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Reaction of the Adrenal Cortex to Emotional Stress

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ALTHOUGH it has been generally assumed that psychological forces influence adrenocortical activity, the number of published studies on this subject is limited. Many of these studies have been made on small animals where the extrapolation of results to man is at best controversial.[7, 9-11, 21, 37, 42] Investigations in man have been generally indecisive because of the inadequacy of methods used to assess adrenocortical function.[6, 8, 13, 15, 19, 25, 28, 30, 31, 33, 38, 40] New methods of analysis for steroids of adrenocortical origin in blood and urine have made possible a more quantitative approach to the problem. This study was designed to investigate the influence of psychological stress upon adrenocortical function, and to compare the changes in the 17-hydroxycorticosteroid levels found during emotional upset with those produced by other physical, chemical and endocrine stresses.

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Subjects were university students, hospital and laboratory personnel, patients on the psychiatric ward, or psychiatric outpatients.

Methods

The concentration of the 17-hydroxycorticosteroids (17,21-dihydroxy,20-ketosteroids) in the peripheral plasma was determined by the method of Nelson and Samuels, and their excretion in the urine by the method of Glenn and Nelson. These techniques permit a more accurate evaluation of adrenocortical function in man, since they approximate the concentration in the blood and urine of free or loosely conjugated 17-hydroxycorticosterone, compound F, which is the principal hormone secreted by the adrenal cortex in man.

In the case of blood studies 30-cc. samples were collected at appropriate intervals, using heparin as an anticoagulant. These were centrifuged, and the plasma removed and placed in a refrigerator. The urinary studies were made on 4- to 6-hour specimens which were collected for comparable periods during each test day. It was determined in preliminary studies on normal subjects that there is a diurnal rhythm in the urinary excretion of 17-hydroxycorticosteroids.[27, 34] It was also noted that the quantity of steroid excreted by any single individual during the same 4- to 6-hour period of the day fluctuates very little from day to day.[27] Urine samples were stored in a deep freeze.

Measurement of Emotional Upset

It was possible to measure accurately, with-

in a microgram, the plasma concentration of the 17-hydroxycorticosteroids. The estimate of psychological stress was a less exact procedure, since there are no good techniques available to isolate and to measure accurately different emotions. No attempt was made to distinguish systematically between various types of emotional disturbances such as fear, rage, elation and depression, or conscious and unconscious affect. The degree of emotional disturbance exhibited by subjects, and by this is meant evidence of anxiety and tension, was estimated by one observer (E.L.B.). In addition the experimental subjects were also interviewed to obtain an account from them of their emotional state. Subjects were graded as either relatively calm or emotionally disturbed. At times the reaction was graded on a scale from 0 to 5 in which zero represented complete calm and 5 a disintegrative panic. All estimates of emotional upset were made without knowledge of chemical results. The particular stress experiments will be defined and explained in the section of the paper devoted to experimental results.

Blood Steroids—Normal Data

The normal level of the 17-hydroxycorticosteroids in the plasma at 8 to 8:30 A.M., based upon 267 studies of normal subjects, is 13 μg. with a standard deviation of 6 μg. The 95 percentile range for this normal group is 3.5 μg. to 26 μg. and the absolute range 2 μg. to 34 μg.[5] The normal diurnal rhythm is characterized by highest values in the early morning, and a drop to a lower plateau during the rest of the day and the evening.[5, 27] All experimental results were compared to these data.

Studies of Blood-Steroid Changes

Psychiatric Patients

Early in the study a group of 27 patients admitted to the psychiatric service was investigated. All blood samples were taken at approximately 8:00 A.M. on the morning after admission. Concomitantly, an estimate of emotional disturbance was recorded. Nineteen of these patients were judged to be disturbed and 8 calm. The psychiatric status ranged in the disturbed group from a condition of maniacal excitement in one combative paranoid schizophrenic (Subject W) to mild anxiety and tension in several of the other patients. The majority were schizophrenic and most were suffering from relatively acute psychotic disturbances. The mean steroid value for the disturbed group was 22 ± 8 μg. In contrast, the 8 patients who were judged to be calm and whose anxiety was well controlled demonstrated a mean steroid level of 13μg. Since a group of 267 normal subjects had a mean steroid level of 13 ± 6 μg., the difference between this and the values of the emotionally disturbed patients was highly significant ($p<.001$), indicating less than a 1:1000 probability that this difference may have occurred by chance alone (Fig. 1 and Table 1).

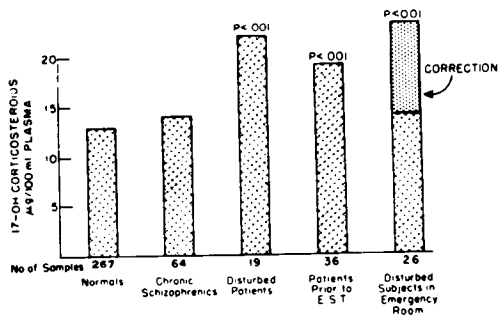

Fig. 1. Mean steroid levels.

Sixty-four studies were made on 26 chronic schizophrenic subjects who had been psychotic for 5 years or more. They were disorganized schizophrenics of the hebephrenic variety whose manifest anxieties and psychological turmoil appeared to be low. Their average steroid values were normal—14 ± 6 μg. per 100 cc. plasma. We have made extensive studies which indicate that schizophrenics have normally responsive adrenocortical systems.[1] It was our interpretation that these chronic schizophrenics had normal steroid levels because their anxieties and tensions were low or, in other words, their anxieties were bound by their delusions, hallucinations.

bizarre behavior and their withdrawal from reality (see Fig. 1).

Although emotionally disturbed patients tended to have elevated steroid levels while those of normal subjects and chronic schizophrenics were lower, there were many individual exceptions. One disturbed patient whose anxiety and tension were judged to be near maximum (level of 4) had a blood level of only 6 μg./100 cc. plasma. In contrast several chronic schizophrenics and apparently undisturbed normal subjects had values of 30 μg./100 cc. plasma or more. It appeared therefore that although group tendencies were clear, it was not possible to predict in any single case what the steroid value might be. It seemed probable that the level of 17-hydroxycorticosteroids in the blood, although influenced by emotional factors, must be controlled also by other mechanisms.

TABLE 1. PSYCHIATRIC PATIENTS

Subject	*Sex*	*Diagnosis*	*Level of anxiety*	*17-OH-CS (μg./100 cc. plasma)*
C.	M	Schizo-affective disorder, manic phase	4	35
E.	F	Schizophrenic reaction, chronic; paranoid type	3	33
J.	F	Schizophrenic reaction, acute; catatonic excitement	4	26
Ch.	F	Schizophrenic reaction	3	22
C.	F	Psychotic depression, moderate agitation	3	21
O.	M	Alcoholism with delirium tremens	2	29
R.	F	Anxiety hysteria with agitated depression	3	22
S.	F	Organic psychosis; bromide intoxication, confusion, and agitation	3	22 22 30
R.	F	Reactive depression	3	25
M.	F	Schizophrenic reaction, acute	4	23
G.	M	Arteriosclerotic brain disease with confusion and disorientation	2	16
S.	F	Reactive depression, moderate	2	14
D.	F	Anxiety reaction, moderately severe	3	19
C.	M	Character neurosis with anxiety and depression	3	18
W.	F	Anxiety hysteria with tearfulness, anxiety and tremulousness	3	12
N.	F	Schizophrenic reaction with anxiety, fearfulness	3	19
W.	M	Schizophrenic reaction, paranoid type severely disturbed, combative	4	6
R.	F	Schizophrenic reaction, calm and flat	0	15
C.	F	Schizophrenic reaction, chronic	0	12
S.	F	Organic psychosis; bromide intoxication	0	12
Se.	M	Schizophrenic reaction	0	14
W.	F	Conversion hysteria	1	11 16
B.	F	Neurotic reaction with polysurgery	1	18
BU.	F	Schizophrenic reaction, chronic	0	2

Values Prior to Electroshock

Another group of subjects was studied at approximately 8:00 A.M. just prior to receiving electroconvulsive therapy. These individuals were disturbed people, primarily acute schizophrenics and depressives. Many were also apprehensive at the prospect of shock therapy. The average level of the 17-hydroxy-

corticosteroids in the peripheral blood of these subjects was 19 ± 4 μg. with a highly significant p value of <.001 (see Fig. 1).

In analyzing the data it may be argued that some of these subjects had received a number of electroshocks and that the repeated administration of electroconvulsive therapy may modify adrenocortical physiology. It seems unlikely, however, that repeated electroconvulsions produce any more than transient disturbances in adrenocortical activity since the increases in the level of blood steroids are slight and last for no more than 2 hours after shock therapy. Steroid concentrations then return rapidly to normal levels.[3] Furthermore, electroconvulsive treatments were given infrequently—usually 3 times a week and at times less often.

"Emergency Room"

To determine further whether a consistent elevation in blood steroids occurs under conditions of emotional stress, another group of disturbed subjects was selected and studied. A physician was stationed in the emergency room of the County Hospital. It was his task to take blood specimens from individuals who came in to the emergency room in a near panic. No subject was included unless he was medically well. In the main, the individuals selected were those whose children, wives, friends, or parents had recently been injured or suddenly stricken with an acute illness.

In all, 26 subjects were examined. A brief description of the circumstances, the hour, age of the individual, and steroid levels in the plasma has been tabulated (Table 2). Since all blood samples were drawn at hours other than 8:00 in the morning, it was necessary to correct these values in order to compare them to the normal values at 8:00 A.M. The uncorrected mean value for the group was 14 μg. When recalculated, by the statistical technique of standard scores, in respect to the normal diurnal curve,[5, 27] the equivalent was 23 ± 7 μg. at 8:00 A.M. This represented a highly significant increase over normal levels, with a p value <.001 (see Fig. 1). Again, there were several individuals whose values were in the lower range despite considerable emotional disturbance.

Medical Examinations

Subjects were studied in another emotionally disturbing situation. Sophomore medical students were bled between 8:00 and 8:30 A.M. prior to their comprehensive examination on the work of their first two years. Considerable emphasis had been placed upon the examination by the faculty and this was well known by the students.

A comparable group of 23 junior medical students were investigated on the morning of their final examination in clinical medicine. Although this examination is usually not too difficult, it had acquired a reputation for "tricky" questions and strict grading, and consequently was the most feared final examination in that year.

In addition, to the normal group of 267 values, three other normal groups were established as controls. These were composed of 14, 52, and 96 studies on students and residents. As can be seen in Fig. 2, plasma steroid levels were significantly elevated on the morning of both examinations. One group just prior to examination averaged 18 ± 6 μg. and the other 20 ± 7 μg.

Fourteen students were studied during a control period as well as on the day of the examinations. Their blood steroid responses and levels of anxiety are charted (Fig. 3). With three exceptions, all steroid levels were higher on the test day. In the 3 cases where patterns were reversed, one subject reported an anxiety level of 1 and the others of 2. In a single subject, a level of 43 μg. occurred on the day of the examination. This value has been included on the chart, although it was such a deviant value that it may represent a laboratory error.

Individual Studies

Two "normal" subjects (M.M. and R.R.) were studied over a period of several months (Fig. 4). Bloods were drawn at intervals of 1–3 times a week. On each occasion the emotional tension of the individual was estimated by both investigator and subject.

TABLE 2. EMERGENCY-ROOM SUBJECTS

Subject	Sex	Age	Time of sample	Level of anxiety	17-OH-CS μg./100 cc. plasma	Stressful circumstance
M. G.	M	43	10:00 P.M.	3	20	Son fell off bike, received lacerations of scalp with considerable bleeding. Father (M. G.) nervous and excited.
T. F.	F	35	9:00 P.M.	3	12	Son detonated shotgun shell and cap lodged in his arm. Began to scream and rushed to hospital by mother (T. F.), who was quite disturbed.
B. B.	M	21	10:00 P.M.	3	11	Brought friend with acute abdominal pain to hospital.
H. B.	M	23	8:30 P.M.	4	17	Baby son developed fever 104° F., vomited and coughed. Father (H. B.) distraught.
E. L.	F	53	2:00 P.M.	4	12	Husband brought to hospital in morning for examination. She (E. L.) feared he might have an abdominal malignancy, and was tearful, upset, and felt faint.
R. W.	M	43	1:00 P.M.	4	13	Father injured in auto accident and son called to emergency room by police. He (R. W.) was obviously extremely upset.
G. G.	M	22	10:00 P.M.	4	10	Wife attempted suicide with mercury at 3:30 P.M. He (G. G.) was still very anxious and upset.
W. G.	F	30	11:30 P.M.	4	15	Argument with husband while driving car. Jumped out of auto when it had almost stopped and landed on buttocks. There was no injury but she was upset—crying and angry.
R. G.	M	27	11:30 P.M.	3	18	Husband of W. G. He was upset and guilty.
R. H.	F	52	1:30 P.M.	5	23	Elderly asthmatic; mild attack, wheezing but frightened and disturbed.
H. D.	M	38	11:30 P.M.	5	15	12-year-old daughter sick 3 days with pyelonephritis. He (H. D.) crazy with worry, hasn't slept, chain-smoked.
G. P.	F	24	8:00 P.M.	4	13	Cardiac neurotic. Husband to have operation. She (G. P.) frightened that she was about to have heart attack.
M. L.	F	32	2:00 P.M.	4	11	Brought daughter to hospital, fearful she might have appendicitis. Mother (M. L.) was fearful, tense, apprehensively watched every movement of doctor.
L. M.	F	28	10:30 P.M.	3	11	Noticed "boils" in her throat. "Boils" proved to be taste buds. She was excited and apprehensive.
J. B.	F	19	12:00 P.M.	3	13	Divorced for 9 months but now 13 weeks pregnant. Came to be examined for "swollen vagina" which proved to be an uninflamed, nontender Bartholin cyst. She was guilty, upset, "very unstrung."
C. G.	M	36	1:30 P.M.	4	23	Wife had 2 grand mal seizures. Both brought to hospital by police ambulance. He (C. G.) was distraught and nervous; "always the nervous type."
D. C.	F	35	10:30 P.M.	5	11	Father brought to hospital with severe compound fractures of leg after auto accident. Daughter (D. C.) crying and nearly "hysterical."

TABLE 2 (*Continued*)

Subject	*Sex*	*Age*	*Time of sample*	*Level of anxiety*	*17-OH-CS μg./100 cc. plasma*	*Stressful circumstance*
G. H.	M	24	2:00 P.M.	4	18	Wife admitted with acute appendicitis. He (G. H.) was nervous and excited about her condition, almost fainted when his blood was drawn.
M. M.	F	27	6:30 P.M.	4	7	2-year-old child fell on glass and severely lacerated himself. Mother (M. M.) was crying, feeling guilty, and chain-smoking.
R. M.	M	27	6:30 P.M.	3	7	Husband of M. M. He also was quite upset.
J. G.	F	26	9:30 P.M.	4	15	Being treated in O.P.D. for neurosis. She had argument with husband in the early evening, and now feels angry and "shaky."
I. H.	F	38	6:00 P.M.	3	12	Son lacerated finger which bled profusely. Mother couldn't locate family physician. She (I. H.) was afraid "something might have happened to his finger."
J. A.	M	33	10:30 A.M.	4	19	1-year-old daughter spilled a cup of hot coffee over her chest. Father brought screaming baby to emergency room. He (J. A.) was pacing floor, very upset.
R. M.	M	28	12:30 A.M.	4	13	While he (father) was watching a movie at a drive-in theatre, his 14-year-old child had 3 convulsions. Father (R. M.) was shaken and nervous.
C. F.	F	25	1:00 A.M.	5	14	Her mother had an attack of dyspnea, began to pull her hair and tear at her dress. The subject (C. F.) rushed her mother to the hospital. She was very upset, crying that her mother was suffocating.
K. F.	M	22	1:00 A.M.	4	22	Brother of C. F. and son of patient. He drove car and, although not as upset as his sister, he was quite apprehensive.

Unstable Personality

Patient R.R. stated "I feel depressed, started after writing report, fighting neurosis, tense, and feel need to talk about troubles." He was classified as disturbed and his steroid titer was

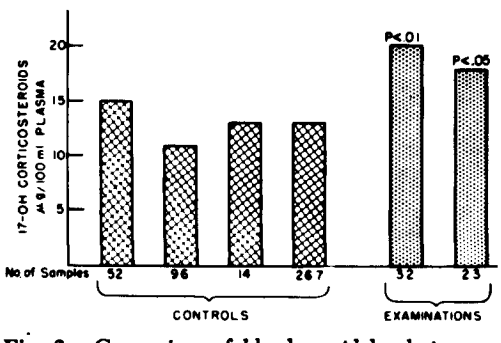

Fig. 2. Comparison of blood-steroid levels in controls and students apprehensive of examinations.

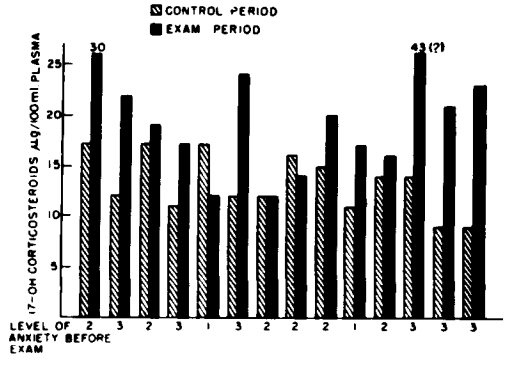

Fig. 3. Comparison of responses of 14 students before and on day of examination.

31 μg. On another occasion the same subject announced he was "feeling pretty good today, optimistic, buoyant, outgoing, aggressive, somewhat happy, calmer than I've been in the last two weeks, mentally alert," and he was adjudged to be relatively calm. His steroid level was 17 μg.

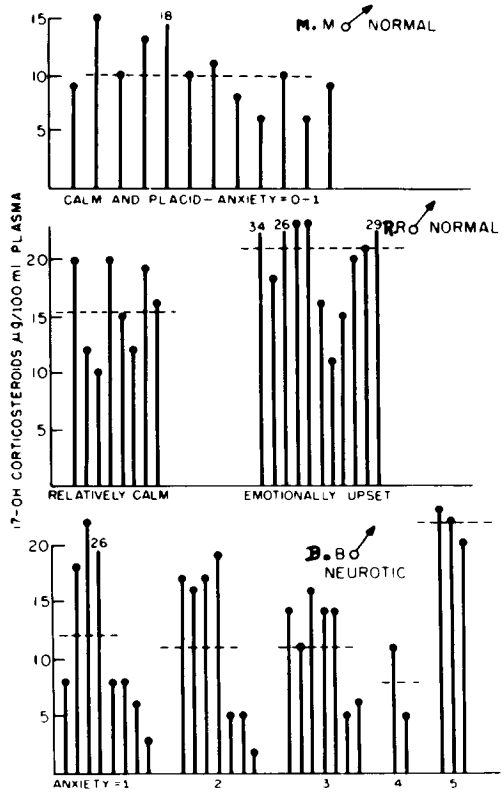

Fig. 4. Fluctuations in blood-steroid level in 3 individual studies. *Note:* The last six values during both the "calm" and "upset" periods of Subject R. R. (normal) were determined on blood drawn at 12 noon. All studies on Subject B (psychoneurotic) were made at 5:00 or 6:00 P.M. In each case values were recalculated by the technique of standard scores as explained earlier in the text, and all have been represented on the figure by the equivalent values at 8:00 A.M. All other blood samples were drawn at approximately 8:00 A.M. The broken lines represent the average levels for the groups of values.

Patient R.R. was selected for study because he was an intense, anxiety-laden individual with wide mood swings. Blood steroid values in his case were classified into two groups. One represented those days when he was relatively calm and the other those times when he was upset, disturbed, and anxious. Although there was some overlapping in values between the two groups, the average for the periods of emotional disturbance was 5 μg. higher than for those days when he was calm.

Stable Personality

Another subject, M.M., was a stable, well-integrated, generally happy and untroubled person. Not only was he an excellent emotional contrast to the first subject but as it developed later considerably different "steroid-wise" as well. Mood fluctuations were rare, and during the entire course of the study his level of anxiety was never higher than 1. During this period his blood steroid levels fluctuated between 6 and 18 μg. The average was 10 μg. The variations in steroid levels in his case did not correlate with any obvious changes in his affective state. At both extremes of steroid levels, he judged himself and was evaluated by the examiner to be unusually free of anxiety.

Two explanations seemed plausible. Either these fluctuations were related to emotional changes too subtle and well concealed to be detected by these crude procedures, or the steroid variations were related to other unidentified physiological activities. It was interesting that at least in this single untroubled individual, the average blood steroid level over a period of several months was in the lower range of normal.

Severe Psychoneurosis

Patient B.B. was followed in psychotherapy for over a year and a half. He was suffering from a severe neurosis, characterized by phobias, obsessional ruminations, and periods of depersonalization. He was classified as a severe psychoneurotic but could have been called with equal validity a "borderline" schizophrenic. His moods fluctuated constantly between states of moderate tension and severe panic. On these latter occasions he would be overwhelmed by a feeling of inner dissolution,

so terrifying that heavy sedation and hospitalization were necessary. Before every therapeutic session, which took place at 4:00 or 5:00 P.M., he would estimate his level of anxiety and tension. Since he was a conscientious and meticulous person, this was all done with exactitude. The therapist during the course of the hour also made his own estimate. The patient was studied on three

troshocks. Ten blood studies were made on him during his 4 months' stay in the hospital. There was a concordance between the degree of psychomotor disturbance and the level of the 17-hydroxycorticosteroids in his peripheral blood. Although not exact, the periods of disturbed behavior usually coincided with steroid levels between 20 and 35 μg. whereas 2 steroid values obtained at the termination of

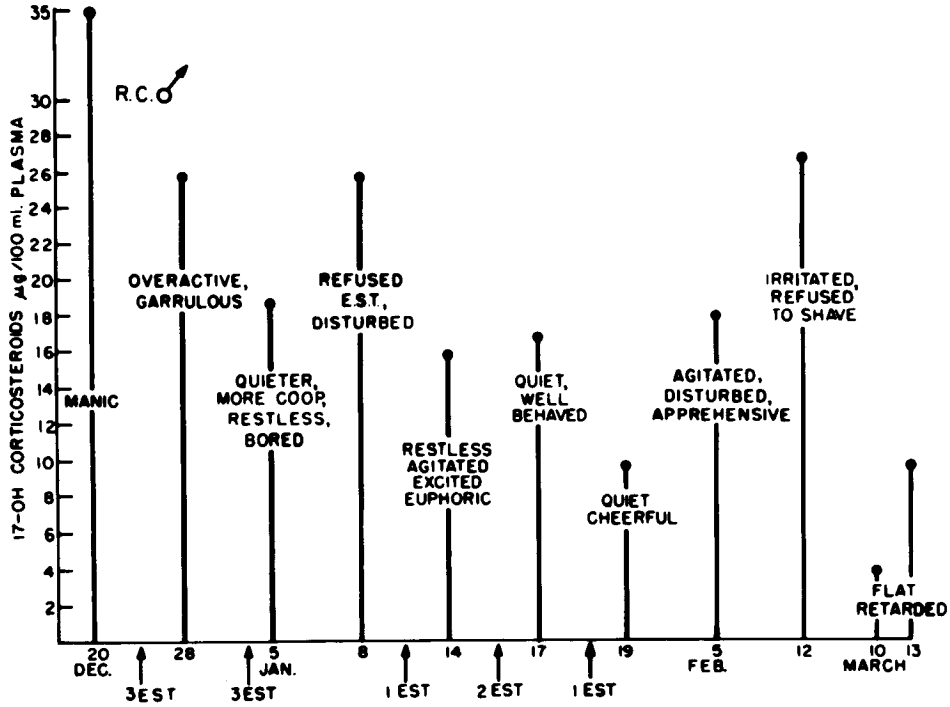

Fig. 5. Blood-steroid levels in schizophrenic patient undergoing electroshock therapy.

different occasions when his anxieties had reached the intensity of a panic and the average of his steroid levels was 10 μg. higher than during the other periods (see Fig. 4).

Manic Conditions

Two hyperactive hypomanic patients were also investigated. Patient R.C. entered the hospital in an overtalkative, overenergized state. This maniacal picture was contaminated by a thought disorder and the diagnosis of a schizoaffective reaction was made. In the course of therapy he received a series of electreatment, when he was affectively flat and retarded, were less than 10 μg. (Fig. 5).

Another, Patient E.E., was examined on admission when he was hyperactive and "supercharged." On that day the steroid level was 28 μg. The next day his psychomotor disturbance was less intense and the steroid value was 19 μg. The following day he was quite calm and his steroid titer was 14 μg.

Experimental Emotional Stresses

The preceding observations were made upon subjects who developed anxiety under

naturally occurring, uncontrolled circumstances. In such situations it was not possible to determine to what degree associated muscular activity, variations in sleep pattern, etc., contributed to the alterations in the concentrations of the 17-hydroxycorticosteroids in the plasma. Therefore, a group of rigorously controlled procedures were devised to test the influence of an artificially induced emotional disturbance upon the level of the 17-hydroxycorticosteroids in plasma.

Dull Monotonous Tasks

Four students were seated at individual desks in a one-way-vision room. They were separated by a high partition so that each was isolated. All were instructed by the experimenter, who was located in the adjoining room concealed behind the one-way-vision mirror, to draw "pumpkin faces" as rapidly as possible on paper supplied for that purpose. They were admonished not to communicate with one another. Every 3 minutes they were interrupted and asked to write briefly how they were feeling. This procedure was continued with monotonous regularity as each subject drew hundreds of small "pumpkin faces" for 1½ hours. Steroid studies were made at hourly intervals.

It had been anticipated that this dull repetitive process would prove to be disturbing, but this was not the reaction. Only one subject became moderately tense. The general pattern for the group was one of psychological withdrawal, fatigue, and disinterest, as they drew pumpkin faces *ad nauseam* (Fig. 6).

Drug Stress (Lysergic Acid)*

The psychosis-producing properties of lysergic acid (*d*-lysergic acid diethylamide) have been emphasized in recent scientific reports.[17, 26, 32, 39] Similarities between the emotional and ideational responses evoked by this drug and those seen in schizophrenia have been described. The drug appeared to be an ideal vehicle to induce an acute psychotic disturbance in the laboratory which could then be studied to elucidate the nature of the adrenocortical reaction to an acute cataclysmic psychotic episode. In actuality, the emotional reactions observed in this study were unpredictable and not schizophrenic in character. Disturbances were in the nature of "toxic" psychoses. Many of the subjects described the reactions as one of intoxication "just like being drunk." Out of the group of 15 subjects who received the drug, 9 reacted with significant emotional disturbances.

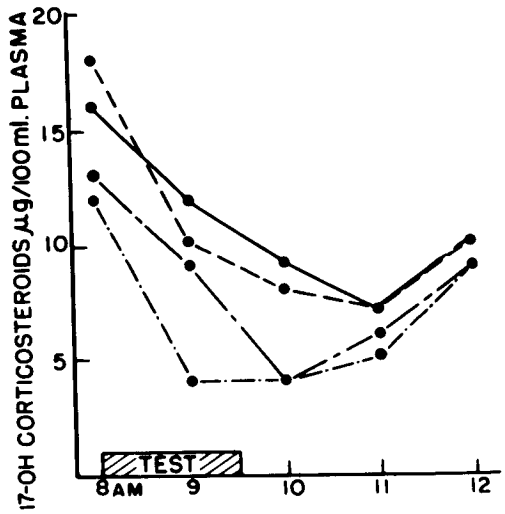

Fig. 6. Blood-steroid levels of subjects drawing pumpkin faces. These curves and the response of "emotionally calm" subjects in Fig. 7 are typical of the *normal* diurnal response of the 17-hydroxycorticosteroids in the blood.

The drug was administered orally at 8:00 A.M. in amounts of 50 to 100 µg. The effects became manifest in one-half to one hour and were maximum from 10:00 to 11:00 A.M. in most subjects.

Five individuals appeared to experience little or no emotional upset. Their mean steroid responses followed a downward curve. Five other subjects became quite disturbed. One ran through the history of her turbulent life experiences; another was overwhelmed by the terror of losing his intellectual control and a sense of depersonalization; and a third developed a short-lived but intense agitated

* We wish to thank Harry Althouse of Sandoz Pharmaceuticals, San Francisco, Calif., for the generous supplies of lysergic acid.

depression. For this group the average of the steroid values was elevated during the period of maximum emotional disturbance. The third group of subjects developed a euphoric response. One subject described it in retrospect as "a laughing jag. Whenever I saw anybody smile I would break out in practically uncontrollable laughter. I remember feeling it was quite silly to behave in such a way and

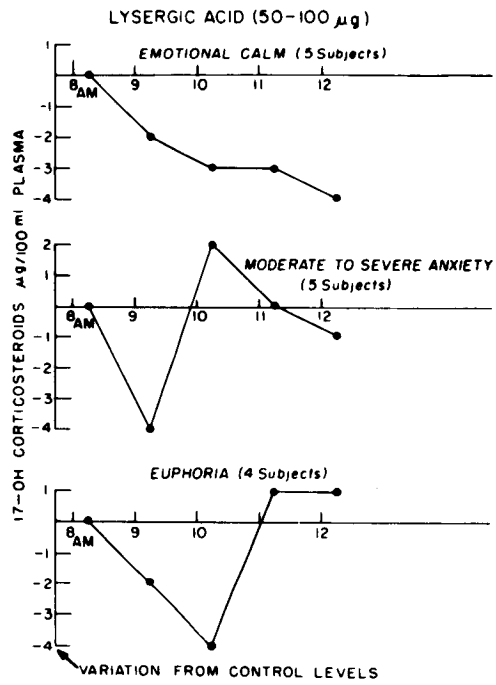

Fig. 7. Blood-steroid responses after administration of lysergic acid.

tried hard to control my laughter." All experienced paroxysms of gaiety. Several felt drunk and all acted like happy drunks. Steroid values did not follow the normal pattern. Between the hours of 10:00 A.M. and 12 noon plasma 17-hydroxycorticosteroids rose in conjunction with the euphoria (Fig. 7).

Stressful Interviews

In conjunction with steroid studies 4 psychiatric patients were interviewed for approximately 1 hour each. In each case areas of great concern to the patient were probed (Fig. 8).

"Self-Analysis"

Four normal subjects were asked to report to the laboratory for routine study. Blood samples were drawn and then each in turn was conducted to the one-way-vision room. At the door each was given a slip of paper, told to enter the room, to read the directions, and follow them. The paper read: "This is a one-way-vision room. The large mirror on the wall is a one-way-vision mirror. The people on the other side of the mirror can see and hear you but you can neither see nor hear them. You will face the mirror and at the signal begin to *talk about yourself*. You will continue for approximately ten minutes until a signal is given to stop. A number of judges will be watching you and evaluating your performance. You will be judged on clarity, fluency, and organization." After the subject spoke for a few minutes, he was interrupted routinely by an impersonal voice over the public speaking system. He was admonished in measured tones "you are not talking about yourself." Each subject floundered, stuttered, or filibustered for about 15 minutes as the case might be, and then was escorted in silence from that room to another where he remained alone for the next one-half to one hour (Fig. 9).

Stressful "Examination"

A variation on the preceding technique was used with the next group of subjects. All were students in the undergraduate school who were completing a course in elementary psychology. The night before their final examination they were informed over the telephone by their instructor that their records in the course had been excellent and they would be excused from the final test. They were asked to report instead to the Department of Psychiatry the next morning. This situation was intentionally described in the vaguest possible terms. All 5 students appeared at the Department of Psychiatry the next morning, curious, anticipating some suitable reward for their scholastic excellence. Instead, blood samples were drawn immediately. Each in turn was

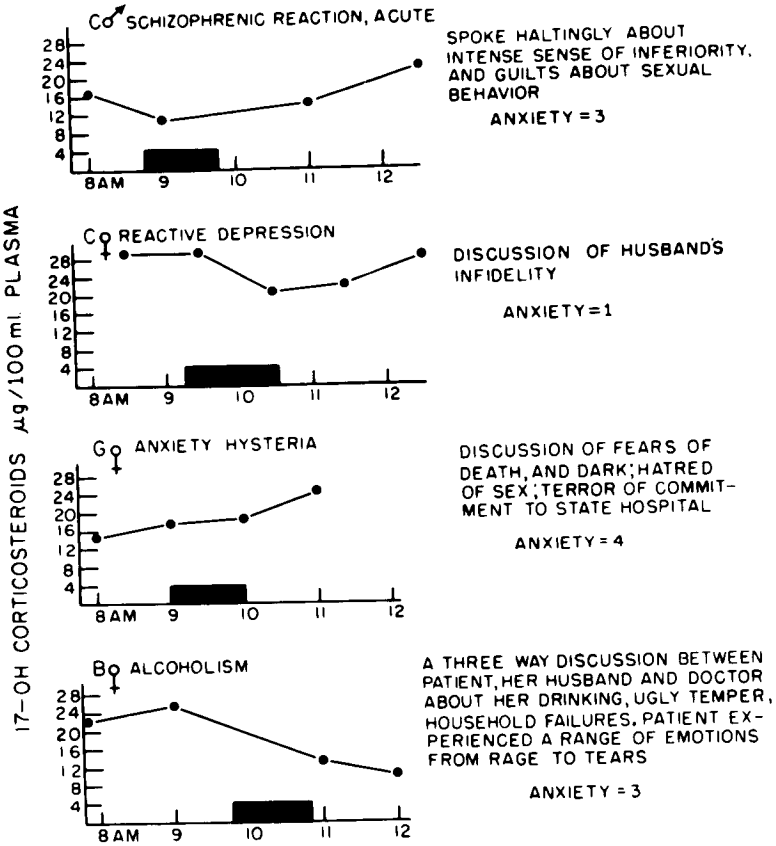

Fig. 8. Blood-steroid levels in 4 psychiatric patients undergoing stressful interviews. The black blocks represent the periods of interview.

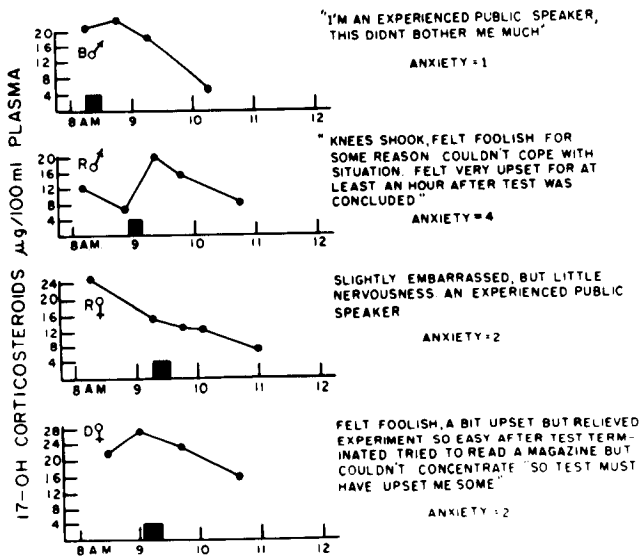

Fig. 9. Blood-steroid levels in subjects instructed to "talk about yourself."

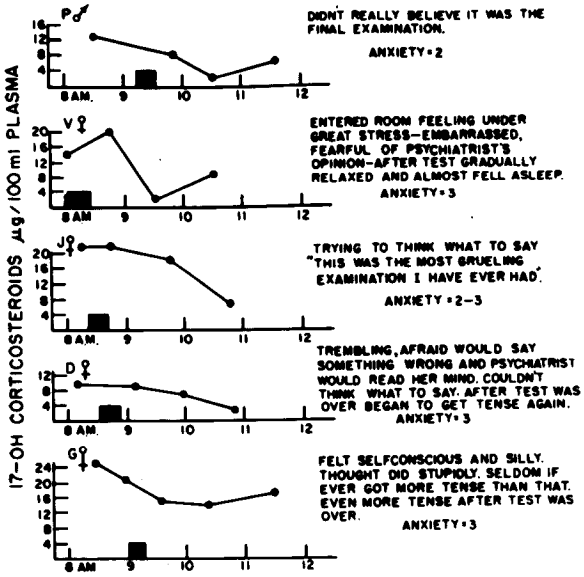

Fig. 10. Blood-steroid levels in subjects taking oral psychology "examination."

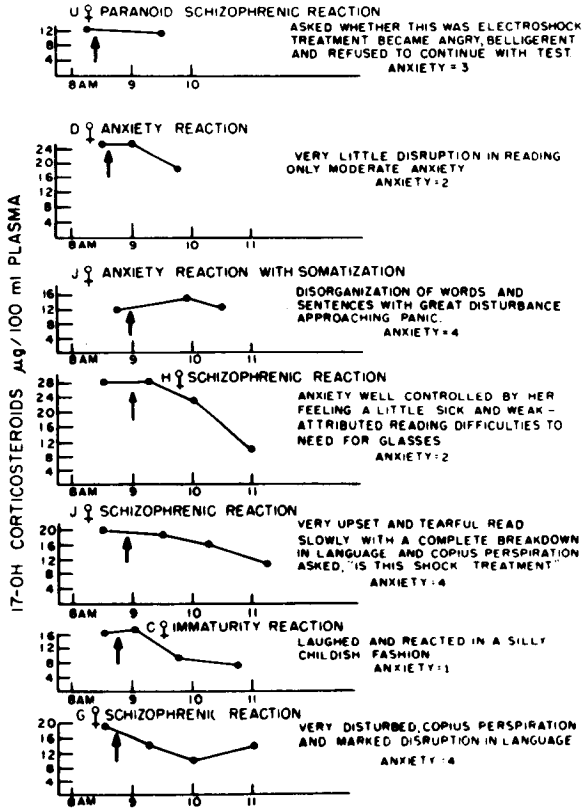

Fig. 11. Blood-steroid levels of psychiatric patients subjected to delayed speech feedback.

led to the one-way-vision room and handed a slip of paper with the following instructions: "This is a special examination which has been devised by the Department of Psychology in cooperation with the Department of Psychiatry. It is meant to test your ability to think clearly and to organize your material. This is a one-way-vision room; the large mirror on the wall is a one-way-vision mirror. The people on the other side of the mirror can see and hear you but you can neither see nor hear them. Special examiners are seated behind the mirror. They will evaluate your performance and their rating will be *your grade for the examination in Psychology* 5. You will be judged on your clarity, insight and organizational ability. You will face the mirror and at the signal begin to talk freely about yourself, your personal problems and how the material which you studied in this course has increased your understanding of yourself. You will continue to talk until the signal is given to stop." All were interrupted after a few minutes and warned they were not talking about themselves. The oral examination lasted 15 minutes. Each subject was then conducted in silence to another room where he sat alone for the next one-half to one hour (Fig. 10).

Delayed Speech-Feedback Apparatus

Seven psychiatric patients whose diagnoses ranged from that of schizophrenia to immaturity reaction were studied. All were unstable, labile individuals subject to periods of intense anxiety. Each was asked to read a short passage from a book. The written material was factual and impersonal. All subjects wore earphones and read into a microphone. The words were then fed through an electronic unit and were returned to subject via his headphones with a slight temporal delay.[23, 24, 41]

The time it takes for the word to travel from one's voice box to one's ear is a constant interval to which we are accustomed. The machine lengthens this period and in so doing disrupts established patterns. This often causes a marked disturbance in reading and thinking which is emotionally upsetting to some individuals (Fig. 11).

Results

In all, 6 different experimental stresses were employed. Although some subjects responded to these with evidence of an intense emotional reaction, other subjects were relatively unaffected. Steroid changes after these "stresses" were at the most modest, even in those subjects who experienced severe emotional disturbance.

Since steroid changes were small, and as the number of subjects studied by a single stress technique was limited, statistical evaluation of any one procedure was not possible.

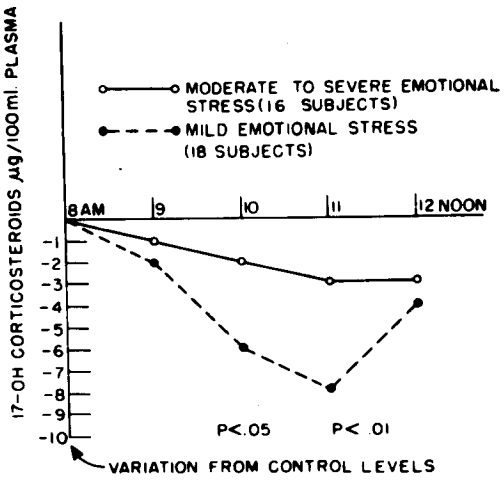

Fig. 12. Summary of responses to all experimental emotional stresses.

Furthermore, the meaning of minor steroid changes was difficult to interpret in any single trial. However, when all the results of the tests were consolidated there were sufficient data for statistical analysis. Subjects who showed little or no emotional disturbance in these stressful situations were placed in one group. This comprised 18 individuals. The other group was composed of those who responded with a moderate to severe emotional reaction and they numbered 16. The results are charted in Fig. 12. At both 10:00 A.M. and 11:00 A.M. differences between the two groups were statistically significant. On the average, emotional upset appeared to elevate the level

of 17-hydroxycorticosteroids in the peripheral blood 4 to 5 μg./100 cc. of plasma.

Individual Subject of Experimental Emotional Stress

One subject, R., was studied on 3 separate occasions with experimental "emotional stress" techniques (Fig. 13). During two of these experiments he became deeply disturbed, whereas he was calm and unaffected by the third. He was one of the individuals who was tested in the one-way-vision room. When asked to talk about himself he became flustered. He was then interrupted and told "you are not talking about yourself." For the next 15 minutes he struggled obviously disturbed and upset. When questioned an hour after the ordeal he commented, "My knees shook and my voice quivered. I felt foolish not to have talked about myself and remarked to myself 'you're an idiot.' For some reason I couldn't cope with the situation. I'm still quite upset." His steroids rose 13 μg., a most significant disruption of the normal diurnal curve.

On another occasion he received 50 μg. of lysergic acid and became euphoric. The next morning he described his feelings in greater detail to the examiner. He explained that several years ago he drank heavily, although this was contrary to the tenets of his Mormon faith. This had created a major emotional upheaval since his religious mother vehemently objected to his behavior. After a soul-shaking conflict he had conceded to his mother and abandoned alcohol. For the first time since his vow of abstinence he was intoxicated again under the influence of lysergic acid. Although aware intellectually that this was the effect of the drug and not due to alcohol, he nevertheless felt as profoundly guilty as if he had failed his mother and deserted his religious principles. In association with these disturbing intrapsychic happenings, his blood steroids rose 6 μg.

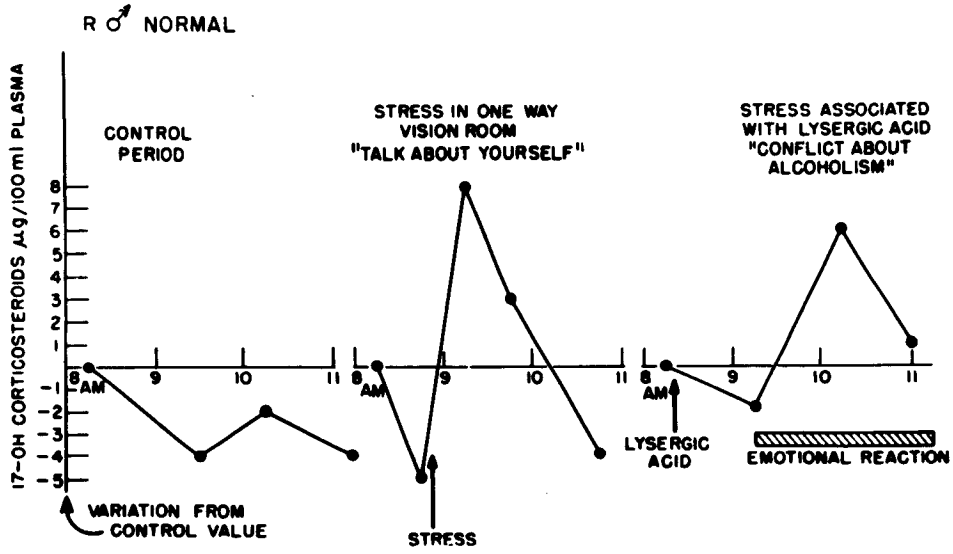

Fig. 13. Response of Subject R. to "talk about yourself" and lysergic acid.

He was also a subject a third time. During this experimental period (designated as "Control Period" in Fig. 13) he was attached to an electroencephalographic machine to determine the effects of photic stimulation on both the electrical activity of the brain and the adrenal steroids. The photic apparatus was defective and he sat for 1 hour quite calmly in the chair while the investigator vainly struggled with the recalcitrant gadget. The subject was un-

disturbed and at most mildly amused and sympathetic. His steroids followed a downward curve well within normal limits.

These three studies on the same subject were fortunate accidents. However, they did suggest dramatically the positive, albeit modest, influence of emotional upset upon the level of adrenal cortical steroids in the circulating blood.

Studies of Urinary-Steroid Changes

Urinary studies were less extensive due to the later development of the urinary technique as well as its greater complexity. Consequently, these data are incomplete and less conclusive.

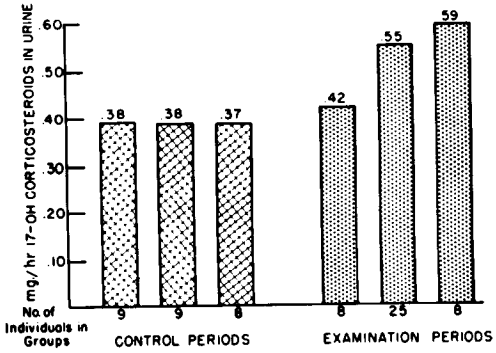

Fig. 14. Urinary-steroid levels of students before and on day of examination.

Medical Examination

Urine samples were collected in conjunction with the blood samples, from the students who took the sophomore correlative examination and the junior final examination in clinical medicine. The stress samples were taken the morning of the test. They encompassed the hours of 7:00 A.M. to 9:00 A.M. preceding the examinations as well as the next 3 hours of the examination proper—approximately 5 hours in all.

Control samples for the same period of the day were obtained from 26 students several weeks before the examinations. These samples were divided at random into 3 groups of 9, 9, and 8 specimens. The pooled samples were then analyzed. The hourly concentration of the 17-hydroxycorticosteroids was virtually identical for the 3 control groups (Fig. 14).

Stress specimens were divided into 3 groups also. One comprised the composite samples from 25 sophomores while the other 2 were collections from the juniors, subdivided into 2 groups of 8 each. All 3 values for the stressful period were higher than control levels (see Fig. 14).

The urine of 7 students who reported considerable anxiety (level of 3) before the examination were analyzed separately. In each case, values during the examination period were higher than control levels, although the maximum increase was twofold and that occurred in only 1 case ($p < .05$) (Fig. 15).

Urine volumes in general were higher on the day of the examination. However, this did not appear to be a crucial factor since there were steroid increases also in those cases where the urinary output was lower on the stressful day. Trends were remarkably consistent in the direction of an increase in the secretion of 17-hydroxycorticosteroids in the urine during this emotionally disturbing period.

Individual Study

Subject B.B., a severe neurotic whose blood-steroid responses have been described, was also studied. His urine samples were all afternoon aliquots. Consequently, values tended to be generally lower, conforming to the normal diurnal pattern of a diminished steroid excretion of adrenal steroids in the urine during the afternoon and evening hours. In this single case there was little difference in the concentration of urinary steroids during periods of relative calm and intense anxiety (Fig. 16).

Comparative Data

Plasma Steroids

It seems clear that the level of 17-hydroxycorticosteroids in the peripheral blood rises coincident with emotional upset. What remains to be documented is the relative potency of affective disturbances in this regard.

In Figs. 17 and 18 the comparative data have been graphed. In the first figure the *average* changes in the 17-hydroxycorticosteroids are depicted after intravenous injection of ACTH, Piromen, and insulin; electroconvulsion; moderate exercise; and experimentally induced emotional stress. The next figure illustrates the *maximum* changes which we have observed with these same modalities.[2, 3, 4]

It is evident that ACTH is the "master" activator under all conditions, whereas the changes observed after experimental emotional upset are the least prominent, although significant. The same hierarchy was evident when the data were analyzed to determine the maximum concentration to which the blood steroids rise after administration of various stressful agents. It was not rare for blood-steroid titers to increase to absolute levels of 50 to 70 μg. with intravenous ACTH. Piromen and electroshock both caused elevations to 35 or 40 μg., whereas emotional disturbance of the severest variety did not cause values to

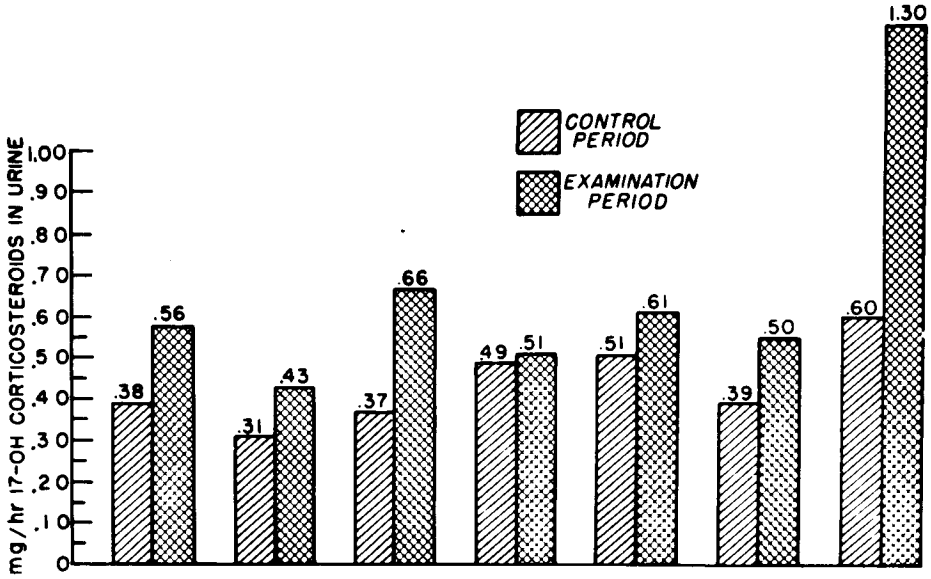

Fig. 15. Urinary-steroid levels of 7 students who reported anxiety levels of 3 before examination.

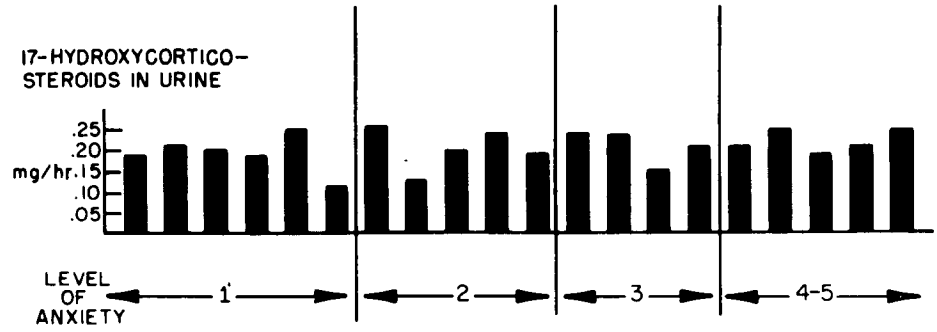

Fig. 16. Urinary-steroid levels of neurotic Subject B. B. (see Fig. 4).

rise beyond the normal physiological limits of 34–35 μg., with one exception. On several occasions under the impact of emotional stress the 17-hydroxycorticosteroids reached a concentration in the low 30's, although values usually ran lower.

Seen *in toto* there is a good reason to believe that psychological upset has a moderate effect on the concentration of the 17-hydroxycorticosteroids in the blood, that this is striking rise under circumstances of anxiety. Increases were no greater than twofold in contrast to the much larger increases reported after ACTH.[34]

Discussion

"Natural" Stress

Many emotional stresses were investigated to learn with what regularity and to what

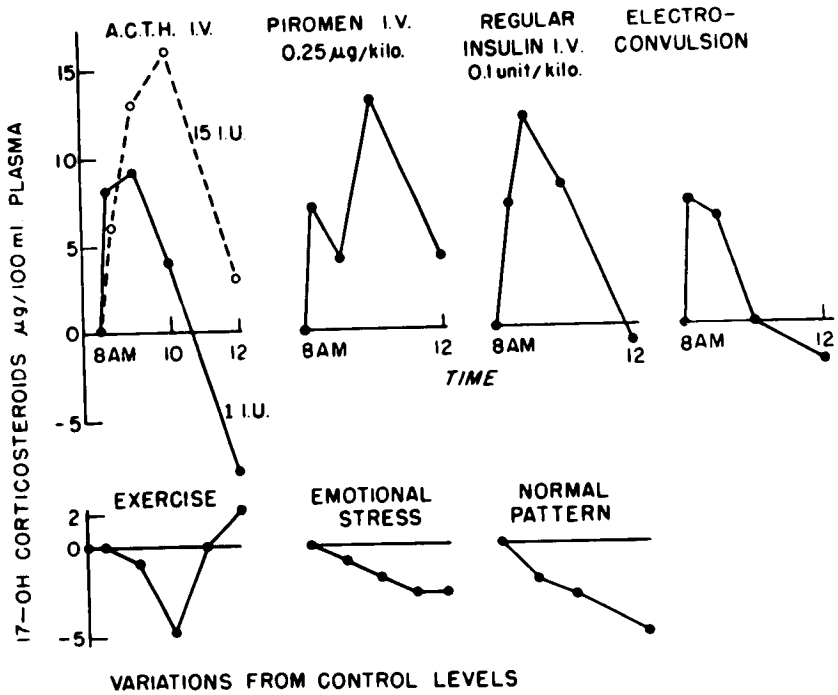

Fig. 17. Average increases in blood-steroid levels after stress.

and significant, but considerably less than the effects produced by ACTH, electroshock, insulin, and Piromen.

Urinary 17-Hydroxycorticosteroids

The mode of behavior of the urinary 17-hydroxycorticosteroids has been less well documented. The data on the students who were struggling with important medical examinations under circumstances of moderate emotional disturbance indicated a tendency for the urinary 17-hydroxycorticosteroids to degree the level of the adrenal steroids in the blood fluctuates under the impact of a variety of emotional upsets. For this reason the adults chosen for study ranged from normal subjects to chronic schizophrenics and demonstrated psychological disturbances ranging from anxiety about medical examinations to guilt over a sexual conflict.

Trends were remarkably consistent for both individual and group studies. Emotionally disturbed patients admitted to the psychiatric unit; distraught subjects seen in the emer-

gency room of the county hospital; medical students examined prior to crucial examinations; and patients about to receive electroshock therapy—as groups, all demonstrated elevated concentrations of 17-hydroxycorticosteroids in the plasma with mean values in the close vicinity of 20 μg.; an average increase of 7 μg. above normal levels. For every

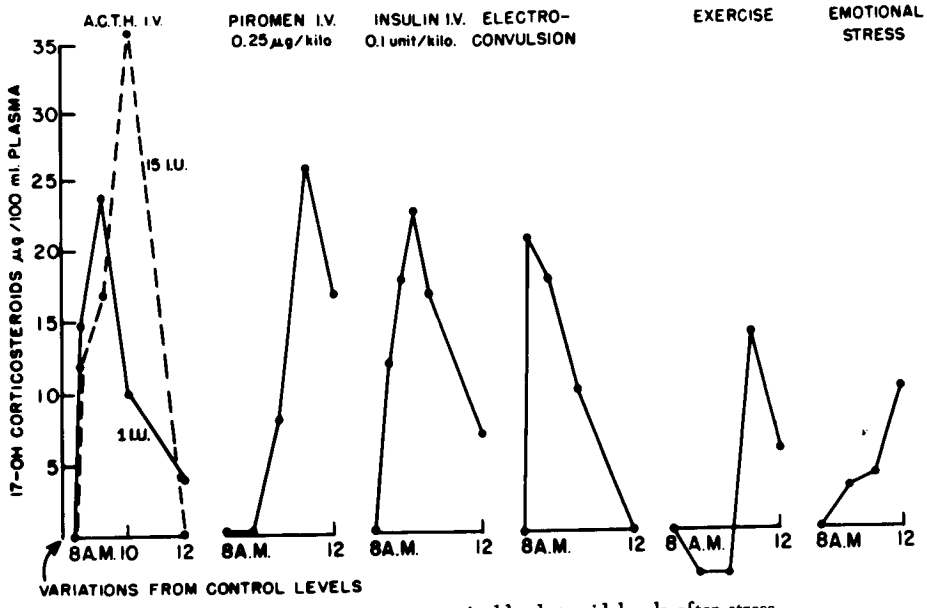

Fig. 18. Maximum increases in blood-steroid levels after stress.

one of these groups the elevation in the titer of adrenal steroids in the plasma was very significant. This was true also for individual studies. Individual medical students studied prior to examinations, the 2 normal subjects, the disturbed psychoneurotic, and the 2 patients with manic syndromes all confirmed the previous observation that emotional perturbation is usually associated with an increase in the level of the 17-hydroxycorticosteroids in the plasma. These increases, although consistent, were not large. In general, they averaged 5–10 μg. over normal.

Experimental Stress

In contrast, experimental emotional stresses were short-lived and in many cases failed to produce dramatic emotional responses. In any single study steroid changes could not be clearly evaluated since variations were small and inconsistent. It was only after the subjects were separated into those who exhibited clear-cut affective disturbances and those who were relatively undisturbed that a significant change could be demonstrated. Here again adrenal steroids in the plasma rose moderately under the influence of emotional upset.

Significance of Higher 17-Hydroxycorticosteroid Level

In all studies, with one exception which may have been the result of a technical error, plasma steroid values under the impact of emotional disturbance failed to rise beyond the normal limits of 34 to 35 μg. All fluctuations were within the normal range, although a number of values were in the highest 5 percentile of the normal distribution. Since a variety of individuals were studied under conditions of diverse emotional stress, and as the results were consistent, it seems probable that states of emotional disturbance and height-

ened anxiety are routinely, although perhaps not invariably, associated with small but significant elevations in the level of the adrenocortical steroids in the plasma. Restated, this indicates that a concentration of adrenal steroids somewhat higher than normal is available to tissues of the body under these circumstances.

It must be recognized that the level of the 17-hydroxycorticosteroids in the blood represents the dynamic balance between the rate of secretion of the hormones from the adrenal cortex and the rate at which the steroids are lost to the circulation by metabolism and excretion. Increases in the concentration of these steroids in the blood may not necessarily mean an increase in adrenocortical activity. These increments may also represent the release of steroids bound to peripheral tissues or the diminished catabolism of steroids.

However, it does seem probable that emotional stress causes a *true* increase in output of steroid from the adrenal cortex. This is suggested by the simultaneous occurrence of elevations in concentration of both blood and urinary 17-hydroxycorticosteroids in the case of medical students harassed by examinations.

Chronic Emotional Tension

Most of the stresses studied were acute and data on sustained chronic emotional tension were limited. Two series of observations indicate that prolonged emotional upset may be associated with persistent elevations of the blood steroids. Many of the disturbed psychiatric patients who were admitted to the psychiatric ward had been in a state of turmoil for a number of days, even weeks, before being studied. Blood steroid levels were nonetheless elevated, despite the chronicity of the emotional upset. Furthermore, one manic patient whose blood levels were spot-checked over a course of 3 months maintained elevated levels for a period of weeks during the period of hyperactivity and emotional disturbance.

Although there was clear-cut evidence that emotional stress is associated with elevated blood steroid titers, it should be emphasized that these were modest variations always within normal physiological limits. They did not compare in magnitude to those elicited by intravenous administration of ACTH.

Mechanism of Steroid Increase

It is not clear how an emotional upset can be transformed physiologically into an increase in the concentration of the 17-hydroxycorticosteroids in the peripheral blood. There is good evidence that this is not the result of the discharge of adrenaline, since this substance even in unphysiological concentrations does not influence the level of the plasma or the urinary 17-hydroxycorticosteroids.[22, 35]

It is possible that emotional upset influences blood steroid levels via the hypothalamus, the "portal system," and the anterior pituitary gland.[16, 18] At present, this can only be an attractive hypothesis without adequate experimental confirmation in man.

Any explanation of the data must account for the moderate steroid elevations, the consistency in steroid increases which averaged 5–10 μg. for any group of subjects, and the limitation of values to the normal physiological range of 2 to 35 μg.

At present, the simplest explanations consistent with the data are those of Sayers, Ingle, and Engel. Under conditions of stress, in this case severe emotional disturbance, the metabolic needs of the organism rise, necessitating a higher concentration of adrenal steroids to sustain cellular processes at an optimum level. The increased needs of the organism are met by a rise in the concentration of circulating adrenal steroids. When emotional perturbation subsides, the needs of the organism fall, as does the concentration of the blood steroids. This is admittedly an oversimplified statement of a highly complex process. Further details are available in the references cited.

Exogenous Steroids

It is true that exogenous ACTH, hydrocortisone, and cortisone may induce remissions of rheumatic fever, rheumatoid arthritis, ulcerative colitis, and so on, or exacerbations of peptic ulcers, even perforations. These changes occur, however, after the administration of large amounts of drug. Under these

conditions, the concentration of the 17-hydroxycorticosteroids in the plasma may rise to unphysiological levels of 40–100 μg. This is a far cry from the meager elevations caused by emotional stress, and it is questionable whether the two sets of data can be related.

Summary

Adrenocortical reaction to emotional stress was determined in groups of subjects who were studied during life situations of emotional perturbation, as well as under conditions of experimentally contrived emotional disturbances.

The level of the 17-hydroxycorticosteroids in the peripheral blood and 17-hydroxycorticosteroids conjugated as glucuronides in the urine served as the measures of adrenocortical function.

These emotional disturbances caused consistent but modest increases in the 17-hydroxycorticosteroids in the blood and urine. Plasma steroid values remained within the normal physiological range under the influence of emotional upset. These changes were less than those observed following the intravenous administration of ACTH, Piromen, insulin, or electroshock treatment and moderate exercise.

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