cross Species Analyses," in G. Newton, ed., *Early Experience and Behavior,* pp. 627-764. Springfield: Charles C. Thomas, 1968.

Brooks, F. P. "Central Neural Control of Acid Secretion," in W. F. Hamilton and P. Dow, eds., Handbook of Physiology, Sect. 6. *Alimentary Canal,* Vol. 2, pp. 805-826. Washington: American Physiological Society, 1967.

Bunney, W. E. "A Psychoendocrine Study of Severe Psychotic Depressive Crisis," *Am. I. Psychiatry,* 122 (1965), 72-80.

Bygdeman, S., and U. S. von Euler. "Resynthesis of Catechol Hormones in the Cat's Adrenal Medulla," *Acta Physiol. Scand.,* 44 (1958), 375-383.

Carlson, L. A., L. Levi, and L. Oro. "Plasma Lipids and Urinary Excretion of Catecholamines during Acute Emotional Stress in Man and Their Modification by Nicotinic Acid," *Forsvars Med.,* 3 (1967), 129-136.

Cassem, N. H., and T. P. Hackett. "Psychiatric Consultation in a Coronary Care Unit," *Ann. Intern. Med.,* 75 (1971), 9-14.

Chodoff, P., S. B. Friedman, and D. A. Hamburg. "Stress, Defenses and Coping Behavior: Observations in Parents of Children with Malignant Disease," *Am. J. Psychiatry,* 120 (1964), 743-749.

Christian, J. J., J. A. Lloyd, and D. E. Davis. "The Role of Endocrines in the Self-Regulation of Mammalian Populations," *Recent Prog. Horm. Res.,* 22 (1965), 501-571.

Dahl, L. K. “Possible Role of Salt Intake in the Development of Essential Hypertension,” in K. D. Bock and P. T. Cottier, eds., *Essential Hypertension,* pp. 53-65. Berlin: Springer, 1960.

D’Angelo, S. A., J. Snyder, and J. M. Grodin. “Electrical Stimulation of the Hypothalamus: Simultaneous Effects on the Pituitary-Adrenal and Thyroid Systems of the Rat,” *Endocrinology,* 75 (1964), 417-427.

Day, G. “The Psychosomatic Approach to Pulmonary Tuberculosis,” *Lancet,* 260 (1951), 1025-1028.

De La Mettrie, J. O. L’Homme Machine. Leyden: Luzac, 1748.

Denenberg, V. H., J. T. Brumaghin, G. C. Haltmeyer et al. “Increased Adrenocortical Activity in the Neonatal Rat following Handling,” *Endocrinology,* 81 (1967), 1047-1052.

Descartes, R. “The Discourse on Method,” in E. S. Haldane and G. T. R. Ross, eds., *The Philosophical Works of Descartes.* Cambridge: Cambridge University Press, 1911.

Dicara, L. “Plasticity in the Autonomic Nervous System: Instrumental Learning of Glandular and Visceral Responses,” in F. O. Schmitt, ed., *The Neurosciences: Second Study Program,* pp. 218-223. New York: Rockefeller University Press, 1971.

Ebert, P., R. Vanderbeek, R. Allgood et al. “Effect of Chronic Cardiac Denervation on Arrhythmias after Coronary Artery Ligation,” *Cardiovasc. Res.,* 4 (1970), 141-147.

Edstrom, J. E., D. Eichner, and N. Schor. “Quantitative Ribonucleic Acid Measurements in Function: Studies of the Nucleus Supraopticus,” in S. S. Kety and I. Elkes, eds., *Regional Neurochemistry*, pp. 274-278. New York: Pergamon, 1961.

Engel, G. L. “Studies of Ulcerative Colitis: The Nature of the Psychologic Processes,” *Am. J. Med.,* 19 (1955), 231-256.

----. “A Life Setting Conducive to Illness: The Giving-Up, Given-Up Complex,” *Arch. Intern. Med.,* 69 (1968), 293-300.

Erikson, E. *Childhood and Society*, 1st ed. New York: Norton, 1950.

Evans, C. S. and S. A. Barnett. "Physiological Effects of 'Social Stress' in Wild Rats: 3. Thyroid," *Neuroendocrinology,* 1 (1965-1966), 113-120.

Falconer, I. R. and B. S. Hetzel. "Effect of Emotional Stress and TSH on Thyroid Vein Hormone Level in Sheep with Exteriorized Thyroids," *Endocrinology,* 75 (1964), 42-48.

Feitelberg, S. and H. Lampl. "Warmetonung der Grosshirnrinde bei Erregung und Ruhe bzw," *Arch. Exp. Pathol. Pharmacol.,* 177 (1935), 725-736.

Fenz, W. D. and S. Epstein. "Gradients of Physiological Arousal in Parachutists as a Function of an Approaching Jump," *Psychosom. Med.,* 29 (1967), 33-51.

Ferrario, C. M., C. J. Dickinson, P. L. Gildenberg et al. "Central Vasomotor Stimulation by Angiotensin," *Fed. Proc.,* 28 (1969), 394.

Figar, S. "Conditional Circulatory Responses in Men and Animals," in W. F. Hamilton and P. Dow, eds., Handbook of Physiology, Sect. 2. *Circulation* Vol. 3, pp. 1991-2036. Washington: American Physiological Society, 1965.

Forsyth, R. P. "Blood Pressure and Avoidance Conditioning," *Psychosom. Med.,* 30 (1968), 125-135.

----. "Blood Pressure Responses to Long-Term Avoidance Schedules in the Restrained Rhesus Monkey," *Psychosom. Med..,* 31 (1969), 300-309.

Freedman, D. X. and G. Fenichel. "Effect of Midbrain Lesions in Experimental Allergy," *Arch. Neurol. Psychiatry,* 79 (1958), 164-169.

Friedman, S. B., R. Ader, and L. A. Glasgow. "Effects of Psychological Stress in Adult Mice Inoculated with Coxsackie B Viruses," *Psychosom. Med.,* 27 (1965), 361-368.

Friedman, S. B., J. W. Mason, and D. A. Hamburg. "Urinary 17-Hydroxycortico-steroid Levels in Parents of Children with Neoplastic Disease: A Study of Chronic Psychological Stress," *Psychosom. Med.,* 25 (1963). 364-376-

Garvey, H. and K. Melville. “Cardiovascular Effects of Lateral Hypothalamic Stimulation in Normal and Coronary Ligated Dogs,” *J. Cardiovasc. Surg.,* 10 (1969), 377-385.

Glowinski, J., J. Axelrod, I. J. Kopin et al. “Physiological Disposition of H Norepinephrine in the Developing Rat,” *J. Pharmacol. Exp. Ther.,* 146 (1964), 48-53.

Greene, W. A. Jr. “Psychological Factors and Reticuloendothelial Disease: I. Preliminary Observations on a Group of Males with Lymphomas and Leukemia’s,” *Psychosom. Med.,* 16 (1954), 220-230.

Hackett, T. P., N. H. Cassem, and H. A. Wishnie. “The Coronary Care Unit: An Appraisal of Its Psychologic Hazards,” *N. Engl. J. Med.,* 279 (1968), 1365-1370.

Hamburg, D. A. “Plasma Urinary Corticosteroid Levels in Naturally Occurring Psychological Stress,” *Res. Publ. Assoc. Res. Nerv. Ment. Dis.,* 40 (1962), 406-413.

----. “Genetics of Adrenocortical Hormone Metabolism in Relation to Psychological Stress,” in J. Hirsch, ed., *Behavior-Genetic Analysis,* pp. 154-175. New York: McGraw-Hill, 1967.

Hamburg, D. A. and J. E. Adams. “A Perspective on Coping Behavior,” *Arch. Gen. Psychiatry,* 17 (1967), 277-284.

Hamburg, D. A., C. P. Artz, E. Reiss et al. “Clinical Importance of Emotional Problems in the Care of Patients with Bums,” *N. Engl. J. Med.,* 248 (1953). 355-359.

Hamburg, D. A., B. Hamburg, and S. Degoza. “Adaptive Problems and Mechanisms in Severely Burned Patients,” *Psychiatry,* 16 (1953), 1-20.

Harlow, H. F. “The Development of Affectional Patterns in Infant Monkeys,” in M. Foss, ed., *Determinants of Infant Behavior,* pp. 75-88. London: Methuen, 1961.

Harris, G. W. “Sex Hormones, Brain Development and Brain Function,” *Endocrinology,* 75 (1964), 627-648.

Harris, G. W. and S. Levine. “Sexual Differentiation of the Brain and Its Experimental Control,” *J. Physiol.,* 181 (1965), 379-400.

Hartmann, H. (1939) Ego Psychology and *the Problem of Adaptation.* New York: International Universities Press, 1958.

Harvey, N. A. "The Cybernetics of Peptic Ulcer," *N.Y. State J. Med.,* 69 (1969), 430-435.

Hays, M. T. "Effect of Epinephrine on Radioiodide Uptake by the Normal Human Thyroid," *J. Clin. Endocrinol. Metabol.,* 25 (1965), 465-468.

Hellman, L. "Production of Acute Gouty Arthritis by Adrenocorticotropin," *Science,* 109 (1949), 280-281.

Hellman, L., R. E. Weston, D. J. W Escher et al. "The Effect of Adrenocorticotropin on Renal Hemodynamics and Uric Acid Clearance," *Fed. Proc.,* 7 (1948), 52.

Henry, J. P., D. L. Ely, and P. M. Step hens. "Role of the Autonomic System in Social Adaptation and Stress," *Proc. Int. Union Physiol. Sci.,* 8 (1971), 50-51.

Henry, J. P., J. P. Meehan, and P. M. Stephens. "The Use of Psychosocial Stimuli to Induce Prolonged Systolic Hypertension in Mice," *Psychosom. Med.,* 29 (1967), 408-432.

Henry, J. P., P. M. Stephens, J. Axelrod et al. "Effect of Psychosocial Stimulation on the Enzymes Involved in the Biosynthesis and Metabolism of Noradrenaline and Adrenaline," *Psychosom. Med.,* 33 (1971), 227-237.

Himwich, W., J. M. Davis, and H. C. Agraual. "Effects of Early Weaning on Some Free Amino Acids and Acetylcholinesterase Activity of Rat Brain," in J. Wortis, ed., *Recent Advances in Biological Psychiatry,* pp. 266-270. New York: Plenum, 1968.

Hinde, R. A. and Y. Spencer-Booth. "Effects of Brief Separations from Mother on Rhesus Monkeys," *Science,* 173 (1971), 111-118.

Hinkle, L. E. and S. Wolf. "A Summary of Experimental Evidence Relating Life Stress to Diabetes Mellitus," *J. Mt. Sinai Hosp.,* 19 (1952), 537.

Hofer, M. A. "Regulation of Cardiac Rate by Nutritional Factor in Young Rats," *Science,* 172 (1971), 1039-1041.

Hofer, M. A. and H. Weiner. “The Development and Mechanisms of Cardiorespiratory Responses to Maternal Deprivation in Rat Pups,” *Psychosom. Med.,* 33 (1971), 353-362.

Jacob, F. and J. Monod. “Genetic Regulatory Mechanisms in the Synthesis of Proteins,” *J. Mol. Biol.*, 3 (1961), 318-356.

Jaffe, D., L. K. Dahl, L. Sutherland et al. “Effects of Chronic Excess Salt Ingestion: Morphological Findings in Kidneys of Rats with Differing Genetic Susceptibility to Hypertension,” *Fed. Proc.,* 28 (1969), 422.

Kahlson, G. and E. Rosengren. “New Approaches to the Physiology of Histamine,” *Physiol. Rev.,* 48 (1968), 155.

Kasl, S. V., S. Cobb, and G. W. Brooks. “Changes in Serum Uric Acid and Cholesterol Levels in Men Undergoing Job Loss,” *JAMA,* 206 (1968), 1500-1507.

Katz, J. L., P. Ackman, Y. Rothwax et al. “Psychoendocrine Aspects of Cancer of the Breast,” *Psychosom. Med.,* 32 (1970), 1-18.

Katz, J. L., H. Weiner, T. F. Gallagher et al. “Stress, Distress and Ego Defenses,” *Arch. Gen. Psychiatry,* 23 (1970), 131-142.

Kaufman, I. C. and L. Rosenblum. “Effects of Separation from Mother on the Emotional Behavior of Infant Monkey?,” *Ann. N.Y. Acad. Sci.,* 159 (1969), 681-696.

Kennedy, J. A. and H. Bakst. “The Influence of Emotions on the Outcome of Cardiac Surgery: A Predictive Study,” *Bull. N.Y. Acad. Med.,* 42 (1966), 811-845.

Kimball, C. “A Predictive Study of Adjustment to Cardiac Surgery,” *J. Thorac. Cardiovasc. Surg.,* 58 (1969), 891-896.

Kissen, D. M. “Psychological Factors, Personality, and Lung Cancer in Men Aged 55-64,” *Br. J. Med. Psychol.,* 40 (1967), 29-43.

Kleinschmidt, H. J. and S. E. Waxenberg. “Psychophysiology and Psychiatric Management of Thyrotoxicosis: A Two Year Follow-up Study,” *J. Mt. Sinai Hosp.,* 23 (1956), 131.

Kraus, A. S. and A. M. Lilienfeld. “Some Epidemiological Aspects of the High Mortality in a Young Widowed Group,” *J. Chronic Dis.,* 10 (1959), 207-217.

Kvetnansky, R., G. P. Gewirtz, V. K. Weise et al. “Effect of Hypophysectomy on Immobilization-Induced Elevation of Tyrosine Hydroxylase and Phenylethanolamine-N-Methyl Transferase in the Rat Adrenal,” *Endocrinology,* 87 (1970), 1323-1329-

Kvetnansky, R. and L. Mikulaj. “Adrenal and Urinary Catecholamines in Rats during Adaptation to Repeated Immobilization Stress,” *Endocrinology,* 87 (1970), 738-743.

Kvetnansky, R., V. K. Weise, and I. J. Kopin. “Elevation of Adrenal Tyrosine Hydroxylase and Phenylethanolamine-N-Methyl Transferase by Repeated Immobilization of Rats,” *Endocrinology,* 87 (1970), 749.

Langworthy, O. R. “Development of Behavioral Patterns and Myelinization of the Central Nervous System in the Human Fetus and Infant,” *Carnegie Inst. Contrib. Embryol.,* 24 (1933), 1-57.

LeShan, L. L. “An Emotional Life History Pattern Associated with Neoplastic Disease,” *Ann. N.Y. Acad. Sci.,* 125 (1966), 780-793.

Levine, R. J. and E. C. Senay. “Studies on the Role of Acid in the Pathogenesis of Experimental Stress Ulcers,” *Psychosom. Med.,* 32 (1970), 61-65.

Levine, S. “Plasma-Free Corticosteroid Response to Electric Shock in Rats Stimulated in Infancy,” *Science,* 135 (1962), 795-796.

----. “The Psychophysiological Effects of Infantile Stimulation,” in E. Bliss, ed., *Roots of Behavior,* pp. 246-253. New York: Harper & Row, 1962.

----. “Influence of Infantile Stimulation on the Response to Stress during Preweaning Development,” *Dev. Psychobiol.,* 1 (1968), 67-70.

----. “The Pituitary-Adrenal System and the Developing Brain,” *Prog. Brain Res.,* 32 (1970), 79-85.

Levine, S., M. Alpert, and G. W. Lewis. “Differential Maturation of an Adrenal Response to Cold

Stress in Rats Manipulated in Infancy," *J. Comp. Physiol. Psychol.,* 51 (1958), 774-777.

Levine, S. and R. F. Mullins, Jr. "Hormonal Influences on Brain Organization in Infant Rats," *Science,* 152 (1966), 1585-1592.

----. "Hormones in Infancy," in G. Newton and S. Levine, eds., *Early Experience and Behavior,* pp. 168-197. Springfield, Ill.: Charles C. Thomas, 1968.

Lidz, T. "Emotional Factors in the Etiology of Hyperthyroidism," *Psychosom. Med.,* 11 (1949), 2.

Löfving, B. "Cardiovascular Adjustments Induced from the Rostral Cingulate Gyrus with Special Reference to Sympathoinhitory Mechanisms," *Acta Physiol. Scand.,* 53 *Suppl.* 184 (1961), 1-82.

Lower, J. S. "Approach-Avoidance Conflict as a Determinant of Peptic Ulceration in the Rat," Medical Dissertation, Western Reserve University, 1967.

McCubbin, J. W. "Interrelationship Between the Sympathetic Nervous System and the Renin-Angiotensin System," in P. Kezdi, ed., *Baroreceptors and Hypertension,* pp. 327-330. New York: Pergamon, 1967.

McKenzie, J. M. "Humoral Factors in the Pathogenesis of Graves' Disease," *Physiol. Rev.,* 48 (1968), 252-310.

Mason, J. W. "Psychological Influences on the Pituitary-Adrenal Cortical System," in Pincus, ed., *Recent Progress in Hormone Research,* pp. 345-389. New York: Academic, 1959.

----. "Organization of Psychoendocrine Mechanisms," *Psychosom. Med.,* 30 (1968), 565-808.

Mason, W. A., R. K. Davenport, Jr., and E. W. Menzel, Jr. "Early Experiences and the Social Development of Rhesus Monkeys and Chimpanzees," in G. Newton and S. Levine, eds., *Early Experience and Behavior,* pp. 440-480. Springfield, Ill.: Charles C. Thomas, 1968.

Melzack, R. "The Role of Early Experience on Emotional Arousal," *Ann. N.Y. Acad. Sci.,* 159 (1969),

721-730.

Meneely, G. R., R. G. Tucker, W. J. Darby et al. "Electrocardiographic Changes, Disturbed Lipid Metabolism and Decreased Survival Rates Observed in Rats Chronically Eating Increased Sodium Chloride," *Am. J. Med.,* 16 (1954), 599.

Menguy, R. "Current Concepts of the Etiology of Duodenal Ulcer," *Am. J. Dig. Dis.,* 9 (1964), 199-211.

Milkovic, K. and S. Milkovic. "The Influence of Adrenalectomy of Pregnant Rats on the Reactiveness of the Pituitary-Adrenal System of Newborn Animals," *Arch. Int. Physiol. Biochem.,* 67 (1959), 24-28.

----. "Reactiveness of the Pituitary-Adrenal System of Newborn Animals," *Endokrinologie,* 37 (1959), 301-310.

Miller, N. E. "Learning of Visceral and Glandular Responses," *Science,* 163 (1969), 434-445.

Mueller, R. A., H. Thoenen, and J. Axelrod. "Increase in Tyrosine Hydroxylase Activity after Reserpine Administration," *J. Pharmacol. Exp. Ther.,* 169 (1969), 74-79.

----. "Inhibition of Transsynaptically Increased Tyrosine Hydroxylase Activity by Cycloheximide and Actinomycin D," *Mol. Pharmacol.,* 5 (1969), 463-469.

----. "Effect of Pituitary and ACTH on the Maintenance of Basal Tyrosine Hydroxylase Activity in the Rat Adrenal Gland," *Endocrinology,* 86 (1970), 751-755.

Parker, D. L. and J. R. Hodge. "Delirium in a Coronary Care Unit," *JAMA,* 201 (1967), 702-703.

Parkes, C. M. "Recent Bereavement as a Cause of Mental Illness," *Br. J. Psychiatry,* 110 (1964), 198-204.

Pepler, W. J. and A. G. E. Pearse. "The Histochemistry of the Esterase of Rat Brain with Special Reference to Those of the Hypothalamic Nuclei," *J. Neurochem.,* 1 (1957). 193-202.

Perlman, L. V., S. Ferguson, K. Bergum et al. "Precipitation of Congestive Heart Failure: Social and

Emotional Factors," *Ann. Intern. Med.,* 75 (1971), 1-7.

Pickering, G. W. *The Nature of Essential Hypertension.* New York: Grune & Stratton, 1961.

Rahe, R. H. and R. J. Arthur. "Stressful Underwater Demolition Training: Serum Urate and Cholesterol Variability," *JAMA,* 202 (1967), 1052-1054.

Rahe, R. H., R. T. Rubin, R. J. Arthur et al. "Serum Uric Acid and Cholesterol Variability: A Comprehensive View of Under-water Demolition Team Training," *JAMA,* 206 (1968), 2875-2880.

Rapaport, D. "The Theory of Ego Autonomy," Bull. Menninger Clin., 22 (1958), 13-35.

Richter, D. "Brain Metabolism and Cerebral Function," Biochem. Soc. Symp., 8 (1952), 62.

Rothlin, E., H. Emmenegger, and A. Cerletti. "Versuche zur Erzeugung Audiogener Hypertonie an Ratten," *Helv. Physiol. Pharmacol. Acta,* 2, *Suppl.* C25 (1953-1954), 11-12.

Rubeson, A. "Alterations in Noradrenaline Turnover in the Peripheral Sympathetic Neurons Induced by Stress," *J. Pharm. Pharmacol.,* 21 (1969), 878-880.

Rubin, R. T., R. H. Rahe, R. J. Arthur et al. "Adrenal Cortical Activity Changes during Underwater Demolition Team Training," *Psychosom. Med.,* 31 (1969), 553-563.

Rubin, R. T., R. H. Rahe, B. R. Clark et al. "Serum Uric Acid, Cholesterol, and Cortisol Levels: Interrelationships in Normal Men Under Stress," *Arch. Intern. Med.,* 125 (1970), 815-819.

Rushmer, R. F. *Cardiovascular Dynamics*, 3rd ed. Philadelphia: Saunders, 1970.

Ryss, S. and E. Ryss. "Modem Concepts of Etiology and Pathogenesis of Peptic Ulcer: Disorders of the Regulating Mechanisms," *Scand. J. Gastroenterol.,* 3 (1968), 513-524.

Sachar, E. J. "Psychological Homeostasis and Endocrine Function," in A. Mandell and M. Mandell, eds., *Psychochemical Strategies in Man: Methods, Strategy and Theory,* pp. 219-233. New York: Academic, 1969.

Sachar, E. J., L. Hellman, D. K. Fukushima et al. "Cortisol Production in Depressive Illness. A Clinical and Biochemical Clarification," *Arch. Gen. Psychiatry,* 23 (1970), 289-298.

Sachar, E. J., J. M. Mackenzie, W. A. Binstock et al. "Corticosteroid Responses to Psychotherapy of Depressions: I. Elevations during Confrontation of Loss," *Arch. Gen. Psychiatry,* 16 (1967), 461-470.

Sachar, E. J., J. W. Mason, H. Kollmer et al. "Psychoendocrine Aspects of Acute Schizophrenic Reactions," *Psychosom. Med.,* 25 (1963), 510-537.

Schapiro, S., E. Geller, and S. Eiduson. "Corticoid Response to Stress in the Steroid-Inhibited Rat," *Proc. Soc. Exp. Biol. Med.,* 109 (1962), 935-937.

Schmale, A. H., Jr. "Relation of Separation and Depression to Disease: I. A Report on a Hospitalized Medical Population," *Psychosom. Med.,* 20 (1958), 259-277.

Scroop, G. C. and R. D. Lowe. "Central Pressor Effect of Angiotensin Mediated by the Parasympathetic Nervous System," *Nature,* 220 (1968), 1331-1332.

Sedvall, G. C. and I. J. Kopin. "Acceleration of Norepinephrine Synthesis in the Rat Submaxillary Gland *in vivo* during Sympathetic Nerve Stimulation," *Life Sci.,* 6 (1967), 45-51.

Selye, H. *Stress.* Montreal: acta, 1950.

Serota, H. M. and R. W. Gerard. "Localized Thermal Changes in the Cat's Brain," *J. Neurophysiol.,* 1 (1938), 115-124.

Shapiro, D., B. Tursky, and G. E. Schwartz. "Differentiation of Heart Rate and Systolic Blood Pressure in Man by Operant Conditioning," *Psychosom. Med.,* 32 (1970), 417-423.

Shoemaker, W. J. and R. J. Wurtman. "Perinatal Undernutrition: Accumulation of Catecholamines in Rat Brain," *Science,* 171 (1971), 1017-1019.

Sines, J. O. "Strain Differences in Activity, Emotionality, Body Weight and Susceptibility to Stress-Induced Stomach Lesions," *J. Genet. Psychol.,* 101 (1962), 209-217.

Skinner, B. F. *Beyond Freedom and Dignity.* New York: Knopf, 1971.

Smelik, P. G. "Relation between the Blood Level of Corticoids and Their Inhibiting Effect of the Hypophyseal Stress Response," *Proc. Soc. Exp. Biol. Med.,* 113 (1963), 616-619.

Stein, S. and E. Charles. "Emotional Factors in Juvenile Diabetes Mellitus: A Study of Early Life Experiences of Adolescent Diabetics," *Am. J. Psychiatry,* 128 (1971), 700-704.

Stone, L. *The Psychoanalytic Situation.* New York: International Universities Press, 1961.

Szentivanyi, A. and G. Gilipp. "Anaphylaxis and the Nervous System. Part II," *Ann. Allergy,* 16 (1958), 143.

Taylor, K. M. and S. H. Snyder. "Brain Histamine: Rapid Apparent Turnover Altered by Restraint and Cold Stress," *Science,* 172 (1971), 1037-1039.

Thoenen, H., R. A. Mueller, and J. Axelrod. "Increased Tyrosine Hydroxylase Activity after Drug-Induced Alteration of Sympathetic Transmission," *Nature*, 221 (1969), 1264.

----. "Transsynaptic Induction of Adrenal Tyrosine Hydroxylase," *J. Pharmacol. Exp. Ther.,* i6g (1969), 249-254.

----. "Neuronally Dependent Induction of Adrenal Phenylethanolamine N-methyl-transferase by Hydroxydopamine," *Biochem. Pharmacol.,* 19 (1970), 669-673.

----. "Phase Difference in the Induction of Tyrosine Hydroxylase in Cell Body and Nerve Terminals of Sympathetic Neurons," *Proc. Natl. Acad. Sci. U.S.A.,* 65 (1970), 58-62.

Thoman, E. B. and S. Levine. "Influence of Adrenalectomy in Female Rats on Reproductive Processes: Effects on the Fetus and Offspring," *J. Endocrinol.,* 46 (1970), 297-303.

Uvnäs, B. "Central Cardiovascular Control," in W. F. Hamilton and P. Dow, eds., Handbook of Physiology, Sect. 1, *Neurophysiology,* Vol. 2, pp. 1131-1162. Baltimore: Williams & Wilkins, i960.

Von Euler, U. S. "Adrenergic Neurotransmitter Functions," *Science,* 173 (1971), 202-206.

Weinberg, S. J. and J. M. Fuster. "Electrocardiographic Changes Produced by Localized Hypothalamic Stimulation," *Ann. Intern. Med.,* 53 (1960), 332-341.

Weiner, H. "Some Recent Neurophysiological Contributions to the Problem of Brain and Behavior," *Psychosom. Med.,* 31 (1969), 457-478.

----. "Experiences in the Development of Preclinical Curricula in the Sciences Related to Behavior," *J. Nerv. Ment. Dis.,* 154 (1972), 165.

Weiner, H., M. T. Singer, and M. F. Reiser. "Cardiovascular Responses and Their Psychological Correlates: A Study in Healthy Young Adults and Patients with Peptic Ulcer and Hypertension," *Psychosom. Med.,* 24 (1962), 477-498.

Weiner, H., M. Thaler, M. F. Reiser, and A. Mirsky. "Etiology of Duodenal Ulcer: I. Relation of Specific Psychological Characteristics to Rate of Gastric Secretion (Serum Pepsinogen)," *Psychosom. Med.,* 19 (1957), 1-10.

Weinshilboum, R. M. and J. Axelrod. "Dopamine-/J-Hydroxylase Activity in Human Blood," *Pharmacologist,* 12 (1970), 214.

Weinshilboum, R. M., R. Kvetnansky, J. Axelrod et al. "Elevation of Serum Dopamine--Hydroxylase Activity with Forced Immobilization," *Nature (New Biol.),* 230 (1971), 287-288.

Weiss, T. and B. T. Engel. "Voluntary Control of Premature Ventricular Contractions in Patients," *Am. J. Cardiol.,* 26 (1970), 666.

Welch, B. L. and S. A. Welch. "Effect of Grouping on the Level of Brain Norepinephrine in White Swiss Mice," *Life Sci.,* 4 (1965), 1011-1018.

----. "Differential Activation by Restraint Stress of a Mechanism to Conserve Brain Catecholamines and Serotonin in Mice Differing in Excitability," *Nature,* 218 (1968), 575-577.

Winkelstein, W., Jr., S. Kantor, M. Ibrahim et al. "Familial Aggregation of Blood Pressure. Preliminary Report," *JAMA,* 195 (1966), 848-850.

Wolff, C., S. B. Friedman, M. A. Hofer et al. "Relationship between Psychological Defenses and

Mean Urinary 17-Hydroxy-corticosteroid Excretion Rates: I. A Predictive Study of Parents of Fatally Ill Children," *Psychosom. Med.,* 26 (1964), 576-591.

Wurtman, R. J. "Brain Monoamines and Endocrine Function," *Neurosci. Res. Prog. Bull.,* 9 (1971), 182-187.

Wurtman, R. J. and J. Axelrod. "Control of Enzymatic Synthesis of Adrenaline in the Adrenal Medulla by Adrenal Cortical Steroids," *J. Biol. Chem.,* 241 (1966), 2301-2305.

Yates, F. E. and J. Urquhart. "Control of Plasma Concentrations of Adrenocortical Hormones," *Physiol. Rev*., 42 (1962),359-443.

Young, M., B. Benjamin, and C. Wallis. "The Mortality of Widowers," *Lancet,* 2 (1963), 454-456.

Young, W. C. "The Hormones and Mating Behavior," in W. C. Young, ed., *Sex and Internal Secretions,* Vol. 2, pp. 1173-1239. Baltimore: Williams & Wilkins, 1961.

Young, W. C., R. W. Goy, and C. H. Phoenix. "Hormones and Sexual Behavior," *Science,* 143 (1964), 212-218.

Notes

1For a full discussion of this point of view, see Rapaport.