ADRENAL ACTIVITY IN ANXIETY

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CHAPTER 4

ADRENAL ACTIVITY IN ANXIETY*

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SYNOPSIS

A considerable number of studies done in the past 20 years indicates that many psychological stresses result in increased secretion of cortisol by the adrenal cortex. Anticipation of a stress also causes increased adrenal cortical activity. In mentally ill persons, activation of the adrenal cortex is greater at times when ego defenses are low and when environmental pressures are high.

Adrenal cortical hormones have widespread physiologic effects, including increasing the activities of several glucocorticoid-sensitive hormones. The endogenous production of abnormally methylated compounds has been suggested as a possible biochemical substrate of psychosis, and one enzyme involved in methylation pathways has been shown to be inducible by glucocoticoids. It may be hypothesized; therefore, that psychotogenic metabolites may be produced during psychological stress via increased adrenal cortical activity and hormone induction of transmethylating enzymes.

In this symposium Drs. Lidberg and Levi have presented research on the adrenal medullary hormones, epinephrine and norepinephrine, in anxiety. Since my main research interest has been adrenal cortical activity in various stress states, I would like to confine my report to the adrenal cortex, or more specifically, to changes in the release of cortisol and their potential role in anxiety states.

Hans Selye (1956) implicated activation of the adrenal cortex in response to stress in his general adaptation syndrome, and since then there has been a plethora of studies on adrenal cortical activity in many different types of anxiety, both naturally occurring and experimentally contrived. From these studies, it is now axiomatic that in anxiety-provoking situations, adrenal cortical activity is increased (Mason, 1959; Hamburg, 1962; Michael and Gibbons, 1963; Levitt *et al.*, 1964; Rubin and Mandell, 1966; Miller, 1968; Mason, 1968). Direct measures of this increase used in the past 20 years have included plasma cortisol levels, urinary excretion of cortisol and its metabolites, and cortisol secretion rate as determined by the isotope dilution technique (Cope, 1965).

These studies have employed both cross-sectional and longitudinal methodologies. Hamburg (1962) reviewed 12 studies of groups of persons under naturally occurring conditions of fairly intense distress. Mean early morning plasma cortisol levels were about 20 μg %, while control subjects in the same laboratories had mean blood levels of 12 to 13 μg % at the same time of day. Several studies of urinary 17-OHCS excretion revealed that anxious subjects had a mean excretion level about 50% greater than control subjects. Conversely, subjects who had been placed in a deep hypnotic trance were found to have lower than normal plasma cortisol levels (Persky *et al.*, 1959; Sachar *et al.*, 1965; Sachar *et al.*, 1966).

In several longitudinal studies of mentally ill patients, adrenal cortical activity was found to be increased at times when the patients' ego defenses were minimal (Rubin and Mandell, 1966). Sachar *et al.* (1963) demonstrated greater urine 17-OHCS excretion in four acutely schizophrenic soldiers during the "acute psychotic turmoil" and "anaclitic depression" phases compared to the "psychotic equilibrium" and "recovery" phases of their psychoses. Bunny *et al.* (1965), in a study of a manic-depressive patient with 48-hour cycles, demonstrated a greater urine 17-OHCS excretion on the alternate depressive days compared to the manic days.

As a result of these kinds of studies, psychological features common to various emotional states and types of illness which correlate well with the biochemical data have been recognized. The emphasis has shifted from the concept of disease-specific alterations in adrenal cortical activity to one of heightened activity of the CNS-pituitary-adrenal axis as a concomitant of such psychological variables as "felt" anxiety, absence of denial, insight into the severity of the illness, and depressive affect.

These variables have been grouped under the heading of "failing psychological defense strength," that is, the breakdown of psychological mechanisms which

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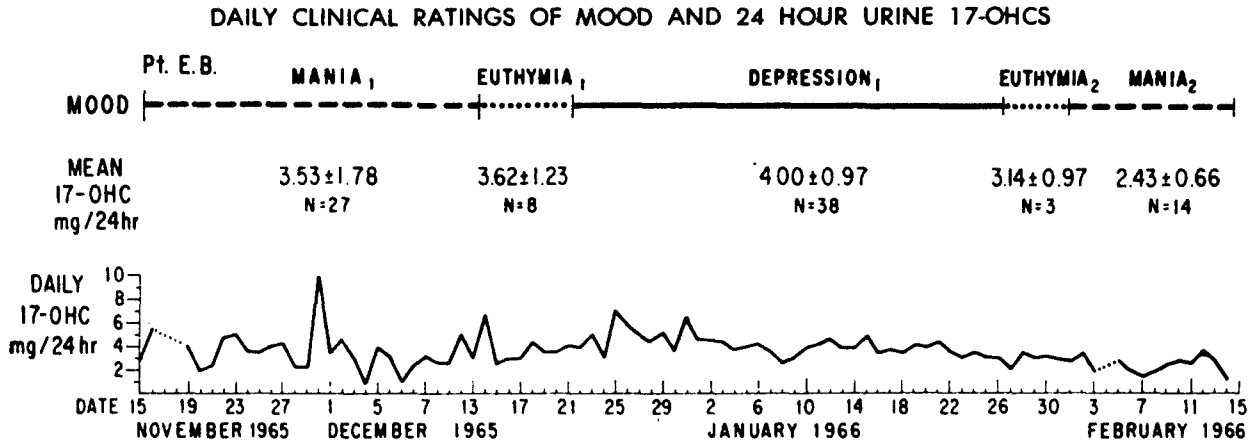

Figure 1. Urinary 17-OHCS excretion in a rapidly cycling manic-depresive patient.

reduce the awareness of illness or threat of injury or loss. This occurs in various phases of both schizophrenic and depressive reactions. Anxiety states also may be conceptualized in this context to be a result of "failing defenses."

In our studies of rapidly cycling manic-depressive patients (Rubin, 1967; Rubin, 1968; Rubin *et al.*, 1968) we, too, have found greater urine 17-OHCS excretion during depression than during mania, but these differences were evident only after the patients had acclimated to the hospital environment. Figures 1 and 2 illustrate these data in two patients. For each, mean 17-OHCS excretion during the first episode of mania was not significantly different from the mean excretion during depression, but mean 17-OHCS excretion during subsequent episodes of mania was significantly lower than that during depression. These findings suggested that an interaction between intrapsychic ego defense strength and external milieu stresses was an important determinant of the level of adrenal cortical activity. Sachar *et al.* (1967) held the same view following his demonstration of increased urine 17-OHCS in depressed patients when, during psychotherapy, they were confronted with the loss that precipitated the depression.

In situations in which the anxiety-provoking stimulus is prolonged, the adrenal response also may be prolonged and may be associated with an increased metabolism of cortisol (Rubin and Mandell, 1966; Curtis *et al.*, 1966). If some mastery of the stress situation is achieved, there may be a rapid psychoendocrine adaptation to the stress (Mason, 1964; Mason *et al.*, 1968). A recent study of U.S. Navy underwater demolition team trainees illustrates both these aspects (Rubin *et al.*, 1969). Twenty men who successfully completed a 16-week UDT training program underwent thrice weekly serum cortisol determinations. Mean daily cortisol values during the first two months of training (Fig. 3) ranged between 20 and 26 μg %, indicating a fairly high sustained level of adrenal cortical activity throughout the course. Against this background, transient increases in mean serum cortisol occurred coincident with novel experiences about which the men had some anticipatory anxiety. These included the start of swimming practice on January 9, the introduction of the face mask on January 23, "hell week" from January 30 through February 4, the introduction of swim fins and UDT weaponry on February 16, and the first ocean drops and pickups by helicopter on February 23. However,

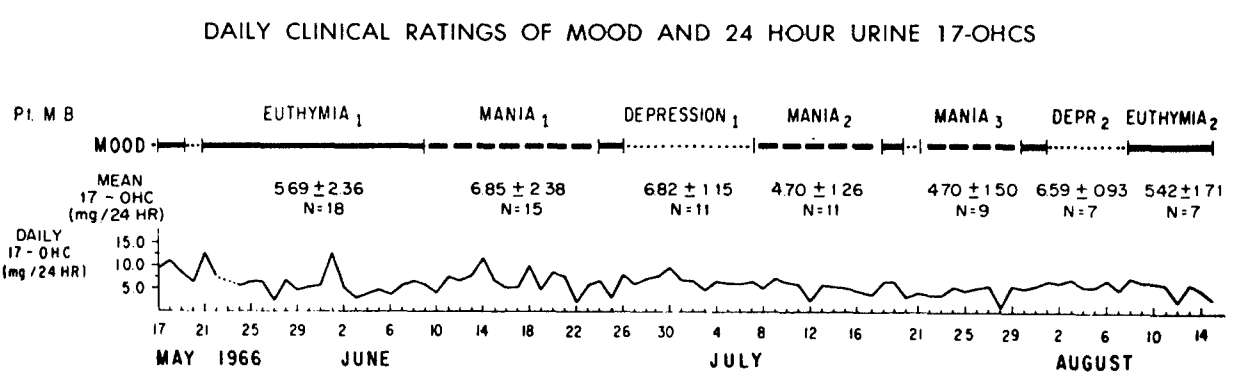

Figure 2. Urinary 17-OHCS excretion in a rapidly cycling manic-depressive patient.

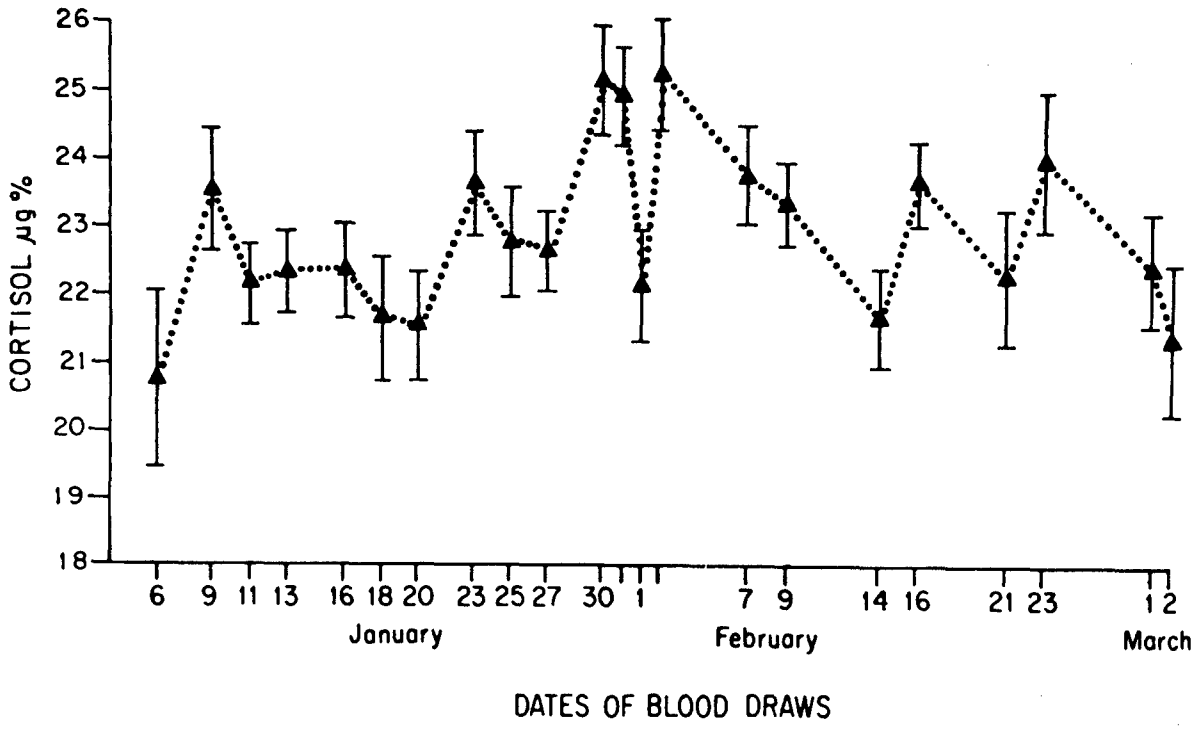

Figure 3. Mean plasma cortisol levels and standard errors for 20 subjects during two months of Navy underwater demolition team training.

as each new technique was practiced and became familiar to the trainees, cortisol levels trended lower, even though increasing demands for the use of the new technique were being made by the instructors.

The possibility that varying role demands upon human subjects in stress situations may be a major influence on their physiological responses has been examined in only a few studies. Brady *et al.* (1958) showed that if a pair of monkeys is subjected to a noxious stimulus in an avoidance situation, the "executive" monkey, e.g. the one permitted to press a lever to avoid the noxious stimulus to both, develops gastrointestinal lesions, whereas the other animal, which has no control over the stimulus, does not. This experimental method has been applied to pairs of human subjects, one of whom was able to press a button to avoid a strong auditory stimulus to both, while the other subject was a passive control (Davis and Berry, 1963). The "executive" members of the pairs were shown to have a significantly greater amplitude of gastric contractions than the control subjects. We considered this experimental paradigm in a study of adrenocortical responses to a naturally occurring stress situation — paired Navy pilots and flight-officers attempting their first aircraft carrier landings in the two-man F-4B Phantom jet aircraft (Rubin, Miller *et al.*, 1969). The pilot, in the front cockpit, has complete flight control over the aircraft. The radar intercept officer, in the rear cockpit, has excellent visibility but no flight control. The actual landing procedure is quite hazardous. At one mile from touchdown the entire ship appears about the size of a pencil eraser held at arm's length; in the F-4B this last mile is covered in 36 seconds. Serum cortisol determinations done immediately following day and night landing practice (CARQUALS) and compared to control levels on a non-flying day revealed a highly significant 230% increase over control for the pilots, but only an insignificant 40% increase for the radar interceptor officers (Table 1). In the context of the "executive" monkey paradigm, the "executive" naval aviator, who must perform a highly complex task while avoiding serious potential harm to himself, his partner, and his aircraft, showed an unequivocal adrenocortical stress response. The passive partner, on the other hand, showed only a slight adrenal response. These results point to the importance of the active versus the passive role as a determinant of stress intensity in human subjects exposed to naturally ocurring stress situations.

The adrenal cortical response to anxiety may be an important link in the understanding of possible neurochemical substrates of psychoses and affect disorders. Knox (1963) discovered that cortisol induced the enzymes tryptophan pyrrolase and tyrosine transaminase, and postulated this phenomenon to be a means by which cells may be signalled to increase their metabolic handling of certain compounds. Whereas substrate induction is a purely local, intracellular "milieu" response, hormonally regulated enzyme induction is an evolutionary advance whereby cells may be informed of the states of distant cells of

TABLE 1

Mean serum cortisol levels, standard deviations, t-tests of differences between correlated means for control day compared to flying days, and one-tailed probabilities for pilots and RIO's.

Activity	*Serum Cortisol (μg%)*	*t*	*df*	*p*
PILOTS (N = 9)				
Control	4.03 ± 1.64	—	—	—
Day CARQUAL	13.24 ± 6.00	5.61	16	<.0005
Night CARQUAL	9.21 ± 5.98	2.74	16	<.01
RIO'S (N = 10)				
Control	6.15 ± 3.39	—	—	—
Day CARQUAL	8.58 ± 4.99	1.32	18	N.S.
Night CARQUAL	7.96 ± 4.11	1.02	18	N.S.

the organism. This induction may be a biochemical correlate of psychologically determined stress responses via adrenal cortical activation.

Cortisol induction of tryptophan pyrrolase, the rate-limiting enzyme in the formation of kynurenine from tryptophan, has been demonstrated in intact man using serial liver biopsies to measure the formation of new enzyme protein (Altman and Greengard, 1966). Because serial liver biopsies are not feasible in a psychiatric population, a tracer technique was developed as an indirect reflection of steroid-induced changes in tryptophan turnover along inducible pathways in the intact human (Mandell and Rubin, 1966). This technique consists of intravenous administration of C^{14} labelled tryptophan, with measurement of the radioactivity of kynurenine excreted in the urine, and was used on two of our previously described manic-depressive patients during both phases of their cycles (Rubin, 1967). In both patients the radioactivity of urine kynurenine was increased severalfold during the depressive phases, when plasma steroids were high, as compared to mania, when plasma steroids were low (Figs. 4 and 5). This finding suggests a peripheral metabolic effect of stress-induced adrenal cortical activation, namely corticoid induction of hepatic tryptophan pyrrolase.

Conceivably, a psychological stress of a particular magnitude and duration in a genetically susceptible person may cause reversible shifts in intermediary metabolic pathways, via activation of the pituitary-adrenal axis and corticoid induction of susceptible enzymes, resulting in endogenous production of aberrant metabolites which may have psychotogenic or other central nervous system effects. Tschudy *et al.*

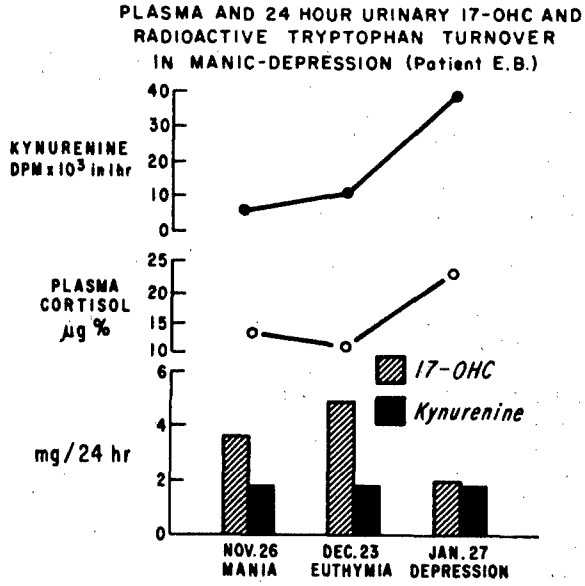

Figure 4. Radioactive tryptophan metabolism in a rapidly cycling manic-depressive patient.

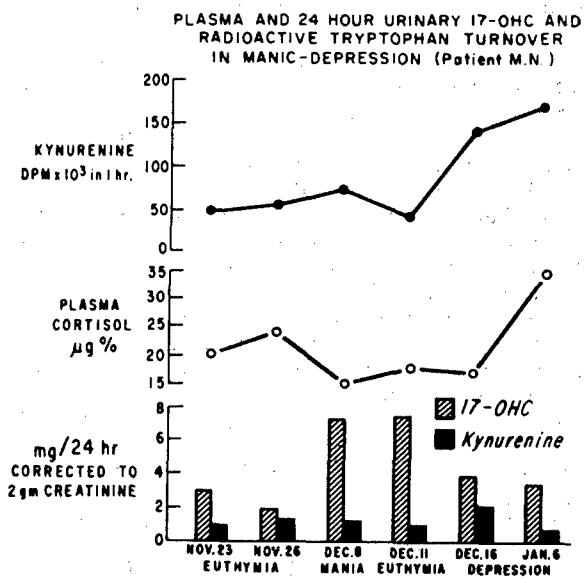

Figure 5. Radioactive tryptophan metabolism in a rapidly cycling manic-depressive patient.

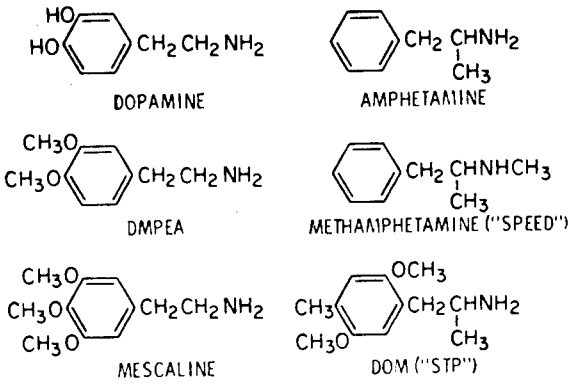

Figure 6. Some phenylethylamine-like compounds pertinent to psychiatry.

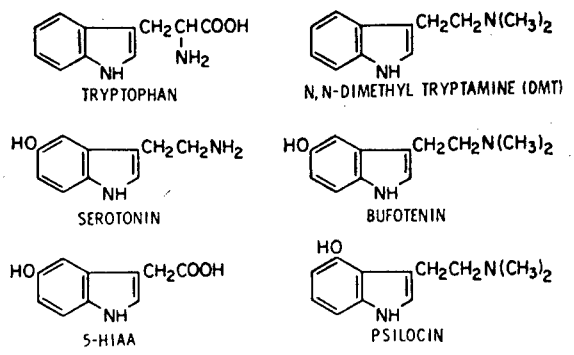

Figure 7. Some indole compounds pertinent to psychiatry.

(1965) showed this mechanism to be operative in exacerbations of acute intermittent porphyria in which there is a severalfold increase, by induction, of the rate-controlling enzyme of porphyrin biosynthesis. This was the first demonstration of a genetically inherited "overproduction" disease. Several investigators have suggested that increased shunting of tryptophan through the kynurenine pathway may lead to a deficiency of 5-hydroxytryptophan, or serotonin, in depression (Richter, 1967; Lapin and Oxenkrug, 1969).

Also, a number of methylated indole and phenylethylamine compounds are psychotogenic, and an abnormality of transmethylation pathways has been suggested as a biochemical substrate of psychoses (Kety, 1967). Figure 6 illustrates some methylated phenylethylamines. Dopamine is a naturally occurring central neurotransmitter. DMPEA has been found by some investigators to occur more commonly in the urine of schizophrenics than in normals. Mescaline is a potent hallucinogen, and amphetamine, methamphetamine, and DOM are all psychotogenic. Figure 7 illustrates some methylated indolamines. Tryptophan is an essential amino acid. Serotonin is a naturally occurring central neurotransmitter; 5-HIAA is its urinary end metabolite. DMT, bufotenin, and psilocin are all capable of producing mental symptoms. Recently an enzyme important in transmethylation, methionine adenosyltransferase, was shown to be inducible by corticoids (Pan *et al.*, 1968), providing a biologic basis for another link in the theoretical chain between psychological stress or anxiety and endogenous production of aberrant psychotogenic metabolites.

REFERENCES

Altman, K., and Greengard, O. (1966). Tryptophan pyrrolase induced in human liver by hydrocortisone; effects on excretion of kynurenine. *Science*, **151:** 332.

Brady, J. V., Porter, R. W., Conrad, D. G., and Mason, J. W. (1958). Avoidance behaviour and the development of gastroduodenal ulcers. *J. Exper. Anal. Behav.*, **1:** 69.

Bunney, W. E., Jr., Hartmann, E. L., and Mason, J. W. (1965). Study of a patient with 48-hour manic-depressive cycles II. Strong positive correlation between endocrine factors and manic defence patterns. *Arch. Gen. Psychiat.*, **12:** 619.

Cope, C. L. (1965). Some adrenal facts and fancies. *Proc. Roy. Soc. Med.*, **58:** 55.

Curtis, G. C., Fogel, M. L., McEvoy, D., and Zarate, C. (1966). The effect of sustained affect on the diurnal rhythm of adrenal cortical activity. *Psychosom Med.*, **28:** 696.

Davis, R. C. and Berry, F. (1963). Gastrointestinal reactions during a noise avoidance task. *Psychol. Rep.*, **12:** 135.

Hamburg, D. A. (1962). Plasma and Urinary Corticosteroid Levels in Naturally Occurring Psychologic Stresses, in Korey, S. (ed.): *Ultrastructure and Metabolism of the Nervous System*. Baltimore, Williams & Wilkins.

Kety, S. S. (1967). The Relevance of Biochemical Studies to the Etiology of Schizophrenia, in Romano, J. (ed.): *The Origins of Schizophrenia*. Amsterdam, The Netherlands: Excerpta Medica Foundation.

Knox, W. E. (1963). The adaptive control of tryptophan and tyrosine metabolism in Animals. *Trans NY Acad. Sci.*, **25:** 503.

Lapin, I. P. and Oxenkrug, G. F. (1969). Intensification of the central serotoninergic process as a possible determinant of the thymoleptic effect. *Lancet*, **1:** 132.

Levitt, E. E., Persky, H., and Brady, J. P. (1964). Hypnotic Induction of Anxiety: A Psychoendocrine Investigation. Springfield, Charles Thomas.

Mandell, A. J. and Rubin, R. T. (1966). ACTH-Induced changes in tryptophan turnover along inducible pathways in man. *Life Sci.*, **5:** 1153.

Mason, J. W. (1959). Psychological influences on the pituitary-adrenal cortical system. *Rec. Prog. Horm. Res.*, **15:** 345.

Mason, J. W. (1964). Psychoendocrine Approaches in Stress Research, in *Symposium on Medical Aspects of Stress in the Military Climate*. Washington, D.C., Walter Reed Army Institute of Research.

Mason, J. W. (1968). A review of psychoendocrine research on the pituitary-adrenal cortical system. *Psychosom. Med.*, **30:** 576.

Mason, J. W., Brady, J. V., and Tolliver, G. A. (1968). Plasma and urinary 17-hydroxycorticosteroid responses to 72-hr avoidance sessions in the monkey. *Psychosom. Med.*, **30:** 608.

Michael, R. P. and Gibbons, J. L. (1963). Interrelationships between the endocrine system and neuropsychiatry. *Internat. Rev. Neurobiol.*, **5:** 243.

Miller, R. G. (1968). Secretion of 17-hydroxycorticosteroids (17-OHCS) in military aviators as an index of response to stress: a review. *Aerosp. Med.*, **39:** 498.

Pan, F., Chang, G., Lee, S., and Tang, M. (1968). Induction of methionine adenosyltransferase in rat liver by corticosteroids. *Proc. Soc. Exper. Biol. Med.*, **128:** 611.

Persky, H. Grosz, H. J., Norton, J. A., and McMurtry, M. (1959). Effect of hypnotically-induced anxiety on the plasma hydrocortisone level of normal subjects. *J. Clin. Endocr.*, **19:** 700.

Richter, D. (1967). Tryptophan Metabolism in Mental Illness, in Himwich, H. E.; Kety, S. S.; and Smythies, J. R. (eds.): *Amines and Schizophrenia*. Oxford, England: Pergamon Press.

Rubin, R. T. (1967). Adrenal cortical activity changes in manic-depressive illness: influence on intermediary metabolism of tryptophan. *Arch. Gen. Psychiat.*, **17:** 671.

Rubin, R. T. (1968). Multiple biochemical correlates of manic depressive illness. *J. Psychosom. Res.*, **12:** 171.

Rubin, R. T. and Mandell, A. J. (1966). Adrenal cortical activity in pathological emotional states: a review. *Amer. J. Psychiat.*, **123:** 387.

Rubin, R. T., Young, W. M., and Clark, B. R. (1968). 17-hydroxycorticosteroid and vanillylmandelic acid excretion in a rapidly cycling manic-depressive. *Psychosom. Med.*, **30**: 162.
Rubin, R. T., Rahe, R. H., Arthur, R. J., and Clark, B. R. (1969). Adrenal cortical activity changes during underwater demolition team training. *Psychosom. Med.*, in press.
Rubin, R. T., Miller, R. G., Arthur, R. J., and Clark, B. R. (1969). Differential adrenocortical stress response between navy pilots and their flight officers during aircraft carrier landing practice. *Psycho. Reports*. In press.
Sachar, E. J., Mason, J. W., Kolmer, H. S., and Artiss, K. L. (1963). Psychoendocrine aspects of acute schizophrenic reactions. *Psychosom. Med.*, **25**: 510.
Sachar, E. J., Fishman, J. R., and Mason, J. W. (1965). Influence of the hypnotic trance on plasma 17-hydroxycorticosteroid concentration. *Psychosom. Med.*, **27**: 330.
Sachar, E. J., Cobb, J. C., and Shor, R. E. (1966). Plasma cortisol changes during hypnotic trance. *Arch. Gen. Psychiat.*, **14**: 482.
Sachar, E. J., Mackenzie, J. M., Binstock, W. A., and Mack, J. E. (1967). Corticosteroid responses to psychotherapy of depressions. I. Elevations during confrontation of loss. *Arch. Gen. Psychiat.*, **16**: 461.
Selve, H., (1956). *The Stress of Life*. New York. McGraw-Hill.
Tschudy, D. P., *et al.* (1965). Acute intermittent porphyria: the first overproduction disease localized to a specific enzyme. *Proc. Nat. Acad. Sci.*, **53**: 841.

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	ROLE	WT	ROLE	WT	ROLE	WT
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Corticol steroids						
Anxiety						
STress						
Human subjects						