John W. Mason

CLINICAL PSYCHOPHYSIOLOGY:

Psychoendocrine Mechanisms

American Handbook of Psychiatry

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Clinical Psychophysiology: Psychoendocrine Mechanisms

Some Theoretical Implications of Psychoendocrinology

The recognition that endocrine systems are remarkably sensitive to both acute and enduring psychological influences is a relatively recent and notable historical development. Only since the 1950s have biochemical methods for hormone measurement become sufficiently specific, sensitive, and precise to permit reliable experimental exploration of the scope and significance of psycho-endocrine relationships. As a result, it has now become clear that, in viewing central nervous system organization, the endocrine systems are properly regarded as representing a *third effector* or *motor system* of the brain, along with the autonomic and skeletal-muscular systems. The far-reaching implications of this new insight for biology, in general, and for psychophysiology and psychosomatic medicine, in particular, are still only beginning to be recognized and put to creative use.

Perhaps the broadest of these implications lies in the new and strategically important leverage that recent knowledge of neuroendocrine systems provides in gaining an understanding of the organization of central mechanisms which *integrate the internal environment.* While the innervation of smooth and cardiac muscle and exocrine glands by the autonomic nervous

system has been long recognized as a mediating link between the brain and selected visceral structures, the discovery of neuroendocrine systems extends the scope of central nervous system (CNS) coordination of the *internal* environment to the level of virtually every body tissue and cell via the circulatory distribution of hormones. In a historical perspective, then, it is clear that lack of knowledge of this major mediating link between the brain and peripheral bodily processes severely impeded earlier efforts to deal with the important problem of how the many separate unit functions of the body are integrated or coordinated in the overall fashion necessary to maintain the exquisite homeostatic equilibrium of the organism as a whole. This problem has long been regarded by biological theoreticians as one of the most fundamental and crucial issues in biology. In general, the implications of neuroendocrine linkages for psychosomatic medicine may be viewed in two closely interrelated perspectives. First, hormonal responses may be viewed, from principally a psychiatric orientation, as *reflecting intrapsychic processes* and as providing a relatively objective approach to the qualitative and quantitative study of psychological mechanisms. As knowledge develops that particular psychological processes are determinants or correlates of particular endocrine reactions, then the psychoendocrine approach can become a very useful tool for the testing and development of psychiatric theory, particularly in the elusive area of emotional and related intrapsychic processes. Secondly, psychoendocrine reactions may be viewed, from

principally a medical orientation, in terms of their possible significance in the *mediation* of the effects of psychopathological processes upon bodily tissues in the pathogenesis of psychosomatic disorders. It may be possible from a strategic standpoint, for example, to initiate an endocrinological search for abnormal hormonal profiles or altered response patterns in patients with psychosomatic illnesses, independently of psychological collaboration, if necessary, in order to test the hypothesis that characteristic endocrine abnormalities, reflecting integrative disorders, are regularly present in such illnesses. If such endocrine imbalances can be demonstrated, then the second phase, involving the more complicated and laborious work of defining the relevant psychological concomitants, of evaluating the role of nonpsychological factors, and of establishing criteria for evaluating the pathogenetic significance of hormonal changes, could be undertaken with greater confidence that this conceptual approach warrants such a large investment of effort.

In the relatively brief span of two decades, there have been only a few preliminary ventures in psychoendocrine research into the study of psychosomatic patients, but psychoendocrinologists have been mainly preoccupied with the basic psychophysiological exploration of the significance of hormonal responses as reflections of intrapsychic processes. To put it simply, the principal orientation has been, “what may be learned about psychological processes by the measurement of blood and urinary

hormone levels"? As is often the case following the introduction of revolutionary new methods, developments in the psychoendocrine field have been rapid and wide ranging, with many probing attempts to test the relative power and usefulness of new tools and to define the scope of their application. While the total body of accumulated facts is already quite substantial, the distribution of effort in psychoendocrine research has been rather uneven, with a few areas receiving much attention, while other important issues and approaches have barely been explored. Much necessary attention has also been given to practical obstacles in research technique. Particularly encouraging progress has been made in the developing and refining of difficult new methods, the devising of effective, often novel, strategic and tactical research approaches, and in beginning to solve some of the formidable human and organizational problems hindering efforts to achieve the interdisciplinary cooperation which is so essential to progress.

In summarizing the status of psychoendocrinology, therefore, the general picture might be described as that of a young science emerging from an initial period of considerable flux and preliminary exploration, but now tending to move into a more stable period of consolidation and sharper focusing of effort. A number of reviews provide detailed summaries of research findings and dogma in the field, but also tend to present a somewhat incomplete view of the scope of issues and approaches, because of the disproportionate emphasis on a few selected research objectives and

endocrine systems in most early research efforts (see references 8, 45, 49-51, and 83). Some principal aims in this chapter, therefore, are not only to outline highlights of present knowledge in psychoendocrinology, but also to point out gaps in knowledge, to present a more balanced theoretical perspective of the evolution of issues and approaches in the field, and, hopefully, to convey something of the historical sense of scientific adventure and breakthrough which has pervaded psychoendocrine research in its infancy. In doing so, the personal bias of the author will undoubtedly be evident, both in the conceptual approach and in a predilection often to cite firsthand experimental observations in preference to equally, or more, relevant observations of other workers. It is hoped, however, that the sense of historical and conceptual continuity and the broad overview of issues provided by this frankly personal approach may compensate, in some measure, for the lack of a more eclectic review of the field.

Basic Scientific Foundations of Clinical Psychoendocrinology

While this chapter is oriented primarily in terms of clinical aspects of psychoendocrinology, it is important to recognize that interdisciplinary cooperation between many basic neurosciences has established a solid experimental foundation for the clinical field. Psychoendocrine research may, indeed, be viewed as beginning with the pioneering experimental observations reported in 1911 by Cannon and de la Paz that the adrenal

medulla releases hormone in the cat during the emotional arousal associated with confrontation by a barking dog. The apparent utility of the multiple physiological consequences of sympathetic-adrenal medullary response, in terms of visceral preparation for the strenuous muscular exertion required for flight or struggle or in preparation for injury, was brilliantly elaborated by Walter Cannon. In 1936, Selye provided preliminary evidence that a second endocrine system, the pituitary-adrenal cortical axis, also with extensive influences on many metabolic functions, responded to "mere emotional stimuli" in rats. It was not until about 1952, however, that the major breakthroughs in hormone assay methodology, such as the chromatographic Nelson-Samuel's method for the determination of 17-hydroxycorticosteroid (17-OHCS) levels in plasma, ushered in the modern era of psychoendocrine research which has led to the realization that the scope of endocrine systems involved in psychoendocrine relationships is extremely broad. In the 1970s, in fact, we reach a point where it is difficult to exclude any endocrine system as being entirely independent of psychological or neural influences.

Fortunately, the development of new hormone-assay methods during the 1950s coincided with availability of a number of important new methods and developments in the basic brain and behavioral sciences. The extensive work of Harris and others in neuroendocrinology demonstrated the functional significance of the hypothalamo-hypophyseal portal capillary system as a neuro-humoral link between the hypothalamus and the anterior

pituitary gland. This finding greatly increased the scope of neuroendocrinology, from concern with only the few hormones of the posterior pituitary, sympathetic-adrenal medullary system, and, perhaps, the vago-insulin system, to the inclusion of the many additional hormones of the anterior pituitary gland and of the target endocrine glands of the pituitary trophic hormones. Recognition of the hypothalamic-anterior pituitary linkage as a major point of neuroendocrine articulation, thus, provided an anatomical basis for exploring brain influences on secretion of growth hormone, prolactin, adrenocorticotropin (ACTH) thyrotropin (TSH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and, consequently, cortisol, thyroxine, testosterone, estrogens, progesterone, and related adrenal cortical, thyroid, and gonadal hormones, in addition to the hormones representing previously recognized neuroendocrine linkages, such as epinephrine, norepinephrine, vasopressin, oxytocin, and insulin.

A substantial science of neuroendocrinology has consequently developed since the 1950s with the demonstration, by such neurophysiological techniques as electrical stimulation or ablation of local brain areas in laboratory animals, including primates, that not only the hypothalamus but also such distant brain regions as the amygdaloid complex, hippocampus, and midbrain exert modulating influences on hormone secretion. Much of the work done so far on localization or mapping of neural influences on hormone secretion, however, has been limited to

intrahypothalamic studies and to only a few hormones, particularly those of the pituitary-adrenal cortical system. Modern neuroanatomical knowledge of limbic system-midbrain circuitry and of direct and indirect projection pathways to the hypothalamus presents a most inviting opportunity for future systematic studies of the neural substratum for psychoendocrine processes, which is still a largely unexplored area, particularly in relation to such hormones as testosterone, thyroxine, insulin, and others for which excellent assay methods have recently become available.

Another important series of experiments has been concerned with the demonstration and characterization of neurosecretory releasing hormones in the hypothalamus, which appear to be the specific humoral links between the hypothalamus and anterior pituitary cells. Included are the corticotropin-releasing hormone (CRH), thyrotropin-releasing hormone (TRH), luteinizing-hormone releasing factor (LHRF), follicle-stimulating hormone-releasing factor (FSHRF), growth hormone releasing factor (GHRF), and prolactin-inhibiting factor (PIF). These hormones and factors are presumably secreted by final common pathway neurones in the hypothalamus and then via the hypothalamo-hypophyseal portal system act selectively to bring about changes in the secretion rate of the various anterior pituitary hormones. The hypothalamic final common pathway neurones, incidentally, not only represent an anatomical boundary line, but appear also to define a boundary line between scientific disciplines as well. In general, research at the

hypothalamic level and below has been largely in the field of endocrinology, while research on higher brain influences on endocrine regulation has been pursued largely in the central-nervous-system sciences.

The field of experimental psychology has also made important contributions to the development of a basic science foundation for psychoendocrinology. While naturalistic approaches to eliciting emotional arousal in animals, such as by immobilization, crowding, etc., have been fruitful, the use of behavioral conditioning methods has provided a considerably more sophisticated and systematic approach to psychoendocrine studies in animals. As an example, in a "conditioned avoidance" procedure, during which a monkey must press a hand lever in the presence of a red light in order to avoid an electric shock to the foot, an organized and reproducible pattern of multiple psychoendocrine responses has been observed. The contingencies of such conditioning procedures may be arranged in a great variety of ways in order to vary the quality or intensity of the emotional disturbance which is elicited.

While it is beyond the scope of this chapter to elaborate further on how the basic brain disciplines may be useful, particularly in various interdisciplinary combinations in the study of psychoendocrine mechanisms, it is important for the clinician to keep in mind that a growing body of knowledge, developing from neuroanatomical, electrophysiological,

experimental psychological, neurochemical, and neuropharmacological approaches, is building a substantial basic science foundation which complements, supplements, and illuminates related research in clinical psychoendocrinology-

The Development of Issues and Approaches in Clinical Psychoendocrinology

The Sensitivity of the Pituitary-Adrenal Cortical System to Psychological Influences

While W. B. Cannon had laid the groundwork for psychoendocrinology almost forty years earlier with his work on the sympathetic-adrenal medullary system, it is a curious historical fact that modem psychoendocrine research evolved largely out of a period of intensive, popular interest in the pituitary-adrenal cortical system, following the publication of Selye's sweeping and provocative "stress" concepts in 1950. Selye's "stress" formulations, ascribing special importance to the apparent "non-specificity" of the pituitary-adrenal cortical response to "nocuous" stimuli, had a considerable impact not only on endocrinological research, but also intrigued many behavioral scientists because of the implication of psychological stimuli among the various "stressors" capable of eliciting ACTH release. The findings of Selye and other workers prior to the early 1950s were based on relatively indirect and crude indices of adrenal cortical activity, however, so that a foremost objective in the psychoendocrine field, when the reliable,

chromatographic, microanalytical methods for 17-OHCS measurements in blood and urine became available after 1952, was simply to see if the earlier observations of corticosteroid responses to psychological stimuli could be confirmed by more refined endocrinological and psychological methods. Many endocrinologists were initially rather skeptical that psychological factors would be found to play a significant role in pituitary-adrenal cortical regulation in comparison with such drastic physical stimuli as trauma, exercise, cold, fasting, hemorrhage, and so on. Considerable attention was, therefore, devoted in early psychoendocrine experiments to the elimination or control of physical stimuli as independent variables. The burden of proof, in a sense, was on the psychoendocrinologist to rule out, in rigorous fashion, any remote possibility that concomitant physical stimuli, particularly muscular activity, might be causing corticosteroid changes attributed to psychological influences.

Within several years, substantial and convincing evidence emerged from many laboratories, using a variety of experimental approaches, which established beyond any reasonable doubt the reality of pituitary-adrenal cortical responsiveness to psychological influences. Particularly influential among these early experiments were the rather captivating observations of Thorn, Fox, and their coworkers, on Harvard oarsmen in relation to the annual Harvard-Yale crew race. Indications of increased adrenal cortical activity on the race day were observed, not only in the crew members, but in

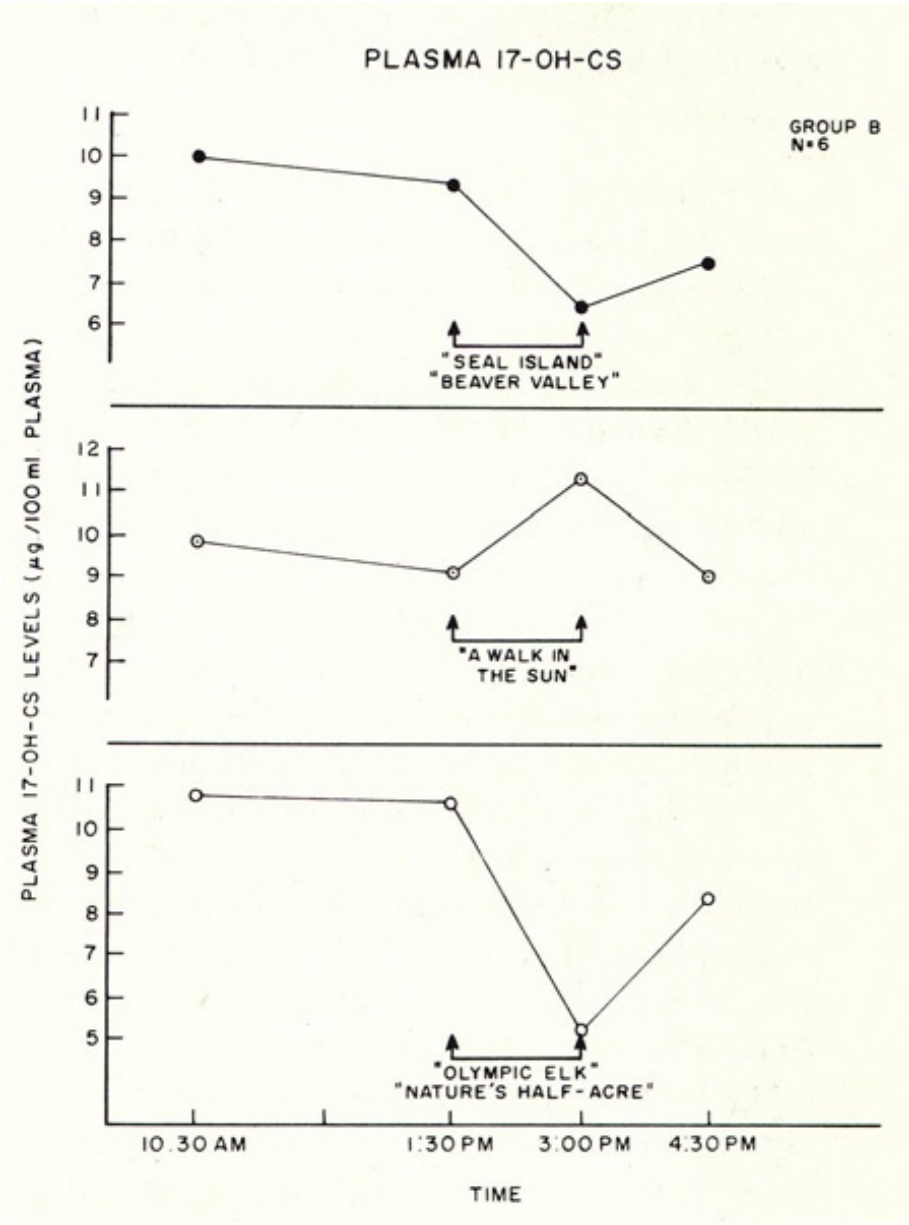
the coach and coxswain as well. In 1956, a report of later extensions of these studies indicated that psychological factors associated with competition or with time-trial sessions were far more potent determinants of urinary 17-OHCS elevations than muscular work alone. Also capitalizing on natural stressful life situations, Bliss and his co-workers reported in 1956 that plasma or urinary 17-OHCS increases were prevalent in medical students taking final college examinations, in relatives of emergency room patients, and in subjects exposed to a variety of other natural and contrived situations associated with emotional reactions. Board et al. reported marked plasma 17-OHCS elevations in acutely disturbed psychiatric patients, and correlations were observed between the intensity of endocrine and psychological disturbances. The demonstration by Mason et al. of consistent plasma 17-OHCS elevations in rhesus monkeys during conditioned emotional disturbances permitted systematic separation of psychological from physical factors as experimental determinants of hormone release. Chair-restrained monkeys pressing a hand lever to avoid an aversive stimulus during “conditioned avoidance” sessions, as one example, showed marked plasma 17-OHCS responses, while the same monkeys, pressing the lever at an equal or greater rate in order to obtain food, showed no 17-OHCS elevations, thus militating against the variable of muscular activity associated with lever pressing as a determinant of 17-OHCS release in the “avoidance” situation. A host of other psychoendocrine studies involving stressful life situations such as aircraft flight, anticipation of

surgery, military combat, hospital admission, etc., compiled overwhelming and consistent evidence of pituitary-adrenal cortical response to emotional stimuli in human subjects.

By the late 1950s, then, it was generally recognized not only that psychoendocrinology rested on a solid experimental foundation, but that psychological stimuli were, in fact, among the most potent of all natural stimuli to the pituitary-adrenal cortical system. The potency of psychological stimuli in ACTH regulation was evident not only in the marked 17-OHCS elevations observed in severely stressful life situations in normal subjects and in the even greater increases seen during some acute psychiatric disturbances, but was perhaps most impressively demonstrated in the striking sensitivity with which relatively subtle environmental or psychological influences were often reflected in 17-OHCS levels. In the rhesus monkey, for example, urinary 17-OHCS levels reflected the day-to-day level of activity in the laboratory in which animals were housed, being highest on Monday, fairly stable from Tuesday to Friday, and decreasing by 30 percent during the weekend when people were absent. When the same monkeys were transferred from a busy, active laboratory setting to a quiet, private room, and screened visually from each other, their chronic, mean basal 17-OHCS level consistently ran 50 percent lower than in the original setting. Many workers were impressed by the sensitivity of 17-OHCS levels to such factors as the “first experience” or novelty effect, population density, and various,

often seemingly minor, social influences. Studies of plasma 17-OHCS levels in normal young adults viewing commercial motion pictures provided one particularly striking demonstration of the sensitivity of this psychoendocrine system. In the same group of subjects, 17-OHCS levels were observed to rise during a distressing war movie, and then to decrease sharply on two other occasions during the observation of Disney nature films, as shown in Figure 24-1. These and many other observations indicated not only great sensitivity of hormonal response to psychosocial stimuli, but also suggested that the concept of "tonicity," similar to that in the autonomic and skeletal-muscular effector systems, applies to the neuroendocrine systems as well. Rather than to use the concept of a "normal," absolute hormonal level,, it may be more valid to think in terms of an ongoing "basal" or "tonic" 17-OHCS level in any given individual which may be either raised or lowered on an acute or chronic basis, depending upon environmental, psychological, or other factors.

Figure 24-1.


PLASMA 17-OH-CS
GROUP B
N=6
"SEAL ISLAND"
"BEAVER VALLEY"
"A WALK IN
THE SUN"
"OLYMPIC ELK"
"NATURE'S HALF-ACRE"
PLASMA 17-OH-CS LEVELS (µg/100 ml PLASMA)
10.30 AM
1:30 PM
3:00 PM
4:30 PM
TIME

Elevation and suppression of plasma 17-OHCS levels in group of normal young adults viewing commercial movies. (U.S. Army photo graph.)

The unequivocal and repeated demonstration of the sensitivity of the pituitary-adrenal cortical system to psychological stimuli, isolated from attendant physical stimuli by various experimental approaches, may be viewed, then, as representing a historically important and decisive first phase of psychoendocrine research which established the field as a viable science and opened the way for future development. If there has been experimental overemphasis in any phase of psychoendocrine research, it was probably in these initial studies directed at the question "Does the pituitary-adrenal cortical system respond to psychological stimuli or not"? For some time after it was settled beyond any reasonable doubt that psychological stimuli elicited ACTH release, there was a tendency for workers to continue to devote considerable research effort to adding still more stressful situations to the list of those in which ACTH-cortisol release occurs. It appears, in fact, that this question was viewed by many as the principal, if not the sole, issue in the field and that much general interest and participation was withdrawn at the conclusion of this phase of psychoendocrine research.

As a smaller group of workers persisted in psychoendocrine research, however, it became increasingly clear that many important issues and approaches remained to be explored. A survey of some of these less well

recognized issues and approaches is a special objective of this chapter. It should be borne in mind that, in the discussion of psychiatric theory, the vantage point of the author is not that of a clinical psychiatrist, but rather of a physiologist who has worked in close collaboration with research psychiatrists for many years. It should also be emphasized that the major part of the work on the development of concepts in psychoendocrinology up to the present time is based upon research on the pituitary-adrenal cortical and sympathetic-adrenal medullary systems. The resultant emphasis on these systems in this chapter should not be construed necessarily as implying that they have a preeminent role in the psychoendocrine apparatus as a whole. Only similarly intensive future study of the pituitary-thyroid, pituitary-gonadal, and other neuroendocrine systems can eventually provide a proper perspective concerning the relative significance of individual systems in psychoendocrinology.

Psychoendocrine Reflections of Emotional States

In the initial phase of psychoendrocrine research when primary emphasis was largely on isolating psychological stimuli in "pure" form from physical stimuli, and on evaluating the relative sensitivity of hormone levels to psychological versus "physical" stimuli, only rather scattered and preliminary efforts were made to define the *nature* of the psychological mechanisms which were reflected in hormonal responses. The general and

plausible assumption was that hormonal levels were probably a rather direct index of emotional state, particularly of the level of anxiety. Many early studies simply employed situational criteria of threat, with the assumption that a given situation would be anxiety-provoking to the subjects, but without validating this assumption by objective psychological assessment of actual emotional reactions in relation to hormonal responses in individual subjects.

A number of laboratories, however, began to deal with this difficult issue directly and to develop or evaluate psychological methods which would permit correlational studies, comparing hormonal levels with specific emotional states. A principal approach was the development of relatively objective and reproducible methods for clinical assessment of the levels of anxiety, depression, and anger on a roughly quantitative rating scale. Special care was taken to evaluate and develop intraobserver and interobserver reliability in these methods. As was expected, such ratings did show significant correlations with 17-OHCS levels under certain conditions. Persky et al., for example, found that objective ratings of increase in anxiety, depression, and anger were proportional to changes in plasma 17-OHCS levels in anxious patients during stressful interviews.

Another approach was the use by Price et al. of projective tests to evaluate affective state and 17-OHCS correlations in patients on the day before elective cardiac surgery. In this study, significant correlations were not

observed between 17-OHCS levels and any specific affective state, such as anxiety or anger, but rather with several measures such as the neutral content, introversive tendencies, extended F+ percent and unpleasant content, all of which may be regarded as reflecting emotionality in a more general sense. As additional experience accumulated in the human, with such techniques as estimates or ratings of affect based on psychiatric interview and observation, clinical psychological testing, and self-reporting by subjects, it was generally found that, while these techniques were useful in establishing rather rough, general correlations between emotional reactions and 17-OHCS levels, this hormonal system did not appear to be related to any one specific affect, such as anxiety. Together with studies in experimental animals, the clinical studies suggested the general conclusion, rather, that 17-OHCS levels reflect a rather undifferentiated psychological state, for which such terms as arousal, hyperalerting, involvement, or anticipation of coping activity might be appropriate. In other words, while 17-OHCS levels may be a useful index of the *occurrence, intensity* and perhaps *duration* of emotional arousal, the pituitary-adrenal cortical system alone did not appear to provide leverage in the study of the *qualitative differentiation* of affective states. It should be emphasized, however, that more intensive, in-depth, psychodynamic studies remain to be undertaken, particularly with regard to such questions, for example, as the 17-OHCS reflections of anger and the various ways anger is handled or expressed, or with regard to pleasant states of arousal. The work

of Levi and his co-workers has indicated that certain pleasant states, such as sexual arousal, are associated with catecholamine elevations and suggests the need for further systematic study of pleasant stimuli in psychoendocrine research.

A rather promising approach to the issue of whether endocrine indices may be used to differentiate emotional states, however, has emerged from other studies of the sympathetic-adrenal medullary system. Although chromatographic methods for measurement of plasma and urinary catecholamines were available during the 1950s, considerably less attention was devoted to the catecholamines than to the corticosteroids in psychoendocrine research. One of the practical reasons for this, no doubt, was the greater difficulty of the fluorimetric methods used for catecholamine analysis, particularly in the plasma. Earlier psychophysiological studies by Ax and by Funkenstein et al., based upon cardiovascular indices, had suggested that epinephrine and norepinephrine might be differentially related to fear and anger reactions. Funkenstein et al., for example, postulated that anger directed "outwardly" is associated with norepinephrine predominance, while anger direct "inwardly" is reflected in epinephrine predominance. Curiously, these intriguing early leads have not yet been thoroughly evaluated with modern psychoendocrine techniques, although a few more or less incidental observations have been made in clinical studies of urinary catecholamine levels which appear consistent with Funkenstein's hypothesis. Some studies

of plasma corticosteroid and catecholamine patterns during acute emotional disturbances in the monkey have also provided encouragement for further exploration of the psychoendocrine differentiation of emotional states. In a study of six different psychologically stressful situations, all associated with plasma 17-OHCS and norepinephrine elevations in the monkey, significant plasma epinephrine elevations were observed in only three of the situations. Thus, two psychoendocrine reaction patterns were defined, pattern 1 with 17-OHCS and norepinephrine, but not epinephrine, elevation and pattern 2 with elevation of all three hormones. In general, the most striking distinction between the situations associated with the two different hormonal response patterns was apparently the presence of a high degree of unpredictability, uncertainty, or ambiguity in the pattern-2 situations. Unpleasant elements were present in all situations, but in the pattern-1 situations the animal knew exactly what to expect, while in the pattern-2 situations the animal knew threatening events were likely, but did not know exactly what they would be or when to expect them. When one also considers that such hormones as thyroxine, testosterone, insulin, growth hormone, and estrone can now be determined quantitatively by reliable assays and have been shown to respond to psychological stimuli, it is clear that the issue of psychoendocrine differentiation of both acute and sustained emotional states remains largely an open question, and there is a need for further resourceful and systematic research along these lines, particularly in longitudinal studies of human

subjects.

Psychoendocrine Reflections of Psychological Defenses

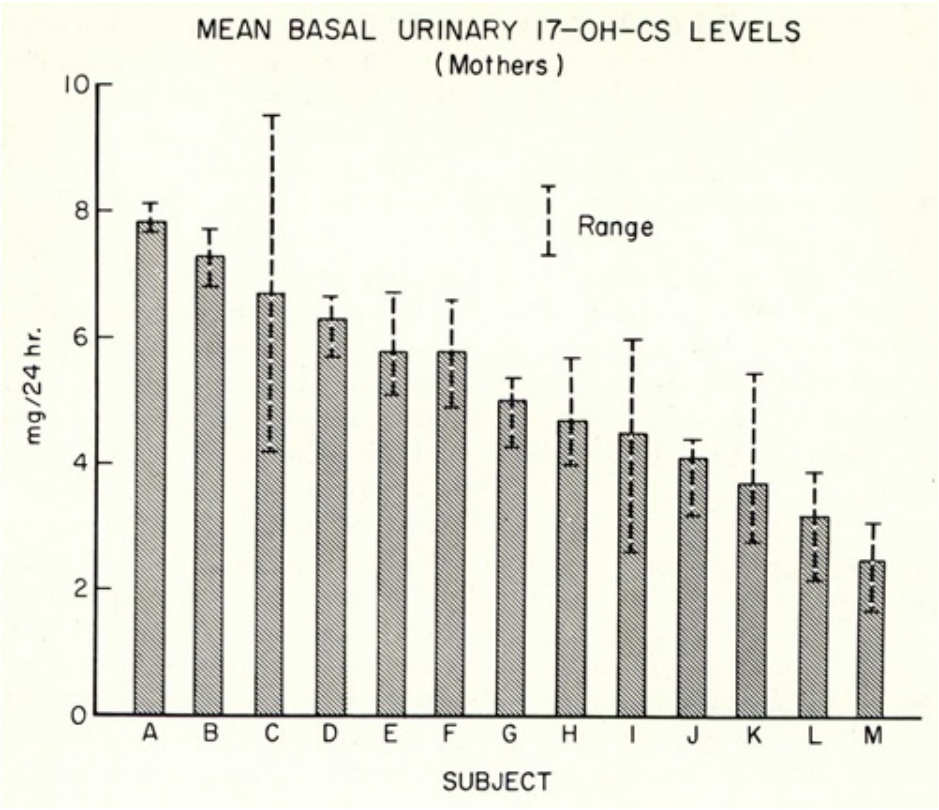
One of the most fascinating and illuminating approaches in psychoendocrinology has developed from recurrent observations of the marked individual variations in psychoendocrine reactions between different people exposed to the same stressful situation. In the face of a real, life-threatening event, such as cardiac surgery, for example, some subjects showed marked anticipatory 17-OHCS responses, while others showed little or no 17-OHCS change. Although such observations were at first often regarded with annoyance, since they diminished the significance of group-mean levels in data analysis, it soon became clear that a fundamental and intriguing question was raised concerning the psychological correlates of these individual differences in endocrine response to a seriously threatening event. The simple logic which emerged as this issue was faced, was that if 17-OHCS levels provide a sensitive index of general emotional arousal, as had already been established, by the same token they should provide a means of studying the opposing psychological forces which prevent, minimize, or counteract emotional arousal in the face of threat.

While a number of early workers recognized this issue, the emergence of this approach is particularly well illustrated in the psychoendocrine studies

by Friedman et al., and Wolff et al., of "chronic psychological stress" in the parents of children with leukemia. One of the most striking findings in these parents was the persistence of characteristic individual differences between subjects in chronic mean basal urinary 17-OHCS levels over periods of months or years. Figure 24-2 summarizes the mean 17-OHCS levels and the range of fluctuation, representing repeated sampling over many months, in a group of mothers during the course of their child's leukemic illness. While a few subjects showed a substantial range of fluctuation, most of the mothers maintained stable levels with a remarkably constricted range and could be characterized with some confidence as individually falling into "high" (above 6 mg./day), "middle" (between 4-6 mg./day), and "low" (below 4 mg./day) subgroups on the basis of chronic mean basal urinary 17-OHCS levels. Considering the tragic and disruptive circumstances, the presence of average or low mean 17-OHCS values in most subjects suggested the operation of remarkably effective defensive psychological mechanisms. Injection of ACTH and other observations indicated that adrenal exhaustion was not the explanation. The fact that some individual subjects with the lowest chronic mean 17-OHCS levels tended to suppress their levels *even lower* on days when stressful or unpleasant events occurred, in contrast to "high" subjects whose levels usually rose still higher on stressful occasions, as shown in Figure 24-3, especially drew attention to the possibility of *suppressive* or *overcompensatory* defensive psychological mechanisms as being reflected in

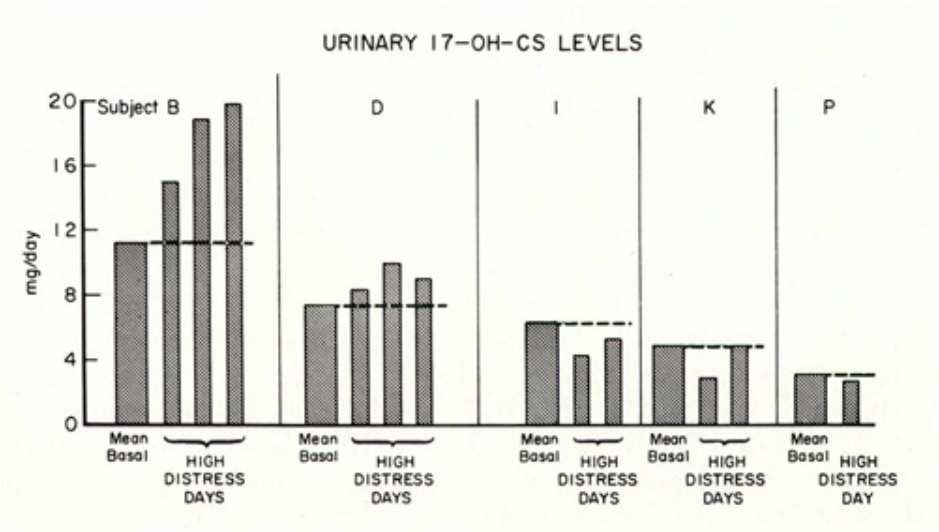
17-OHCS levels in the “low” group. An exploratory survey of defensive organization revealed that several of the subjects with the lowest mean 17-OHCS levels characteristically employed denial to a marked degree in coping with the implications of their child’s illness. These and other preliminary observations were sufficiently suggestive of the reflection of defensive styles in chronic 17-OHCS levels that a predictive psychiatric study was done, in which correlations between mean 17-OHCS level, as predicted by the psychiatric assessment of the effectiveness of psychological defenses, and the actual chronic mean basal level were examined and found to be significant both for the fathers ($r = 0.80$) and the mothers ($r = 0.59$).

Figure 24-2.



Individual differences in chronic mean urinary 17-OHCS levels between mothers of fatally ill children. (U.S. Army photograph.)

Figure 24-3.

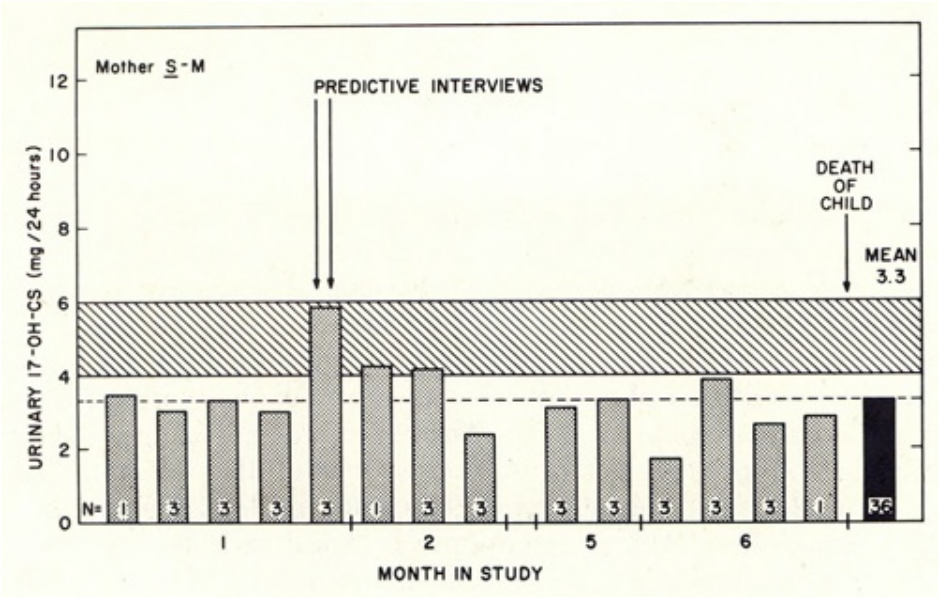


Difference in direction of 17-OHCS response to superimposed acute disturbance in some "high" versus "low" 17-OHCS excretors included in Figure 24-2.47 (U.S. Army photograph.)

There were some particularly illuminating anecdotal observations in certain parents in whom temporary relinquishment or ineffectiveness of habitual defenses were associated with prompt and dramatic 17-OHCS changes. Figure 24-4, for example, presents the case of a mother in whom the predictive psychiatric interviews were associated inadvertently with the undermining of her usual defenses of detachment and rationalization. During the interviews, which represented her first experience with a psychiatrist, there was an outpouring of suppressed, painful thoughts concerning personal problems which she "had not talked to anyone about in years." During and immediately following this period, her urinary 17-OHCS level rose from the

"low" into the "middle" (shaded) range, but with the reestablishment of her usual defenses, her 17-OHCS level declined and never again rose into this range, even during the final days before the death of her child.

Figure 24-4.

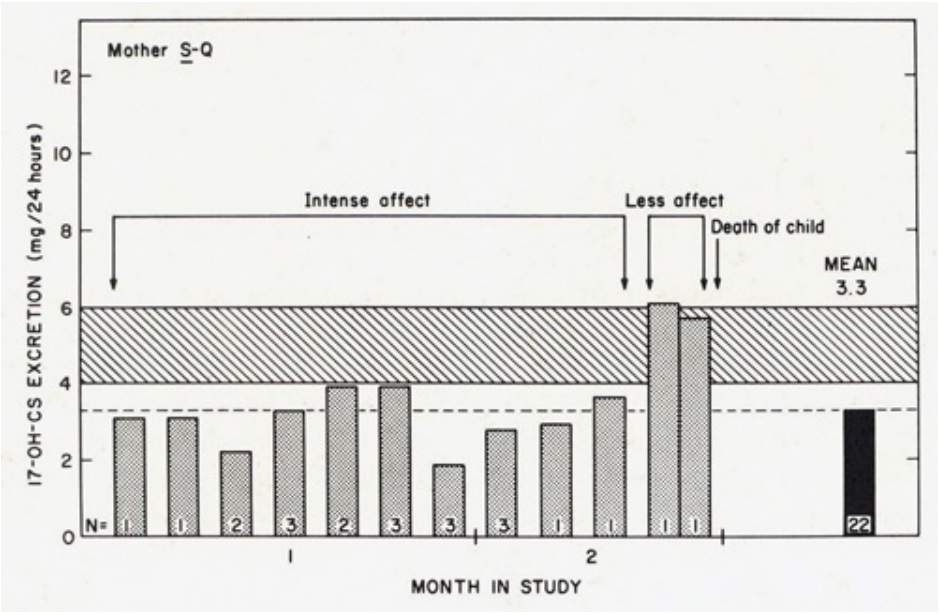


Longitudinal study showing 17-OHCS response to relinquishment of psychological defenses during psychiatric interviews. (U.S. Army photograph.)

A second case presents an impressive example of the pitfalls of assessing affect unilaterally without considering defensive organization in psychoendocrine studies. This mother was by all overt appearances almost constantly upset, as judged by the content and style of her speech, the

associated facial expressions, the tremulous actions, and so on. Accordingly, the ward staff initially regarded her as among the most distressed parents in the entire study. Figure 24-5, however, shows that her urinary 17-OHCS levels were generally quite stable and low, ranging between only 2 to 4 mg./day during a two-month period when such overt signs of intense affective distress were shown. Two days before her child's death, observers were struck with a sudden decrease in outward signs of affective distress, as she attended quietly to her child's needs, during which period her 17-OHCS levels rose to nearly 6 mg./day. This type of dissociation between overt affect ratings and 17-OHCS levels has since been observed in other subjects and appears to reflect a defensive style in which the display of signs of affective distress or frailty serves an effective coping function, perhaps from both an intrapsychic and manipulative standpoint, i.e., in which affect display or expression is employed as a "defense." Psychiatric assessment involving conventional affect ratings alone would, of course, have been misleading in such cases and it is only in the deeper psychodynamic context of defensive organization that the significance of the psychoendocrine data appear to be clarified. The same general conclusion is suggested by other cases in which the reverse relationship of marked 17-OHCS elevations, occurring in the absence of overt evidence of affective distress, was observed in persons who "suffer in silence," or who subjectively are oblivious of inner distress.

Figure 24-5.



Longitudinal study in which 17-OHCS levels reflect use of affective display as a defensive style. (U.S. Army photograph.)

Confirmation of a relationship between chronic 17-OHCS levels and defense effectiveness was reported by Rose et al., in a predictive study of Army recruits during basic training patterned after the parent study. This study, in addition, drew attention to some further methodological and theoretical issues involved in this psychoendocrine approach. In assessing effectiveness of defenses in individuals during basic training, it became especially clear that a particular defensive style is not inevitably associated with a particular characteristic 17-OHCS picture in all situations. The specific demands of the current environmental or social setting must clearly be taken

into account in relation to the individual's coping style. A defensive style which might be quite effective in maintaining psychoendocrine stability during basic training, for example, might be relatively ineffective in another life setting where the environmental realities and demands are quite different. An often overlooked methodological corollary of this conclusion, then, is that one cannot expect a consistent correlation between any specific behavioral trait or test score and hormone level to occur in all situations, but must always view psychological-endocrine correlations in the context of the specific social setting, and make accordingly careful observations and assessment of the relevant social variables. This study made also clear that certain non-psychological variables, such as body weight, environmental variables such as temperature, and historic variables such as early parental death may relate to chronic 17-OHCS level. These findings emphasize the necessity to avoid simplistic methodological approaches and to deal with an increasing range of interacting psychological, social, and nonpsychological factors as multiple codeterminants of chronic 17-OHCS levels.

Still another issue in the psychoendocrine study of defensive organization is illustrated by the work of Mattson et al., who made longterm studies of 17-OHCS levels in hemophilic boys. In judging *psychosocial* adaptation to the illness, he found that those patients regarded by the staff as "good" adapters, being generally cooperative, controlled, and pleasant showed high 17-OHCS levels, while the "poor" adapters, being often

uncooperative, irritable, and complaining tended to have low 17-OHCS levels. A deeper psychodynamic analysis of the two subgroups, however, tended to suggest that the organization of ego defenses in the "poor" adapters, although associated with poor social adjustment, was more effective from an intrapsychic standpoint in minimizing affective distress and maintaining low 17-OHCS levels than that in the socially "good" adapters. These observations indicate the need to recognize that effectiveness of defenses, as viewed in terms of social adaptation, may present quite a different picture than when viewed in terms of internal or physiological homeostatic adaptation.

Finally, the psychodynamic implications of experimental observations suggesting that common mental or psychomotor activities are reflected in 17-OHCS levels should also perhaps be considered in the context of defensive styles. The acute suppression of 17-OHCS levels during the viewing of Disney nature movies, for example, raises the question of the likelihood that many comparable everyday activities may be similarly reflected in psychoendocrine adjustments. Levi has shown similar suppression of urinary catecholamine levels in subjects viewing natural-scenery films. These findings suggest the possibility that such seemingly similar everyday tension-relieving activities as reading, television viewing, knitting, card games, hobbies, or other self-selected recreational or diverting activities may also be reflected sensitively in hormonal adjustments. This is still a largely undeveloped area in psychoendocrine research, but even the limited information available

suggests that it is necessary to bear the role of tension-relieving activities in mind as another variable to be considered in the assessment of the balance between the arousal and antiarousal forces which operate as multiple determinants of psychoendocrine reactions.

One may view the development of psychoendocrine research, then, as providing a succession of insights into the nature and scope of the relevant psychological factors which are codeterminants of hormonal levels. As indicated previously, a broad basic generalization emerging from 17-OHCS studies is that psychoendocrine state at any given point is a resultant of a balance between two sets of opposing forces, those promoting arousal and those defending against arousal. It is increasingly clear that the organization of defensive or antiarousal mechanisms must be considered in a very broad sense, as involving not only the classical intrapsychic defenses, but the full range of mental processes and psychomotor activities which may counteract the mechanisms promoting emotional arousal or involvement.

The practical implications of these generalizations for psychoendocrine methodology relate to the necessity in future studies to assess an increasing array of psychosocial factors concurrently, including quality and intensity of *affect, defensive* or coping mechanisms in the broadest sense, and *social* setting, all in the perspective of the dynamic factors operating in each individual subject. This is a tall methodological order, to be sure, and

represents a major obstacle to future progress in psychoendocrinology. On the other hand, there is already evidence that the feedback from psychoendocrine experiments can facilitate the development of suitable methods for psychiatric assessment of the above psychosocial factors, by providing leverage and economy in several ways, particularly by virtue of the highly objective indices hormone measurements afford in helping dissect out of the maze of psychological and social variables those which bear the greatest *relevance* to the psychoendocrine processes.

Once given the premise that 17-OHCS measurements provide an objective index of the balance between arousal and antiarousal mechanisms, it follows that the research psychiatrist is given a tool which may be applied to the study of many issues in psychiatric theory, such as those concerned with neurotic, psychotic, psychosomatic, social, and developmental processes, insofar as these relate to emotional and defensive mechanisms. The remainder of this chapter will deal mainly with illustrations of such psychoendocrine approaches in diverse and overlapping areas of psychiatric research.

Psychoendocrine Reflections of Neurotic Processes

One of the most striking paradoxes in this field, so far, is the very limited degree to which psychoendocrine approaches have been applied to the study

of neurotic processes. Few, if any, studies have been expressly designed to deal systematically with the testing of theoretical concepts of neurosis or even with the descriptive psychoendocrine study of severely neurotic patients. Most of the few available data suggesting the usefulness of this approach have been incidentally derived from anecdotal observations of individual neurotic patients encountered in “normal” groups or in groups of patients with medical or psychosomatic illnesses.

One such example from the study of parents of leukemic children involved a father with a long-standing neurotic hypersensitivity to rejection by others. Normally, his urinary 17-OHCS level was about 10 mg./day, but one weekend a remarkable elevation to 30 mg./day was noted. This elevation was not attended by any readily evident outward signs or verbal expression of distress, although the ward staff was well-trained and experienced in the clinical rating of emotional behavior. Only a careful reconstruction of the events of the weekend in the psychodynamic context of the patient’s neurotic style appeared to clarify the psychoendocrine findings. During this weekend, the subject had been forced by circumstances for the first time to spend many hours in close contact with his ill child, a teen-age boy with whom the father felt rejected and uncomfortable. Normally, the father on each weekend visit would spend a few minutes with his son and then would busy himself with other activities on the ward or elsewhere so as to avoid all but minimal contact with the child, while the mother stayed in attendance. On the

weekend of the father's marked 17-OHCS elevation, however, the mother was absent from the hospital because of a family emergency at home, and the father was unable to avoid involvement in the interpersonal situation which apparently activated a strong neurotic reaction."

Another case history was that of a young man who volunteered as a normal "control" subject and lived for many weeks in a hospital-ward setting with other young healthy adults. This subject showed evidence of an exaggerated, neurotic need for approval, low self-esteem, and fear of rejection, and was constantly actively seeking out personal contacts with other subjects and the ward staff. His chronic mean basal urinary 17-OHCS level, established over a period of many weeks, was about 11 mg./day. Following his success in becoming engaged to a young woman, also participating in the project as a subject, his 17-OHCS levels sharply fell to a new, stable plateau of about 5 mg./day for the period of several weeks that the engagement lasted. While some mild behavioral changes appeared to coincide with the changes in hormone level adjustment, they did not appear commensurate in intensity with the degree of hormonal change.

A number of other similar observations have been made suggesting that marked, psychologically induced 17-OHCS changes can occur in the absence of *overt* clinical signs of associated emotional disturbance and with virtually *no subjective awareness* of the person of any feelings of affective distress or

arousal. Since it is characteristic of many neurotic subjects, in the process of self-alienation, to have unconsciously learned to lose or repress awareness of certain unacceptable feelings, and since such repression of self-awareness can be a major obstacle to rehabilitative efforts during therapy, the possibility that psychoendocrine changes may objectively reflect intrapsychic processes of the neurotic patient seems well worth further exploration. The discrepancy between the striking magnitude of the somatic or psychoendocrine reaction and the minimal clinical or subjective manifestation of intrapsychic disturbance is the particularly impressive feature of the preliminary observations suggesting this approach. Are neurotic defenses, strategies, or conflicts particularly prone to lead to psychoendocrine or somatic reactions or disorders? Are different patterns of neurotic trends or conflicts reflected in characteristic psychoendocrine reaction patterns? Is there a characteristic psychoendocrine reflection of neurotically repressed anger, as compared to that for anger handled in other manners? These are random examples of many similar questions which have not yet been approached directly and systematically, although it now appears feasible to do so with the tools of modern psychoendocrine research.

Initially, perhaps the most appropriate tactical approach for the exploration of such questions would be the intensive, longitudinal, in-depth psychodynamic study of individual neurotic patients during psychoanalysis, with emphasis on the *post hoc* qualitative study of intrapsychic processes in

the light of recurrent psychoendocrine reaction patterns. Eventually, as this approach yields pilot information and working hypotheses, more objective and predictive methods could be introduced to test the validity of such hypotheses in a more rigorous manner. Finally, because of the relatively high incidence of neuroticism in patients with psychosomatic disorders, the psychoendocrine reflections of neurotic processes in such patients may provide not only objective indices of intrapsychic disorders but offer the possibility of a three-way correlational study of psychological, endocrine and somatic processes. Knapp and his co-workers have performed some valuable pioneering work in the development of methodological guidelines for this approach in their long-term studies of asthmatic patients. While the usefulness of psychoendocrine approaches to the study of neurotic processes is still largely speculative and unproven, there are compelling reasons to regard it as one of the most potentially fruitful and powerful of all psychoendocrine approaches to the testing of psychiatric theory, and certainly so far one of the most unexplored and neglected.

Psychoendocrine Reflections of Psychotic Processes

Early psychoendocrine studies of schizophrenic patients between about 1945 and 1955 led to considerable confusion, largely because of methodological limitations from biochemical, physiological, and psychiatric standpoints. An early hypothesis that chronic schizophrenia was associated

with hypoadrenalism was not subsequently confirmed as methodological approaches became more refined during the 1950s. It should be emphasized that the conceptual approach in early psychoendocrine research on psychosis evolved from the quest for a biochemical abnormality or deficiency which might have pathogenetic significance in schizophrenia. In this respect, the orientation is quite different from the mainstream of recent psychoendocrine research, which has largely viewed hormonal responses as reflections, rather than as determinants, of intrapsychic reactions, although both views are valid and their relative importance remains to be elucidated, as will be discussed later.

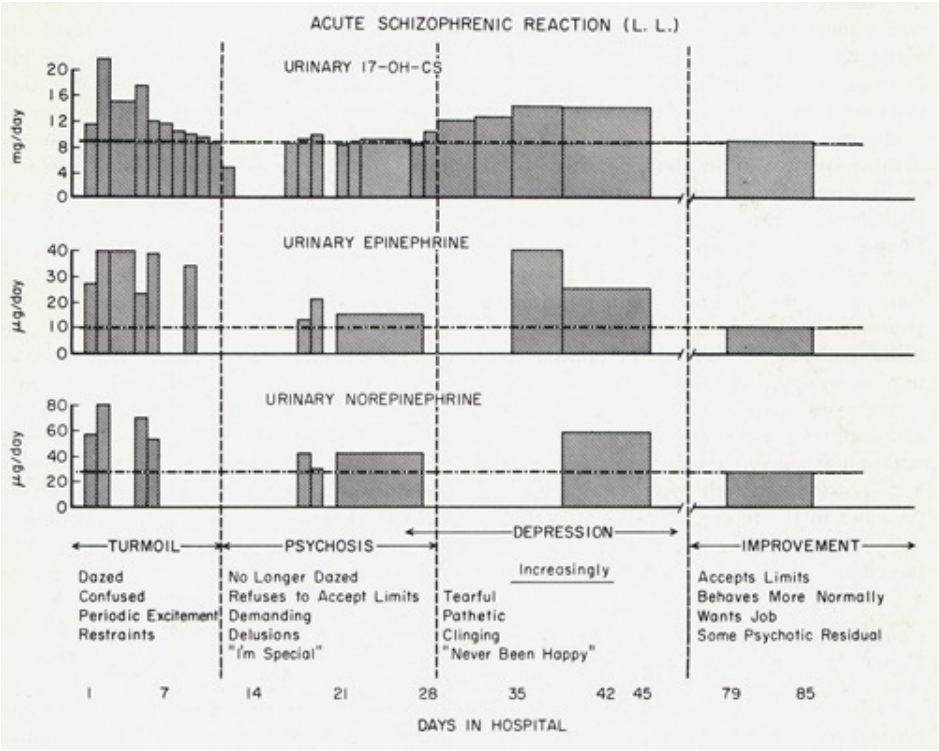
The classical study of acute schizophrenic patients by Sachar represents one of the finest models of the application of psychoendocrine approaches to the testing of psychiatric theory. Using a conceptual view of the natural course of acute schizophrenic reactions as being divided into several clearly defined phases of illness from initial breakdown to eventual recovery, he studied endocrine correlates of such clinical phases. Figure 24-6 presents an example of a case illustrating how closely such clinical phases correlate with equally well-defined phases of endocrine change. During the initial turmoil phase, when the patient's characteristic defense mechanisms have been overwhelmed, emotional distress and 17-OHCS and catecholamine levels are very high. With the subsequent formation of a consoling psychotic delusional system, becoming well established by about the eleventh day, hormone values

subside to a lower, more stable level. During this period of psychotic equilibrium, the patient's picture of himself and his style of interaction with others is completely narcissistic, and affective distress is minimal. Then, as the doctor and ward staff begin to challenge and undermine the patient's psychotic defenses during the 4th week, the patient reveals his true devalued self-image, and the affective distress of anxiety and depression reappears with associated increases in hormone levels. As the patient eventually arrives at a more mature, clinically improved "equilibrium," with minimal affective distress, hormone levels stabilize in a range very close to that observed during the earlier psychotic "equilibrium" phase. Similar correlations between hormonal and psychological phases were observed in longitudinal studies of additional patients of the same type.

These findings suggest that the psychotic system operates defensively to minimize both emotional distress and associated endocrine disturbance. Sachar's observations were among the first to call attention to the important role of psychological defenses in the maintenance of physiological as well as psychological homeostasis. This work also points tion for the earlier confusion and conflicting findings in psychoendocrine studies, when clinical phases were often not evaluated in close relation to the period of hormone sampling. Thus, it is not surprising that "contrast" studies of groups of normal subjects versus patients in chronic psychotic equilibrium may show no differences in group mean 17-OHCS out that it is essentially the *effectiveness*

of defenses, whether they be normal, neurotic or psychotic in character, which is reflected in 17-OHCS levels, thus setting a pattern for later psychoendocrine studies of defensive organization. It is also particularly noteworthy that at the time the patient is the most severely psychotic and withdrawn, emotional distress is often minimal, and 17-OHCS levels are similar to those following eventual clinical recovery. This observation provides a plausible explana-levels. Only when the dynamic factors involved in defensive organization are viewed in relation to the life setting does the significance of the psychoendocrine picture begin to become clarified. Finally, Sachar suggests that endocrine measures may not only provide a form of validation of theoretical classification of key phases in the course of a type of psychosis, but may also provide helpful guidelines to the psychotherapist, as he supports or challenges the patient's psychological defenses.

Figure 24-6.



Longitudinal study showing correlations between clinical and endocrine phases during course of acute schizophrenic reaction. (U.S. Army photograph.)

Another example of psychoendocrine evaluation of psychodynamic issues is provided by studies of the manic state, which clinically has been regarded by some observers as involving considerable intrapsychic distress, and by others as a more comfortable, restitutive state. Longitudinal studies of corticosteroid levels in manic patients have been reported by a number of workers. Generally it has been found that pituitary-adrenal cortical activity is

relatively low during manic phases, in contrast to the higher levels during depressed phases. These findings may be interpreted as providing physiological support for the clinical hypothesis that mania, with its elements of euphoria and denial, represents a counteracting, protective defense against the painful distress associated with depression.

Psychoendocrine Reflections of Depressive Processes

Although a discussion of depressive syndromes obviously overlaps with that in the previous sections on neurotic and psychotic processes, the considerable emphasis on studies of depression in psychoendocrine research merits special mention. In 1956, Board et al., reported marked plasma 17-OHCS elevations in acutely depressed patients shortly after hospital admission. While others confirmed these findings, it was subsequently found in longitudinal studies which extended well beyond the hospital admission period that 17-OHCS levels did not invariably correlate significantly with the severity of depressive symptoms.

In a study by Bunney et al., for example, two general subgroups of depressed patients could be distinguished on the basis of chronic urinary 17-OHCS levels. One group, characterized by high and labile 17-OHCS levels, appeared to be more aware of, and involved in, the struggle with their illness. The second group, although also having high ratings on the depression scale,

had relatively low and stable 17-OHCS levels and appeared to have differently organized defenses, often employing denial of their illness or related problems.

This study indicated that the symptoms of depression alone are not necessarily associated with 17-OHCS elevations, but that, again, a more holistic, psychodynamic view of defensive organization must be taken, particularly in view of the considerable heterogeneity of clinical depressive syndromes.

The incisive studies of Sachar and his coworkers have, in particular, contributed greatly to the clarification of psychoendocrine research on depression. In a study designed to test the psychiatric hypothesis that certain depressive reactions serve a defensive function against acknowledgment of painful feelings of disappointment or anger, dynamic factors were carefully assessed throughout the period of psychotherapy in a relatively homogeneous group of patients with reactive depression. Elevated 17-OHCS levels were generally not observed in those patients except during episodic "confrontation" periods, when the painful losses which precipitated their depressive reactions were being dealt with during therapy. Emphasis was placed on distinguishing the affects associated with loss and mourning from the organized syndrome of melancholia. Sachar also has presented a penetrating critique of early psychoendocrine research on depression which

should be an important guide to future work in this field. The failure of many studies to consider important control issues, such as the psychoendocrine response to hospital admission, the social milieu throughout hospitalization, the interference of certain central-acting medications, the criteria for control data to be compared with illness data, as well as the failure to take psychodynamic factors into account, are implicated as probable reasons for inconsistencies and confusion in early psychoendocrine research on depression.

At present, then, it appears that outward signs of depression are not necessarily associated with 17-OHCS elevations, and that the intrapsychic processes which are associated with the marked 17-OHCS changes often seen in depressed patients remain to be qualitatively characterized in future studies, which take into account dynamic factors as a basis for distinguishing the many different syndromes in which signs of depression are a prominent feature.

Psychoendocrine Approaches to the Study of Developmental Processes

It logically follows that insofar as endocrine measures reflect intrapsychic processes, then such measures may be used to study experiential and genetic influences on the development of those same intrapsychic processes. The marked individual differences in psychoendocrine responses

observed between different subjects exposed to the same stressful situation provides one point of departure for research along such developmental lines. Under relatively highly standardized conditions, for example, six adult rhesus monkeys were exposed to two-week sessions of a conditioned emotional disturbance, conditioned "avoidance," during which they were required to press a hand lever at times in order to avoid an aversive stimulus. Of the six monkeys exposed to this procedure, two showed marked 17-OHCS elevations, two showed mild 17-OHCS elevations, and two animals actually showed *suppression* of 17-OHCS levels, which was not, incidentally, associated with elevated preexperimental 17-OHCS baselines. While no genetic or early developmental data were available on these animals acquired as adults, it was noteworthy that there appeared to be a close correlation between *direction* of 17-OHCS response and the extent of their prior laboratory experience and handling. The monkeys showing marked 17-OHCS elevations were laboratory-naive, while the monkeys showing suppression of 17-OIICS levels were veterans of many laboratory experiments. While these studies of adult monkeys may not be viewed as developmental in the usual sense, they did, along with other observations in animals, suggest the possible importance of even short-term experiential factors in the determination of psychoendocrine reaction patterns and raised the issue of the need for systematic developmental studies.

Some findings perhaps more directly related to this approach emerged

from studies by Poe et al. of childhood history in relation to individual differences in chronic mean 17-OHCS levels in ninety-one Army recruits studied during basic training. Of the fourteen men in this group who had lost a parent by death, twelve had 17-OHCS levels in the upper or lower quartiles. In the "high" 17-OHCS quartile, five of the six subjects had lost their mother, while five of the six subjects in the "low" 17-OHCS quartile had lost their father. So far, no subsequent attempts have apparently been made to pursue this finding further or to search for possible psychological correlates of endocrine differences in subjects who experienced parental deaths during childhood.

More broadly, it appears that psychoendocrine reflections of emotional and defensive mechanisms may provide useful adjuncts to the psychological study of the early development of these intrapsychic mechanisms and represent an objective basis for testing theories of developmental stages based entirely on psychological observations. In addition to the well-established usefulness of corticosteroid and catecholamine levels in defining individual characterological differences, the recent availability of improved methods for determination of testosterone and other sex hormones adds even further interest to developmental approaches. At present, however, there is a dearth of psychoendocrine data on virtually all phases of early development, from the first year through adolescence and this approach awaits further exploration.

Psychoendocrine Approaches to the Study of Social Processes

The social setting of psychoendocrine studies has already been emphasized as an important variable to assess in relation to psychodynamic factors and hormonal reaction patterns. Some of the specific examples of the ways in which social influences may be reflected in hormonal levels suggest in addition that psychoendocrine approaches may be useful to social scientists in the systematic study of social interactions, particularly those occurring in small groups.

One of the social phenomena apparently reflected in psychoendocrine studies is what might be called the "emotional contagion effect." An early observation suggesting this interpretation was the close similarity of 17-OHCS levels in crewmen of a B-52 bomber during a nonstop flight to Argentina under unusually stressful conditions. The pilot had extremely high urinary 17-OHCS levels of about 20 mg./day (compared with a mean normal of about 7 mg./day in men). The other three crewmen, who were back in the plane working closely together, all ran very similar elevated levels of about 13 mg./day. The rarity of 17-OHCS levels of 13 mg./day, even in large groups of human subjects in stressful situations, suggested the possibility that a socially communicated "13 mg./day atmosphere" prevailed in this aircraft on the flight day.

Similar conclusions were suggested in the studies of other small,

closely-knit groups of five to six human subjects. In each of three different groups of young men anticipating ninety-six-hour sleep-deprivation sessions, mean plasma 17-OHCS levels differed appreciably from one group to the next. Yet, within each group, the individual 17-OHCS values clustered very closely around the particular group mean at the end of the control week during which the men had been continuously in close social communication. The tendency for 17-OHCS levels in most individual members of a group anticipating a stressful experience to cluster around an "equilibrium level" was also observed in normal young adults anticipating movie-viewing experiences. In studies of normal young adults during hospitalization, however, it was found that, while some groups had a very narrow range of intragroup corticosteroid levels after the individuals lived together for a while, other groups showed a much wider range of intragroup individual variation in a similar setting. These observations suggest that certain group dynamics may be reflected in psychoendocrine parameters, particularly when the group is relatively small and the members have been together for some time in a relatively intimate and stressful setting.

Many observations in animals have also indicated that such parameters as population density and social hierarchy are reflected in endocrine activity. Of particular interest are the elegant studies by Bose and his coworkers of plasma testosterone levels in monkeys living in social groups. These studies have shown correlations between plasma testosterone levels, dominance

rank, and various levels of agonistic behavior. Testosterone fluctuations in individual male monkeys have also been observed in relation to such social or sexual stimuli as defeat in combat or introduction to a colony of females.79 80

Similarly creative psychoendocrine approaches would appear to be feasible in human groups, for example, in relation to various group-therapy approaches, yet little has been done so far along these lines. The naturalistic character of group interactions, as contrasted to the contrived laboratory investigator-subject settings, seems rather promising as an experimental approach for psychoendocrine studies in human subjects. Again, both the potential and the limitations of this approach are defined by the rationale that to the extent that hormonal reactions reflect emotional and defensive organization, and to the extent which such intrapsychic processes are related to social interactions, then psychoendocrine approaches should be useful to the investigator of social processes.

Psychoendocrine Approaches to the Study of Occupational Activities

The sensitivity of corticosteroid and catecholamine levels to such everyday activities as viewing motion pictures has already been mentioned. It has been shown by Wadeson et al., and Levi that hormonal levels may rise during the viewing of certain movies and fall during the viewing of other movies. These experiments convey a rather dynamic sense of hormonal levels

shifting up or down from one short time segment to another during the day in reaction to an experience not unlike many other common activities of everyday life. The question naturally arises as to whether or not similar hormonal reactions do occur in association with a much larger range of everyday activities, including occupational as well as recreational pursuits, even though we do not normally think of many of these activities as being associated with appreciable changes in affective state.

In a series of resourceful studies, Levi and his co-workers have indeed demonstrated that certain occupational tasks have psychoendocrine reflections in the activity of the sympathetic-adrenal medullary system. He found urinary catecholamine increases and hyperlipoproteinemia, for example, in persons performing an exacting industrial task of sorting out four slightly different sizes of steel balls in the presence of distracting noise and lights. In another study, Levi found that conditions of everyday work, such as whether it is performed on a piecework or salaried basis, were reflected in urinary epinephrine and norepinephrine levels in young women who were invoicing clerks. Frankenhaeuser et al., have also reported urinary catecholamine changes in association with psychological tests involving arithmetic and inductive tasks. In another study, it was found that individual psychoendocrine differences associated with performance of mental activities or tasks may, in turn, be correlated with individual differences in the effectiveness of performance. Subjects showing the greatest improvement in

performance of proofreading or coding tasks in a stressful setting were also those who showed the largest increase in norepinephrine excretion in association with the task.

While we have as yet minimal data with which to evaluate this general approach, it is certainly a provocative notion to consider that our daily routines are composed of a sequence of episodic segments in which hormonal increases and decreases reflect associated shifts in mental and psychomotor activities, which may perhaps be divided into general classes, such as tension-building or tension-relieving, on a psychological basis. The dynamic factors involved in emotional and defensive organization of individual subjects would, of course, have to be taken carefully into account in the interpretation of findings emerging from this approach. Recent research with plasma cortisol measurements at frequent intervals has shown some striking periodic increases and decreases in hormonal levels over the course of the day. One of the issues raised by these findings is whether such "ultradian" fluctuations represent simply an "on and off" physiological mechanism of glandular release of hormone in periodic bursts, or if the fluctuations are largely a reflection of shifting inputs into the neuroendocrine machinery, particularly perhaps a reflection of shifting intrapsychic functioning in relation to moment-to-moment events, thoughts, and activities. While this is certainly a technically difficult issue to approach experimentally, its practical and theoretical implications for occupational stress research and

psychosomatic medicine provide a compelling basis for its further exploration.

Psychological Reflections of Endocrine State

While recent psychoendocrine research has been oriented primarily in terms of the influence of psychological factors upon hormone secretion, the important fact should be kept in mind, of course, that interactions between the brain and the endocrine glands operate in both directions. It is known that many hormones exert influences on neural and psychological processes, although our knowledge of such effects is still very limited, largely because of the unusually difficult methodological problems involved in assessing the affected CNS processes. The early work of Reiss and his associates in England was directed at this "other side of the coin" in psychoendocrinology, i.e., the possible clinical importance of the effects of abnormal hormone levels upon the brain as a pathogenetic factor in various psychiatric disorders. The psychiatric symptoms which often accompany certain clinical endocrinopathies have long been recognized. The hypothesis that a deficiency of gonadal hormone secretion, leading to an immature level of psychosexual functioning, might be a pathogenetic factor in certain schizophrenic patients was formulated many years ago, but could not, at that time, be rigorously tested because of the lack of specific and reliable methods for gonadal hormone measurement in blood and urine. Such methods, however, are now

available. The striking and regular fluctuations in mood state associated with the menstrual cycle in many women provide another example of observations which strongly suggest hormonal influences upon intrapsychic processes and probably presents one of the best natural opportunities for the experimental study of such correlations. The recent development of radioimmunoassay methods for the measurement of the gonadotropins and of the individual gonadal steroids now makes possible a highly refined endocrinological approach to this clinical problem. The research of Rose and his co-workers, involving the study of correlations between plasma testosterone and agonistic behavior, presents another excellent model of how the general problem of viewing psychoendocrine relationships in both directions may be approached experimentally. It is clear that the study of hormonal feedback upon the brain is another aspect of psychoendocrinology which is worthy of greater attention in the future, particularly because of the recent availability of many long-awaited, refined methods of hormone assay.

It should also be mentioned that there is a considerable body of neurochemical and psychopharmacological research which indicates that biogenic amines in the brain may be involved in the development of affective disorders such as depression and mania. The possible role of various hormones upon the metabolism and balance of the biogenic amines within the CNS has, therefore, become yet another area of current interest in psychoendocrine research. Some caution is probably well-advised in this

area, however, for several reasons, perhaps particularly with regard to the pitfall of placing overemphasis prematurely on a single hormone before a broader survey for possible multiple, interacting hormonal influences on the biogenic amines is completed.

Psychoendocrine Approaches to the Study of Psychosomatic Disorders

Most of the psychoendocrine approaches discussed up to this point have been oriented in terms of the study of hormonal changes as reflections of psychological processes. The central issues have revolved around the use of hormone measurements as sensitive, objective, roughly quantitative reflections of the intrapsychic processes involved in emotional and defensive organization. It has also been emphasized that the great bulk of psychoendocrine research since the 1950s, furthermore, has been focused on the pituitary-adrenal cortical and the sympathetic-adrenal medullary systems.

In turning, finally, to the question of the implications of psychoendocrine approaches for psychosomatic medicine, it is necessary to broaden our conceptual approach to consider some fundamental facts of endocrine physiology. The basic question now becomes, “Can psychologically determined hormonal changes play a mediating, pathogenic role, along with concurrent autonomic changes, in the development of somatic illnesses?” In

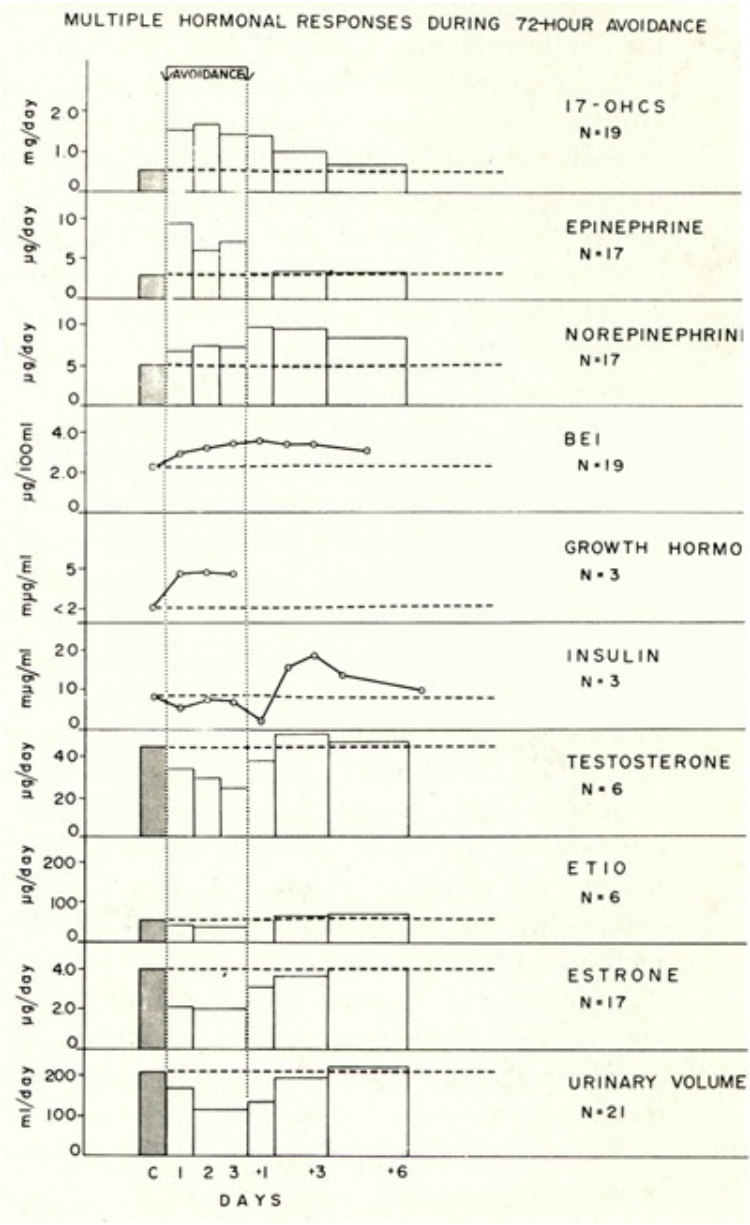
approaching this question, the modus operandi of hormones at the cellular level becomes a highly relevant issue. A particularly crucial fact is that hormones are now known to exert their effects upon metabolic or cellular processes in a complex, *interdependent* way. In general, a given metabolic process is regulated by numerous hormones which are aligned into a balance of opposing and cooperating forces, with antagonistic, synergistic, additive, and permissive relationships present between the hormones in relation to the regulation of any particular cellular process. As a result, no single hormone controls any single metabolic process, but there is always a *balance between interdependent forces.* Thus, in considering the regulation of lipid metabolism, for example, a substantial number of hormones must be taken into account, including norepinephrine, insulin, cortisol, epinephrine, growth hormone, thyroxine, and estrogens. Carried to its logical conclusion, then, this basic feature of endocrine physiology dictates the conclusion that an understanding of the regulation of the functional state of any given cellular process at any given time can only be achieved by viewing the current *overall hormonal balance* as the final, key determinant of the cellular activity in question. In practical terms, this means that little success is to be expected in approaches which attempt to relate psychological processes and somatic illnesses through a view of any *single* mediating psychoendocrine system in isolation. It means that an increasing number of concurrent hormonal measurements, involving as many endocrine systems as possible, should be incorporated into

psychoendocrine studies of psychosomatic disorders.

Another body of evidence supports this conceptual approach in addition to the reasoning based on cellular aspects of endocrine physiology. With the recent, revolutionary advances in hormone-assay methodology, it has become feasible to measure a large number of hormones concurrently and to test the hypothesis that the many endocrine systems, which have anatomical contacts with the brain, are responsive to psychological influences. Figure 24-7 shows the pattern of multiple hormonal responses to a seventy-two-hour conditioned emotional disturbance in a series of "conditioned avoidance" experiments in monkeys. First of all, it is evident that every hormone measured changed in reaction to this stressful situation, although the dynamics of change differ considerably from one hormone to the next, particularly with regard to temporal features. Two general hormone-response subgroups may be distinguished on the basis of initial direction of change. The levels of the corticosteroids, epinephrine, norepinephrine, thyroxine or butanol-extractive iodine (BEI), and growth hormone all rise initially, while the levels of insulin, androgens, and estrogens drop initially. Following the session, the latter hormones tend to rebound above baseline levels. The possibility that the organization of this acute psychoendocrine response pattern represents a "catabolic-anabolic" sequence of coordinated responses in preparation for muscular exertion, according to Cannon's formulation, fits well with our present knowledge of the role of each of these

hormones in relation to energy metabolism. The critical interpretation of these experiments has been discussed at length elsewhere, but their general relevance to psychosomatic studies seems clear. While this stereotyped pattern of acute psychoendocrine response is demonstrable under certain conditions in the monkey, how might the pattern of hormonal balance be variously altered on an acute and chronic basis by the complex psychological machinery which has already been demonstrated in corticosteroid and catecholamine studies to exert such profound and varying effects on endocrine function from one individual to the next? Are particular characterological patterns of psychological organization reflected broadly in the pattern of overall hormonal balance? If we view psychosomatic illnesses as fundamentally *integrative disorders,* does the pattern of organization of overall hormonal balance distinctively reflect the particular integrative disorder involving emotional and defensive processes? If so, does the altered pattern of hormone balance appear to constitute a pathogenetic link to the associated somatic disorder? These questions represent the general lines along which working hypotheses can be perhaps most logically developed in the light of current psychoendocrine data and theory.

Figure 24-7.


MULTIPLE HORMONAL RESPONSES DURING 72-HOUR AVOIDANCE
AVOIDANCE
17-OHCS
N=19
EPINEPHRINE
N=17
NOREPINEPHRINE
N=17
BEI
N=19
GROWTH HORMONE
N=3
INSULIN
N=3
TESTOSTERONE
N=6
ETIO
N=6
ESTRONE
N=17
URINARY VOLUME
N=21
mg/day
μg/day
μg/100ml
mμg/ml
C 1 2 3 +1 +3 +6
DAYS

Organization of multiple hormonal responses to sustained conditioned emotional disturbance (conditioned avoidance) in rhesus monkeys. (U.S. Army photograph.)

As yet, however, only the most preliminary efforts have been made to test the usefulness of this broadly based, holistic psychoendocrine approach to the study of psychosomatic disorders. Such efforts, while quite limited so far, have provided some useful guidelines and leads for future work in this area. In a study of hormonal patterns of recruits during basic training, for example, several hormonal abnormalities were noted during the week prior to onset of acute adenovirus respiratory illnesses. A gradual decline in thyroid hormone levels, spiking corticosteroid and catecholamine elevations several days before the onset of illness, and a high percentage of extremely high or extremely low corticosteroid, thyroid hormone, or androgen levels appeared to characterize the period preceding respiratory infections. These findings suggest that it may be worthwhile to evaluate further the working hypothesis that stress-related, *preillness, multiple* changes in overall hormonal balance may play a pathogenetic role in altering host resistance to infectious illnesses.

In a preliminary study of obese patients, Troyer et al. have observed that two general classes of endocrine abnormalities should be considered. First, the *mean chronic profile* of hormonal balance appears to be altered, with the levels of certain hormones chronically higher or lower than those in

normal groups or other patient populations. Secondly, the pattern of *acute responsiveness* reflected in changes in hormonal balance with psychological or other stimuli may be distinctively altered in patients with psychosomatic illnesses. A number of acute episodes were observed in obese patients, for example, in which the anabolic hormones rose at the same time that the catabolic hormones rose, a pattern quite different from that observed during acute arousal in the normal monkey. It is also especially interesting, incidentally, that these marked acute hormone responses apparently occurred in the patients generally without overt expression or subjective awareness of emotional distress. In two obese subjects studied earlier, however, details of life events and some knowledge of dynamic factors in the individual patient suggested that neurotic processes were suddenly activated at the time of the hormonal changes. These pilot observations require considerable further evaluation, but are mentioned here primarily to indicate the kinds of methodological and theoretical issues which bear consideration in the design of psychoendocrine studies of medical patients. Endocrine sampling in long-term longitudinal studies of patients should yield both a chronic mean hormonal profile and an acute psychoendocrine response pattern so that both of these parameters, in turn, can be studied for possible relationships to psychological and somatic parameters.

While the technical and organizational problems which make this multidisciplinary approach difficult are substantial and require resourceful

and energetic efforts for their solution, historically it now appears within our grasp. It is not often that a generation has suddenly new experimental methods at its disposal which make possible the testing of a promising but unproven concept of disease. While much of medicine, with the ever-increasing trend towards specialization, continues to pursue the course of viewing disease as a local or regional phenomenon, the opportunity is now open to pursue, at a new level of sophistication, a view of many *diseases as disorders of integration.* We have long thought of endocrine systems as largely governed by relatively simple, humoral, nearly infallible self-regulatory mechanisms. The new knowledge that highly complicated psychological influences are superimposed upon the humoral machinery for endocrine regulation raises the possibility that disorders of bodily function may result when the more complex, and probably more fallible, psychological machinery preempts, disrupts, or otherwise works at odds against the simpler, lower-level, humoral machinery of endocrine regulation. Certainly, there are few, if any, conceptual approaches to the genesis of disease presently envisioned in medicine which are potentially more far-reaching, logically appealing, and challenging.

Appendix: Some Control Issues and Experimental Tactics in Psychoendocrine Research

While it is beyond the scope of this chapter to discuss in detail such

relevant research issues as nonpsychological determinants of endocrine activity which may act as interfering independent variables in psychoendocrine studies, control measures in experimental design, selection and validation of hormone assay procedures, etc., it may be useful to review briefly several of the problems which have most commonly proven pitfalls in past psychoendocrine research.

Quality-Control Check System for Hormone-Assay Methods

Since hormone assay methods are generally quite delicate microanalytical procedures, in which such subtle factors as minor variations in day-to-day laboratory technique, fluctuations in environmental temperature, variability in reagent batches, instrument malfunction, glassware contamination, etc., can cause major errors in the accuracy of results, it is *essential* that quality-control checks which are as rigorous and comprehensive as possible be incorporated into every analytical run. Even in the most experienced laboratories, such methods may suddenly give unreliable results and days or even weeks of trouble-shooting may be required in order to locate the source of error. A sound quality-control check system cannot, of course, prevent such breakdowns of methods, nor the associated loss of samples or time, but it has the all-important advantages of providing the investigator with a highly reliable and objective basis for accepting or rejecting biochemical results in each analytical run, and of

greatly reducing the chance of accepting erroneous results as valid. These advantages apply equally whether the biochemical determinations are made by the investigator himself, by a close colleague, or by a distant commercial laboratory. The following system, outlined in a general way, can be applied to most blood or urinary hormone-assay procedures with appropriate modifications.

First, a large pool of plasma or urine should be obtained so as to provide about 100 or more aliquots of the same volume as will be normally collected for individual routine analyses of unknown samples from experimental subjects. The number of aliquots is arbitrary and mainly decided by convenience, in terms of providing a supply to last several months for the method in question. If, for example, the method requires a x-ml. aliquot for each determination, if two control samples are included in each analytical run, and if three analytical runs are made each week, then 102 aliquots would provide a seventeen-week supply of control samples. The concentration of hormone in the original pool should be reasonably close to the concentration range present in the samples from the subject population to be studied. The original raw pool should be divided into three equal subpools, designated C_1; C_2, and C_3. Subpool C_1 should remain untreated, as it was collected. To subpool C_2, a quantity of crystalline or highly purified hormone should be added so as to increase the hormone concentration in each aliquot by an amount just slightly greater than the standard deviation of the method. The

principle involved here is that C_2 should be clearly distinguishable from C_1 by the analytical method, but just barely so. In other words, if aliquots from C_1 and C_2 are repeatedly analyzed in twenty or thirty successive runs, the highest values obtained for C_1 aliquots should only very rarely exceed the lowest values obtained on C_2 aliquots. If too much hormone is added to C_2 and the concentration difference is too great between C_1 and C_2 so that they are too easily distinguishable, then in some methods this may lead to conscious or unconscious bias on the part of the technician. To subpool C_3, then, an amount of purified hormone, twice as great as that added to C_2, should be added so that C_2 and C_3 aliquots will be just comfortably distinguishable by the method and values from the two subpools rarely overlap.

Once the three subpools are thus prepared, and the added hormone in subpools C_3 well-mixed by shaking, each subpool should then be divided into the small individual aliquots for individual analyses. Next comes the important matter of coding the bottles with numbers in such a way as to give no indication to the technician of which subpool is represented. A code sheet is prepared listing numbers from 1 to 100, or whatever total number of aliquots there may be, and samples are then numbered in order after they are drawn at random from the three subpool groups. The code sheet might read, for example, 1 (the only number actually on the tube) = C_2, 2 = C_1; 3 = C_2, 4 = C_3, 5 = C_3, 6 = C_1, etc. The biochemist receives only the tubes with the

numbers 1, 2, 3, 4, 5, 6, etc. The responsible investigator should maintain custody of the code sheet in such a way as to keep the procedure blind, but to supply immediate feedback to the chemist or technician after each run is completed. The control samples should be stored frozen, with a substantial number of aliquots kept in the same freezer as the unknown samples from experimental subjects. If the freezer should ever malfunction, the control samples may provide some valuable indication as to whether serious damage to hormone concentrations has resulted from high temperatures or not. For most methods, at least two control samples should be included in each run, preferably one at the beginning and one at the end of the series of tubes being analyzed. Immediately after the control samples are initially prepared, six to ten samples should be analyzed from each subpool so as to establish an approximate mean value and standard deviation for each subpool before proceeding with the analysis of unknown samples.

While this system provides a reliable check against the great majority of sources of analytical error, it is not infallible and will not detect, for example, an occasional random error caused by the contamination of a single tube. In such an instance, the investigator can only ask for several replicate determinations of any sample giving a value far away from the expected range. In the main, however, the system is extremely valuable in monitoring day-to-day accuracy and in providing reassurance to the investigator, particularly when in search of psychological correlates, that the hormone

values are valid.

Choice of Blood- and Urine-Sample Collection Schedules

There are several guidelines for the design of hormone-sampling schedules which have proven useful in promoting the interpretability of psychoendocrine experiments. The first principle, perhaps, is that the sample-collection times should be closely attuned to the dynamics of the endocrine response and the stimulus under study. It is known, of course, that the levels of some hormones such as epinephrine, norepinephrine, and growth hormone are very labile, showing marked elevations or decreases within a matter of minutes. Other hormones, such as cortisol, thyroxine, or testosterone, apparently change more slowly. While some general guesses about optimal sampling intervals can be made from previous work on various hormones, it is desirable in any particular study, whenever possible, to carry out a few pilot experiments with frequent enough samples so as to define roughly the temporal configuration of hormonal-response curves. Once this is established, a more economical collection design with fewer samples can be devised with greater assurance that response peaks will not be missed because of inappropriate sampling intervals.

Another extremely important practice is the obtaining of *multiple* control or base-line samples *before* the onset of any experimental

manipulations on either an acute or prolonged basis. Because of the well-known potency of anticipatory reactions, especially those involving novelty or uncertainty, as stimuli to many endocrine systems, at least two, and preferably more, preexperimental samples should always be obtained in order to establish the slope of hormonal change against which experimental stimuli are superimposed. It is probable that few factors have led to greater confusion and error in the interpretation of experiments on endocrine regulation than failure to obtain multiple base-line samples.

A number of other control and methodological issues, such as the advantages of longterm "longitudinal" studies of individual patients over "contrast" studies of large groups in the exploratory phases of psychoendocrine research, the importance of social milieu during hospitalization, the selection and validation of psychological methods, the need to consider circadian and ultradian hormonal rhythms in experimental design, and the role of nonpsychological determinants, such as age, sex, medications, smoking, posture, bed rest, muscular activity, environmental temperature, nutrition, etc., have all emerged as important considerations in psychoendocrine research and are discussed in greater detail elsewhere

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