1950

Application of the concept of homeostasis to the problem of schizophrenia

Seymour Rosenblatt
University of Nebraska Medical Center

APPLICATION OF THE CONCEPT OF HOMEOSTASIS TO THE PROBLEM OF SCHIZOPHRENIA

Seymour Rosenblatt

A thesis presented to the faculty of the University of Nebraska College of Medicine in partial fulfillment of the requirements for the degree of Doctor of Medicine.

1950

TABLE OF CONTENTS

		Page
I	Introduction	
	A) The Principles of Homeostasis and the Problem of Schizophrenia	1
II	The Responsivity of Homeostatic Systems in Schizophrenia to Stress	
	The Autonomic Nervous System	4
	Mobilization, Utilization and Dissipation of Energy in Schizophrenia	14
	1) Homeostasis with respect to glucose	14
	2) Homeostasis with respect to oxygen consumption	17
	3) Homeostasis with respect to body temperature	20
	C) The Adrenal Cortex in Schizophrenic Responsivity to Stress	26
	D) Allergy and Schizophrenia	43
	E) Disturbances in the Somatic Nervous System in Schizophrenia	
III	Conclusion--Fact and Fantasy	49
	Bibliography	

I. Introduction

A) Principles of Homeostasis and the Problem of Schizophrenia

In spite of the truly brilliant achievements which characterize modern medicine, there exists in that realm of human experience a pertinacious enigma, an affliction of the human organism which, thus far, has resisted all attempts to disclose its exact causality and nearly all measures that are directed to relieve it. It has been stated that the rate of cure of schizophrenia is scarcely greater today than it was during the age of less sophisticated medicine, and some of our more cynical contend that contemporary methods of treatment are scarcely better, although possibly more humanitarian than those of the dark ages.

This deviation from normal has been carefully studied, its clinical manifestations have been recorded and classified, numerous investigations into its etiology have been performed and nearly as many theories for the disorder have been proferred. At one time or another the following were thought to be fundamental in the etiology of schizophrenia: thyroid deficiency, anatomical defects in brain structure, tuberculosis, specific type of streptococcus infection, sex-hormone abnormality, immature development of the mesodermal structures, gastro-intestinal intoxication, liver disease, a purely psychological reaction pattern to traumatic experiences starting in childhood, and an abnormal biochemistry of various substances e.g. carbohydrates, lipids, proteins, potassium, calcium, etc. (1,2,3). Many of these theories have met with contradictions at the hands of different investigators, especially those which purported to associate schizophrenia with

gross pathological alterations in the structure of various organs and tissues. Contrary to the claims of the earlier investigators it is now generally conceded that there are no quantitative differences in the levels of the various chemical substances in the blood or urine between normals and schizophrenics under basal conditions. Of the early investigations only those that dealt with the autonomic nervous system in schizophrenia have been more or less consistently corroborated by later studies. It was because of this and also because of the coincidental work of W.B. Cannon (4) on the role of the autonomic system in equilibrating the organism to the displacements of exogenous or endogenous stress, that the emphasis was placed by some investigators on the nature of the homeostatic mechanisms in schizophrenia. Thus far this has been one the most fruitful directions taken by medical research in this disease, for not only have the results of experiments which tested different kinds of homeostasis been consistent in their findings but the most recent knowledge on the reactions of the adreno-sympathetic systems to stress has been applied to the study of schizophrenia with impressive results.

Cannon (4) described the living organism as a system which was able to retain its integrity and stability through the operation of regulating mechanisms which tended to restore the system to its original level whenever it was disturbed by some stress either in the external or internal environment. In this way the organism can counter-act otherwise harmful situations and retain its internal milieu at relative constancy. This permits a high degree of independence of the organism from the environment and

the freedom for the development, refinement and activity of the higher nervous system. Most of homeostatic mechanisms which regulate the adaptivity of the organism to the environment (internal and external) are confined to the autonomic-endocrine system and usually have no conscious representation if the mechanisms are compensating adequately. In this way "normal life runs smoothly" for the organism and when the stresses become excessive or threatening the higher voluntary centers contribute to the restoration of the organism from the displacement. Fortunately, because the normal organism has adequate autonomic homeostatic mechanisms, the cortex is seldom "aware" of the biochemical and physiological stresses and strains of daily living and also because of the steadiness of the internal environment it is able to function smoothly and efficiently.

It has been found that the infraconscious homeostatic mechanisms in the schizophrenic subject are defective when compared with the normal. The schizophrenic organism does not respond to changes in the environment with the alacrity and intensity of the normal organism and is unable to attenuate the noxious disturbances to the organism. He is, therefore, unable to maintain the constancy of the internal environment which is so necessary for the smooth operation of all bodily systems, and especially the higher nervous centers. Thus, even "normal living" presents an undue stress for this organism.

This paper will deal with a review of the studies that have been made comparing the responsivity and efficiency of the homeostatic mechanisms in schizophrenic subjects to various types of

experimental stress situations with the responsivity found in normal people under similar conditions.

Before proceeding to the discussion of the purely scientific aspects of this particular problem it will be of interest to bring the socio-economic significance of schizophrenia into sharper focus by referring to a few statistics on the subject. Fifty percent of this country's hospital beds are occupied by patients with various types of mental disorders and of these 25 percent (a conservative figure) are schizophrenics--the largest single group. Many, of course, live outside of the hospital. Each year 40,000 new cases of schizophrenia enter mental hospitals and one state has estimated that ten cents out of the taxpayer's dollar goes for the care of schizophrenics. (5). The majority are not rehabilitated and since the illness often enters the acute stage during the relatively youthful period of the victim's life, whose span is about the same as that of a normal individual, he remains an incompetent social parasite for many decades.

II. Responsivity of Homeostatic Systems in Schizophrenia

A) Autonomic Nervous System

In 1928 Kanner (6) reported on the blood pressure effects induced in 34 cases of schizophrenia and 9 cases of manic-depressive psychoses when 1 cc. of a 1:1000 epinephrine solution was injected subcutaneously. The cases were selected only insofar as those having any physical condition which might influence the blood pressure were eliminated. By determining the systolic pressure every 10 minutes for 70 minutes and constructing appropriate graphs he was able to show that all of the schizophrenics

had vagotonic curves i.e. vagotonicity was remarkably accentuated in response to the epinephrine and apparently insufficient activity of the sympathetic system was mustered to counterbalance the evoked parasympathetic response. In the manic group of the manic-depressive patients epinephrine caused a marked rise in the systolic blood pressure whereas in the depressed group the blood pressure curve showed marked vagotonic features. In addition it was observed that the degree of vagotonicity in schizophrenia depended on the extent of the emotional indifference of the patient rather than the "type" of schizophrenia.

Freeman and Carmichael (7) administered 0.05 mg. of epinephrine, using the intravenous route in normal and schizophrenic subjects under basal conditions. Control readings of blood pressure and pulse rate were taken before the injection and included the possible effects of the stimulus of venipuncture itself. After injection the pulse rate was noted every 3 minutes for 30 minutes and the blood pressure reading was taken within 30 seconds of the pulse rate determinations. The maximum rise in systolic blood pressure occurred within 30 seconds and the mean rise for the 24 normal male subjects was 56.2 mm. while for the 14 schizophrenic male patients it was 43.8 mm. The difference between the means, 12.4 mm., was found to be statistically significant and indicated an altered reactivity to the compound in the patients. The diastolic pressure responses were more complex since they were of a pressor and depressor nature and no significant difference was noted between the groups. The pulse rate increased less for the patients than for the normal subjects (13.6 mm. and 16.3 mm.) but

again the difference was not significant. When plotted on a distribution scale it was seen that for the diastolic pressure and the pulse rate the patients tended to concentrate at the lower levels of response but the variability in the group was much greater than the normals. With a similar but more extensive procedure Funkenstein et.al. (8) plotted the course of the systolic blood pressure for 25 minutes after administering either epinephrine intravenously or mecholyl (acetyl beta-methyl choline) intramuscularly to a variety of mentally ill patients which included 37 schizophrenics. Normal subjects were used as controls. The response to each compound was plotted on the same graph for each individual. It was found that the autonomic-response curves of all the subjects could be divided into 7 distinct patterns and, although all of patients with a similar mental disturbance did not fall exclusively into one type of pattern, there was, nevertheless, a distinct tendency for them to concentrate into one particular type of response curve. Of the 7 autonomic patterns there was one that was in many respects quite different from the 6 other types. It consisted of the poorest response in systolic blood pressure to epinephrine--both in the height of the rise and in the duration of the response. The average rise for this group was 47.1 mm. and the duration of response (until the systolic blood pressure returned to pre-injection levels) was 2.8 minutes. The 6 other autonomic-response patterns showed an average rise in blood pressure ranging from 59.1 mm. to 93.5 mm. and an average duration of response from 3.3 to 5.7 minutes. Whereas the average area of the epinephrine curve in this special group was 12.6 the areas for the other epinephrine curves ranged from 19.3 to 39.2. The mecholyl response

aspect of this autonomic pattern was also significant. It showed a fall in systolic blood pressure of 26 mm. and even after the 25 minutes had not yet begun to return to the pre-injection level while in nearly every other autonomic-response curve the systolic blood pressure had attained pre-injection levels and in most instances it had returned much sooner. The impressive feature about this type of curve was that although only 54% of the schizophrenic patients exhibited this pattern none of the other mentally ill patients (psychoneurotics, psychopaths, involutional psychotics, manic-depressives) or normal subjects showed it. The other schizophrenics showed more sympathetic responsivity and thus fell into more active autonomic groups. It is known (see later) that during the early and acute stages of schizophrenia there is usually a hyper-activity of the sympathetic as well as the somatic nervous systems and this may have accounted for the other 46%. Essentially the peculiar type of autonomic pattern that was seen only in the cases of schizophrenia was a markedly poor response to epinephrine and a failure to attain homeostasis by increasing sympathetic activity after mecholyl.

Another method for measuring responsivity or homeostasis of the autonomic nervous system is to expose the organism to certain external stresses. But before going on to the next group of experiments it will help to recall some of the physical factors in blood circulation in order to understand the significance of some statistical material to be presented. The cardiovascular system is an hydrodynamic unit in which the blood pressure is dependent on the heart rate, its force of contraction, its stroke

volume, the elasticity of the arterial walls, the blood volume and viscosity and the degree of peripheral resistance regulated by the arterioles. If only the rate or the force with which blood is pumped into the arterial conduits varied we would expect the changes in the systolic and the diastolic blood pressures to be parallel with each other, However, if in addition the peripheral resistance were to vary also, then there would be a lesser correlation between systolic and diastolic blood pressures. Thus a measure of the correlation between the changes in systolic and diastolic pressures under various experimental conditions would be a good index of the activity of the autonomic nervous system which controls the state of contraction of the arterioles and thereby the peripheral resistance. A high correlation indicating a more or less inactive autonomic control on peripheral resistance and a low correlation indicating the reverse. Hoskins and Jellinek (9) have reported that the correlation coefficients, between systolic and diastolic pressure for large groups of normal and schizophrenic subjects were 0.43 and 0.62 respectively. Gottlieb (10) determined the effect of heat stress on the changes in the blood pressure correlation coefficients in normal and schizophrenic subjects. Each experiment lasted for 3 hours. After the first hour the temperature in the experimental chamber was raised rapidly from 74°F to 92.5°F and the changes in blood pressures noted. On another day the subjects were exposed for 3 hours to 74°F and this also served as a control. The correlation coefficient at the start of the constant temperature experiment was 0.30 for the normal subjects and 0.64 for the schizophrenics; after 3 hours the

coefficients were 0.55 and 0.59 respectively. Thus under uniform conditions which demand a minimum of vasomotor activity to maintain homeostasis, the normal subjects approached the patients whereas the latter did not change significantly. During the varied-temperature experiment where the stimulus of warm air increases parasympathetic activity and inhibits sympathetic activity, the correlation coefficient for the normals went from 0.36 to 0.64. The patients started with 0.74 and ended at 0.84. Thus for the patients there was (in both instances) already an increased inhibition of sympathetic activity at the start and the increment of inhibition along with the increased parasympathetic activity was not as great as in the normals who manifested a much more active vascular bed. Freeman and Carmichael (7) were also able to show that when epinephrine was injected into schizophrenics the high correlation coefficients were significantly decreased--again showing the pre-existing paucity of sympathetic activity.

Pfister (11) studied the vascular equilibration phenomena in 104 healthy and 184 schizophrenic subjects when changing from a prone to an erect position and back again. For the normal subjects assuming the erect position the pulse rate went from 18¼ beats per minute up to 19¼ beats per minute and then to 17¼ beats per minute on returning to the prone position. The blood pressure remained practically constant during these maneuvers. On the other hand the schizophrenics manifested poor homeostatic mechanisms and Pfister was able to observe progressive changes in the deterioration of homeostasis with the advance of the schizophrenic process. One group of patients which consisted of those in the

acute stages of schizophrenia, whose illness was usually of less than 6 months duration and who displayed psychomotor excitation showed a mean increase in pulse rate of 9 beats per minute and a fair but less than normal ability to maintain the blood pressure on standing erect. A second group of patients, consisting of the chronic, "burned out" schizophrenics, in which the duration of the illness was well over 1½ years, had a constant pulse rate of 15¼ beats per minute during the experiment. On standing up the systolic blood dropped from 5 to 30 mm. in this group and was also very sluggish in compensating. A third category included those patients who showed well-preserved hebephrenic and paranoid forms of the disease and who had behind them the stormy primary (acute) stage or who had developed without this stage. These patients were very variable in their responsivity and fluctuated between the extremes of the other two groups. We may look at acute schizophrenia as a stage in the disease where the organism is reacting with excessive effort but with poor integration to restore displacing stimuli which in the normal individual are controlled with comparative ease. As homeostasis continues to break down (the "original" deterioration process is maintained, accentuated and hastened by the exhaustive and unsuccesful efforts to regain equilibrium during the acute stage) the adjustive mechanisms fail unevenly and exaggerated swings now occur because of the operation of these unbalanced forces. In the chronic stage not only are the homeostatic forces very weak but the autonomic integrative centers have practically ceased to function.

At this point we may introduce briefly some well-known

effects on the autonomic nervous system of the more "successful" methods of treating schizophrenia. Cameron and Jellinek (12) recorded the effect of insulin treatment on the pulse rate and blood pressure of 22 schizophrenic patients, 10 of whom recovered and 12 who did not recover. Normal controls who did not receive insulin were used for comparative purposes. The results are tabulated in Tables I and II.

Table I

Pulse Rate Changes After Insulin Therapy

	Normal Controls	Recovered Patients		Non-Recovered Patients	
Mean Value	62.2	Pre-Insulin 61.7	Post-Insulin 67.6	Pre-Insulin 63.7	Post-Insulin 63.2
Intra-Individual Standard Deviation	3.9	6.0	4.1	7.4	7.4
Significance of difference between means		*P<0.05		P=0.77	

* P stands for the Probability coefficient and in this case means that the chances are less than 5 in 100 that the difference between means could have occurred on a random basis. P values less than 0.05 have high statistical significance.

Table II

Systolic Blood Pressure Changes After Insulin Therapy

	Normal Controls	Recovered Patients		Non-Recovered Patients	
		Pre-Insulin	Post-Insulin	Pre-Insulin	Post-Insulin
Mean Value	115.3	107.6	115.9	114.9	114.9
Significance of difference between means		P=0.01		P=0.70	

After treatment the pulse rate increased significantly in the recovered patients whereas there was no significant change in the patients who did not recover. In addition there was a decrease towards normal in individual variability in the recovered but not in the unrecovered group. The changes in blood pressure were similar to those in the pulse rate. Before treatment the systolic-diastolic correlation coefficients (see before) of both groups were 0.45 and 0.48 (no significant difference) and 0.30 for the normal subjects. After treatment the correlation coefficient for those who recovered changed to 0.29 and for those who did not recover it actually tended to increase to 0.56. As explained previously, a high correlation coefficient indicates a relatively inactive sympathetic nervous system while a low coefficient signifies the reverse. Thus an important factor in recovery was the maintained activation to normal levels of the adreno-sympathetic nervous system. Rinkel et.al. (13) have shown that after bilateral frontal lobotomy the autonomic nervous system becomes much more res-

ponsive to various stimuli. A rather interesting feature of schizophrenia is the failure of psychological as well as physiological response to epinephrine. Dynes and Tod (14) reported that while normal subjects all exhibited some degree of anxiety after administration of adrenalin, this did not occur in any of the schizophrenic patients. The same difference in emotional response was also noted when doryl (carbaminoylcholine chloride), a parasympathetic nervous stimulant, was injected. They concluded that the experiment showed a disorder of the emotions in schizophrena "at the physiologic level".

During insulin coma there is a marked rise in the blood adrenalin levels (15,16). Tietz and Birnbaum (17) determined the amount of free adrenalin plus the adrenalin bound to adrenal cortical steroids in the blood immediately before and during the insulin coma of 29 schizophrenics. They claim that the major portion of the blood adrenalin is combined with some adrenal cortex substance. During insulin shock the adrenalin-cortical level rises above pre-schock values. These analyses were continued daily along with the insulin shock treatments and it was noted that in some patients there occurred a gradual rise in the daily pre-shock blood level of the adrenalin-cortical substance. In addition, the increment produced by insulin gradually diminished until it was practically absent. Significantly, the only patients who were able to maintain excellent adjustments when discharged from the hospital were those who showed this type of pattern. The other patients exhibited a spectrum of improvement ranging from progressive deterioration to partial improvement with sub-

sequent relapse. In none of these cases was the behavior of the adrenalin-cortical compound similar to that of the patients who improved and made good social adjustments. Although the daily increments produced by insulin were as great as in those patients who improved, these unimproved subjects did not show the rise in the pre-shock level. It seemed as though the sympathetico-adrenal system could be stimulated in these patients, but the patient was unable to attain and maintain a basal level of adrenal-cortical activity and always slipped back into an hypoactive state.

B) Mobilization, Utilization and Dissipation of Energy in Scizophrenia.

1) Homeostasis with respect to glucose

Braceland et.al. (18) performing the 2 dose-1 hour Exton-Rose glucose tolerance test on a variety of schizophrenic patients and on normal subjects observed that although the fasting blood sugars of both groups were in the range of accepted normal values there was a decided difference in the glucose tolerance curves. Sixty-five percent of the 102 schizophrenics showed definitely abnormal curves. Of these, 16 were flat or descending indicating perhaps overactivity of the vago-insular system and 49 showed an abnormal rise during the second half-hour (as seen in diabetes mellitus, liver disease and hyperpituitarism). The normal fasting blood sugar, the normal rise of blood sugar during the first half-hour of the test and the absence of glucose in the urine all ruled out diabetes mellitus as the etiologic factor of the abnormal curves. The authors cite the work of many investigators who have shown the presence of some anti-insulin factor

in the blood of schizophrenics and agree that this factor delays the action of insulin on glucose metabolism. They do not believe the defect is due the failure of the pancreas to secrete more insulin since Soskin (19) has shown that a normal glucose tolerance curve can be obtained in pancreatectomized animals with a constant rate of glucose and insulin infusion. Liver disease per se cannot account for the presence of an anti-insulin substance. The authors did not suggest the possibility that the anti-insulin substance might be that anterior pituitary hormone which is known to have anti-insulin properties. As will be shown later, schizophrenics tend to have a rather peculiar type of hypoadrenalcorticalism and the increase in anterior pituitary hormone (ACTH?) may be the result of the release of the pituitary inhibition by a diminished adrenalcortical hormone secretion. Pfister (11) was able to demonstrate another defect in the mechanics of regulating the blood sugar in schizophrenia. When insulin was introduced at the rate of 1/15 unit per kg., normal subjects after showing a 20%-30% fall in blood sugar during the first half-hour were able to regain their original blood levels in about an hour. The schizophrenics on the other hand showed an excessive drop in blood sugar and and the return rise was feeble and delayed. Although the chronic schizophrenic patients had the poorest glucemic homeostasis, all patients showed it to some degree. Again we wonder about the failure of sympathico-adrenal response, especially in the light of the experiments of Paschkis and Boyle (22). After administering insulin to dogs there was a prompt rise in the level of adrenocortical hormones in the blood thus suggesting the par-

ticipation of these substances in counteracting insulin-induced hypoglycemia. The role of the adrenal cortex in the schizophrenia problem will be rigorously treated in a later section.

A close correlation has been shown between the change in the glucose tolerance curve under convulsive therapy for schizophrenia and the prognosis of the illness. Proctor et.al. (20) made this carefully controlled study among a group of 57 schizophrenic patients, chiefly catatonics, whose illness was not over 3 years in duration. Both an intravenous and an oral glucose tolerance test was used. The patients received either insulin or electric shock therapy. Most of the cases in the recovered group of patients, who showed a lessened pre-treatment tolerance to glucose reverted towards a normal curve with therapy The results of the oral test are described in Table III. as the mean areas of the glucose tolerance curves, thereby including the total insulin effect of intensity × time.

Table III

Glucose Tolerance in Recovered and Non-Recovered Before and After Treatment

	Units of Area
Recovered....Pre-Treatment	1536
....Post-Treatment	1034
Unimproved...Pre-Treatment	1472
...Post-Treatment	1680

The area under the oral glucose tolerance curves decreased about 32% in those who recovered after treatment, while in the unimproved group there was actually an increase which amounted to

about 14%. Statistically the changes were very highly significant. Included in the series were several patients who received only routine hospital care and who showed an improvement in their glucose tolerance curves coincident with a complete remission from their personality disturbances. There were a small number of subjects who recovered or improved without showing any change in the glucose tolerance test. A larger number who seemed to improve clinically but manifested simultaneously a significant decrease in glucose tolerance all subsequently relapsed. It was suggested that in such cases the glucose tolerance curve has prognostic value. Greeman and Zaborenke (21) obtained the same results in their series using electro-shock treatment exclusively.

2) Homeostasis with respect to oxygen consumption

It is a well-established fact that the basal metabolic rates of large schizophrenic populations tend to be significantly lower than those found in normal subjects. Hoskins (23) states that although the arterio-venous oxygen difference of the blood from the brain of schizophrenics is the same as in normal subjects, the circulation time is increased in the former and, therefore, one should expect a greater loss of oxygen to the brain in this situation. Since the A-V difference is the same there must be a relative deficiency of oxygen utilization by the brain of schizophrenics. Hoskins also found an abnormal relationship between the glutathione and lactic acid levels of the blood of schizophrenics. Normally the levels of blood glutathione and lactic acid vary independently but in schizophrenics they bear a very close inverse relationship to each other. This is interpreted as demonstrating

that even under basal conditions the schizophrenic has to use reserve accessory mechanisms for oxygen assimilation which the normal individual only calls forth at those rare instances when homeostatic mechanisms are being taxed to their limits. By encroaching on his reserves for relatively normal stress situations, the schizophrenic loses homeostatic flexibility and tends to remain at fixed levels. The defect in the mechanisms of oxygen utilization may be either a lack of oxidative catalysts or the presence of inhibitors. With regard to the former hypothesis, in vitro experiments by Tipton and others (24) have shown that there occurs a significant depression in oxygen consumption along with a considerable diminution in the rate of the oxidation of pyruvic and succinic acids (both essential substances in the glucose oxidative process) by various tissues of adrenal-ectomized animals.

Another factor in schizophrenia which hinders homeostatic adjustments to the changing oxygen requirements of the organism is a decreased excitability of the medullary respiratory center to CO_2. Golla et.al. (25) by increasing the CO_2 content of inspired air to 2% caused a mean increase of 20% in the respiratory volume of 12 normal subjects. Of the 20 schizophrenics undergoing the same experiment, one showed a normal increase, another a smaller increase of 9% while the rest manifested no increase at all. The effect of sodium bicarbonate ingestion on the respiratory volume was also studied by these authors. In the normal subjects, after the initial depression of respiration, there occurred a compensatory hyperventilation to expel the accumulated CO_2 after the bicarbonate was excreted by the kidney. In the schizophrenics

there was a failure of the compensatory hyperventilation to occur although the bicarbonate was excreted at a normal rate, showing again the decreased responsivity of the respiratory center to CO_2. The authors believe that this defect accounts for many of the abnormal acid-base relationships in schizophrenia, e.g. absence of the normal diurnal change in the pH of the urine(it remains on the acid side), frequent absence of the alkaline tide and absence of any correspondence between the pH of the urine and the alveolar CO_2 tension. These acid-base disturbances are similar to those that occur normally during sleep where depression of the respiratory center is also present. It is of more than passing interest that many investigators throughout the years have speculated about the similarity of the psychological and physiological phenomena in schizophrenia and normal sleep. In both instances there occurs the depression of the powerful hypothalamic "vigilance" center with the emanation of the oneiric state.

Another defective entity in the homeostatic control of oxygen consumption in schizophrenia is the thyroid gland. Using a battery of examinations for determining the thyroid activity of schizophrenics, followed by thyroid medication when indicated, Hoskins(26) arrived at the conservative estimate that 10% of schizophrenic patients suffered from hypothyroidism and the psychosis was relieved when these patients were given substitutive therapy. Whereas only 10% of schizophrenics are definitely hypothyroid, there seems to be some peculiar type of perturbation of thyroid metabolism among schizophrenics generally. It consists of a diminished responsivity of the organism to thy-

roid substance. Cohen and Fierman (27) were able to give schizophrenics rather high dosages of thyroid extract (15-18 grains a day) for as long as 69 days without any evidance of toxicity e.g. excessive perspiration, gastro-intestinal disturbances, tremor, exophthalmos, even though striking metabolic, cardiovascular and biochemical changes were registered. Hoskins and Sleeper (28) obtained a similar unresponsivity using 30-40 grains of thyroid extract a day for several weeks. It is believed by Rheingold (29) that the high tolerance to thyroid is due to a failure of the hypothalamus to respond to the thyroid hormone. He cites evidence to indicate that the action of thyroxine is mediated through the hypothalamus rather than peripherally. Presumably the hypothalamus by stimulating the sympathetic nervous system provokes an increased oxygen consumption by the peripheral tissues. Not only is the schizophrenic organism unresponsive to the thyroid substance but Neustadt and Howard (30) have shown that the gland itself is unresponsive to stimuli that would cause an increased activity ordinarily. Whereas there is a decided correlation between moods and blood iodine levels in the manic-depressive psychoses, there is often no change in blood iodine in schizophrenics during states of extreme psychomotor excitation. A rather unusual degree of rigidity of thyroid secretion obtains in these cases.

3) Homeostasis with respect to body temperature.

The changes in oral and rectal temperatures, under different environmental conditions, in normal and schizophrenic subjects were studied by Gottlieb and Lindner (31). The subjects were exposed for 3 hours to either a constant room temperature of

74°F or to a temperature which was rapidly increased from 74°F to 92.5°F. The results were carefully evaluated statistically. Under the condition of constant heat, there occurred an initial drop in the oral and rectal temperatures of both groups. The changes in oral temperature were about the same but the decrease in rectal temperature was considerably greater for the normal subjects. At the start of the constant-heat experiment the mean difference between the oral and rectal temperatures in the normal subjects was 0.78°F which decreased to 0.41°F after 3 hours. The corresponding values for the schizophrenics were 0.42 and 0.41, respectively. It is thereby indicated that the schizophrenic patients had lost the organ-selectivity of shifting blood masses present in normal individuals. Instead the blood moved in a generalized fashion from the various internal structures to the periphery without the adjustment capacity to vary the supply of blood to the mouth and rectum. During the experiment where the external temperature was increased there was a significantly greater increase in both the oral and rectal temperatures of the schizophrenics than of the normal subjects which indicated a more sluggish response of either the local skin vessels or the central heat-regulating mechanisms. The schizophrenic individual tends to resemble the homeostatically defective poikilothermic organism. Pfister (11) studied the problem of temperature homeostasis by determining the change in axillary temperature when the subject immersed his foot for 15 minutes in a water-bath at 40°C followed by another 15 minutes at 20°C. In normal subjects the warm water produced a rise of 0.4°C-0.6°C in

the axillary temperature and the cold water caused an equivalent fall. However, the schizophrenics showed no similar response. There was either no change in axillary temperature or the behavior was paradoxical i.e. a rise in temperature during cold stimulation and a fall with warm stimulation. A more complete investigation along these lines was carried out by Finkelman and Stephens (32) who studied the chemical (heat production) as well as the physical (heat dissipation) regulation of body temperature. After withholding food for 15 hours, the basal oxygen consumption was recorded and 20 minutes later the subject was placed in a bath of water at 60°F-62°F which is an intense cold stimulus (moreso than air at that temperature since water has a greater heat capacity and conductivity). When resting quietly the oxygen uptake was again recorded. After a 15-20 minute exposure the subject was wrapped in blankets, put to bed and 45-60 minutes later the basal oxygen consumption was again taken. Changes in oral temperature were also noted during the entire experiment. The reactions of the schizophrenic patients were less intense than the normal. Whereas the non-psychotics increased their oxygen uptake by 36.5% the increase for the schizophrenics was 24.0%. The oral temperature decreased 0.8°F in the schizophrenics and only 0.2°F in the normals. A breakdown of the figures shows that while 44% of the non-psychotic patients were able to over-compensate and increase their body temperature up to as much as 0.9°F this ability was manifested by only one schizophrenic. Forty-five minutes after the cold exposure the increased oxygen consumption had decreased to a much greater and significant degree in the patients than in the normals. Thus, not only was there a less intense

responsive increase in the metabolism of the scizophrenics but they were also much less able to maintain this augmentation than normal subjects. Another observation was the occurrence of a reactive hyperemia of the skin when the non-psychotic subjects were placed in a warm environment. Concomitantly there was a drop in the internal temperature due to the cooling effect of the still cold skin on the blooding coming from the interior of the body to the dilated superficial vessels. The temperature depression amounted to 0.66°F. This reactive hyperemia was markedly weaker in the schizophrenics as witnessed by a drop in temperature of only 0.02°F. The investigators were also much impressed by the fact that respiratory shock was absent in the schizophrenics who uniformly breathed regularly and without effort from the moment they entered the cold water. All non-pychotic subjects displayed this phenomenon of respiratory shock as well as shivering intensely. The latter was considerably less in the schizophrenics. The authors expressed the opinion that the defect in schizophrenia probably lay at the hypothalamus since it is the principle heat-regulatory center. It is not that the schizophrenic does not actually feel noxious stimuli--but there is an inadequate "defense reaction". In other words, there exists a sort of dissociation between the feeling of cold, a cortical function, and an adequate complex reaction which returns the organism to equilibrium. Freeman and Rodnick (33) placed the heat regulating mechanisms under a stress by suppressing heat loss from lungs through the inspiration of hot moist oxygen. Thereby other processes must be evoked,otherwise the organism is thrown into a phase of thermal dysequilibrium. The experiment was carefully controlled at

all stages and an equal number of schizophrenic and normal subjects were used. Basal readings were taken and then, without the subject's knowledge, the oxygen entering the face mask was heated to 41°C and almost saturated with water vapor. The pre-stress values for systolic blood pressure, heart rate and respiration were about the same for the normal controls and the patients. When the stress stimulus was applied the controls showed an increase in systolic blood pressure of 20 mm., an increase in heart rate of 26 beats per minute and an increase in respiratory amplitude of 80%. The corresponding figures for the schizophrenic subjects were an increase in systolic blood pressure of 5 mm., an increase in heart rate of 10 beats per minute and an increase in respiratory amplitude of 43%. The differences between the schizophrenics and normal controls were statistically significant ($P<0.01$) in each instance --the patients showing a sluggish and inadequate responsive adjustment to the stress situation. The schizophrenics were all in the chronic stages of their illness and there was no correlation between the psychiatric status and the degree of responsivity.

Besides studying the effects of only external stress stimulus Freeman (34) used next a general metabolic stimulant, dinitrophenol, which acts directly on the cells as a catalytic agent and administered 300 mg. orally to schizophrenic and normal subjects. Basal readings were taken on a previous day and the changes induced by dinitrophenol were compared between the two groups of subjects who were selected to pair favorably in age, height, weight, nutritional status, etc. The extremes of adolescence and senescence were excluded so as to minimize physiologic vari-

ations. The investigator went so far as to have the normal subjects live in rooms adjoining the patients, thus maintaining the same environment for both groups before and during the experiment. After ingestion of dinitrophenol the normal controls showed an increase in finger temperature of 2.2°C above basal whereas the increase for the patients was 0.7°C. The oxygen consumption was raised 24%-31% above basal in the controls and 18%-25% in the schizophrenics. The rate of insensible evaporation increased as much as 51% above basal in the controls but only 28% in the patients. It was also noted that the rate of increase of all these values was much faster in the controls than in the patients. Since dinitrophenol is a metabolic stimulant which is not dependent on the intermediary activity of any endocrine or nervous structure the results imply that the schizophrenic process is not confined to the nervous system but is widespread throughout the body tissues. It is suggested by the author that the physiologic and psychologic findings in schizophrenia are to be viewed from the notion of complementarity rather than causality.

A relationship between temperature regulation during insulin treatment and the prognosis of the disease was proferred by Tietz et.al. (35). Insulin coma produces a fall in body temperature and the simultaneously increased adreno-sympathetic activity opposes this drop and acts to restore the normal temperature. It was shown that as the insulin treatments continued there was a gradually lessening hypothermia among the 36 patients who recovered, whereas the 20 unimproved patients displayed no such change. It was also noted that the body temperatures of the re-

covered group were greater than the unrecovered patients.

C) The Adrenal Cortex and Schizophrenic Resposivity to Stress

The literature of schizophrenia is replete with the observations of many writers on abnormalities in the sphere of endocrine development. One particularly interesting revue by Kershbaumer (35) describes his findings over a period of 16 years wherein he came into contact with over 5,000 schizophrenic patients. An early pharmacological study by Freeman and Hoskins (36) suggested the presence of an adrenal cortical deficiency among schizophrenics. They administered orally a glycerin extract of adrenal cortex to normal and schizophrenic subjects daily for 4 weeks and compared the changes that occurred in blood pressure. The results are given in Table IV.

Table IV

Effect of Adrenal Cortical Hormones on Blood Pressure

	Systolic Pressure		Diastolic Pressure	
	Control Period	4th Week	Control Period	4th Week
Normal Subjects	111.3	111.2	67.1	70.8
Schizophrenic Subjects	111.7	125.3	66.5	78.5

A pressor action occurred in 79% of the 19 schizophrenic patients as compared to only 18% of the 17 normal subjects. A statistical analysis showed that the blood pressure changes for the patients were highly significant while those for the normals

were not significant. There is a basic consideration in endocrinology known as the principle of "inverse response" which states that a deficiency of a given hormone renders the subject more reactive to it. Apparently the heightened responsiveness of the end-organs in the schizophrenics to adrenal cortical hormones indicated a pre-existing deficiency. Many of the metabolic abnormalities reported in this illness direct attention to a decreased adrenal cortical function e.g. low rate of oxygen consumption, low basal blood pressure, anemic tendency, subnormal body weight, increased urinary output, hypothermia, etc.

Dougherty and White (37) were among the first to record a decrease in the circulating lymphocytes from the action of adrenal cortical hormones. They demonstrated this with adrenal cortical extracts as well as with pituitary adrenocorticotrophin (ACTH). This phenomenon has been observed with the circulating eosinphiles, too and is due to the action primarily of 11-dehydro, 17-hydroxy corticosterone (Kendall's Compound E) as well as other 11-oxysteroids from the adrenal cortex. It has been well established by Hans Selye and others that one of the prime changes in the organism in response to various non-specific stresses is an increase in the production and secretion of adrenal cortical hormones. In fact, the adrenal is now commonly referred to as the "organ of stress" since the effect of these hormones are numerous and complex, reaching out to control the intimate activity of every cell in the body, influencing them in so integrative a manner as to enable the total organism to withstand and equilibrate the thousands of daily onslaughts of the environment (animate as well as

inanimate) which constantly threaten its very existence. Thus, it becomes of uppermost importance for the understanding of schizophrenia to determine the nature of this master homeostatic mechanism in this "unusual" organism. Pincus et.al. (26,38) observed that in normal men under ordinary conditions of activity there is a characteristic diurnal rhythm in the urinary 17-ketosteroid excretion. The latter is derived mainly from the adrenal cortex and is thus, a quantitative indication of the level of adrenal cortical activity. The maximum titer occurs in the hours immediately following awakening, being from 50% to 80% above the sleep level. The steroid output of 28 schizophrenics studied under the same conditions as the normal subjects showed, on the average, less rise upon awakening than the normals as well as a flattening of the diurnal curve. The diurnal rhythm in blood lymphocytes correlated with the changes in urinary steroid output. In normal subjects the lymphocyte count was at a minimum between 8.00 A.M. and 11.00 A.M., then increased during the rest of the day with maximum counts being obtained between 10.00 P.M. and 3.00 A.M. The lymphocyte count did not drop to a minimum in the morning for the schizophrenics as it did with the normals. Also, the rise during the day was not as steep and was rather irregular. The difference in the slopes of the lymphocyte curves between patients and normals was 30.35 ($P<0.01$)--statistically highly significant. The diurnal rise in the psychotics was 40% less than in the controls. Awakening from the sleep state is indeed a physiologic stress and apparently there is a lessened responsiveness of the adrenal cortex to secrete the hormones in schizophrenia which facilitate the organ-

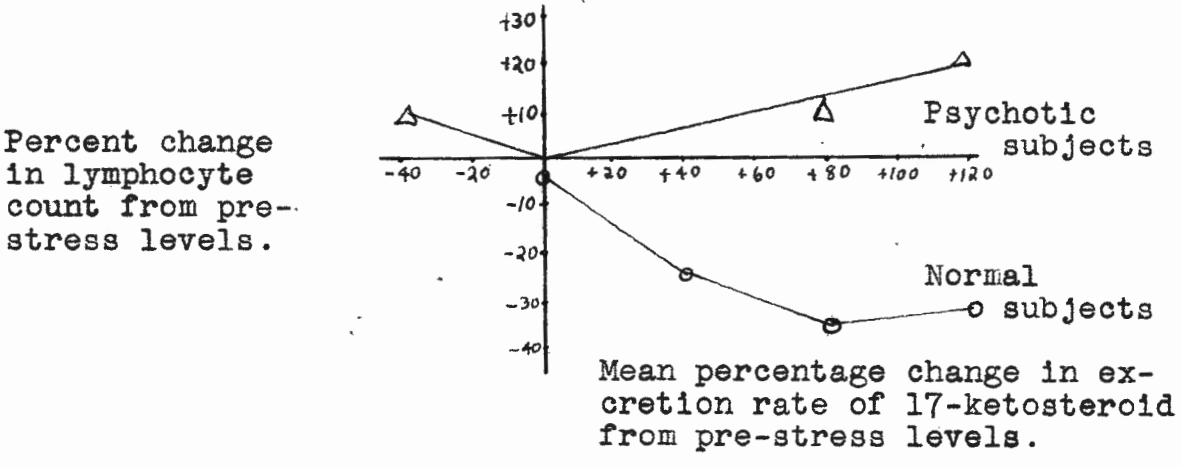
ism's stress reactions. In another experiment Pincus and Elmadjian (39) exposed both normal and schizophrenic subjects to a room temperature of 105°F - 112°F at a relative humidity of 85%-95% for 50-60 minutes. Each subjects consumed a quantity of water during the experiment which was about equivalent to that lost by perspiration (no hemoconcentration occurred in any subject). Lymphocyte counts were taken before, during and 2 hours after the thermal stress period. The mean drop in lymphocyte count in normal subjects after 50-60 minutes of stress was 24.5% while the patients showed either no change or even an increase--a mean rise of 24.2%. The difference between the means was highly significant ($P<0.01$). Whereas all of the control subjects exhibited a lymphocytopenia under stress, 95% of the patients did not show this. Two hours after the stress situation the normals tended to show a rise in lymphocyte count back to pre-stress levels and the patients showed a fall. It was suggested that there may be two factors controlling the lymphocyte count--a lymphopenic factor (adrenal cortex) and a lymphocytotic factor (this is unknown, but it may be another endocrine gland). The patients showed a defect in the adrenal cortical lymphopenic factor which was poorly evoked under stress.

Hoagland et.al. (40) studied adrenal cortical activity by the lymphocyte count when normal and schizophrenic subjects underwent a stressful psychomotor performance. The nature of the stress was the operation of a Hoagland-Werthessen pursuit meter which consists of the subject trying to keep a beam of light focused on a moving photo-electric cell. He is scored by an automatic

counter which registers each time the light slips off the target. A clock also registered the percent of the time that the light was on the target for any chosen interval. The experiment ran continously for one hour. Urine samples were collected before and after the stress period and the 17-ketosteroid excretion was expressed in milligrams per unit of time. The change in excretion rate due to stress was compared to the pre-stress rate. Blood lymphocyte counts were also made before and after the stress period. The fatigue rate was determined by dividing the mean score for the 2nd half of the experiment by that for the first half; a fall of this ratio below unity is a measure of the degree of fatiguing. The normal subjects showed a close correlation between the rise in excretion of the stress 17-ketosteroids and the declining lymphocyte count while in the patient group stress caused either a fall in 17-ketosteroid output or no change or a rise, and thereby the mean results did not show the same correlation as the normal subjects. (Fig.1).

Fig. 1

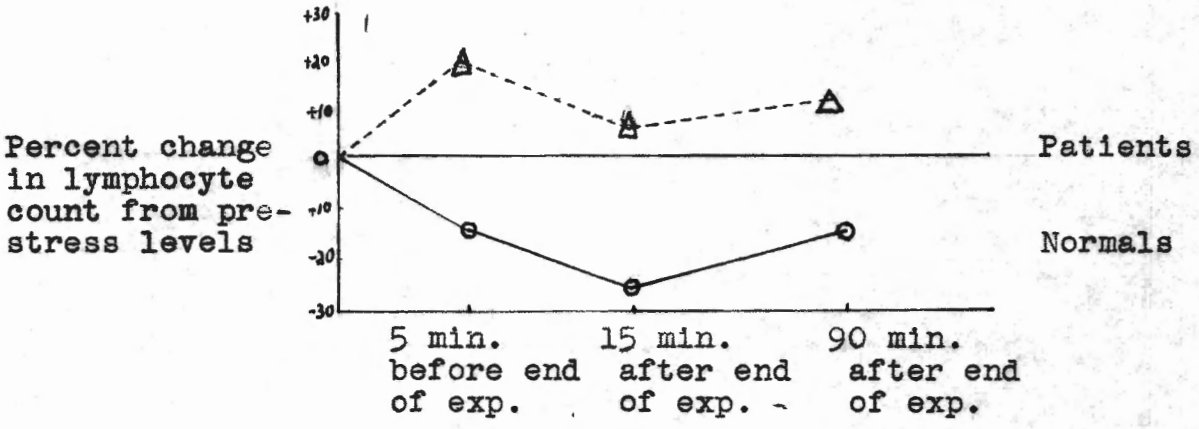
Relationship Between 17-ketosteroid Excretion and Lymphocyte Count



The lymphocyte count declined in the normal subjects under stress and increased in the schizophrenics. (Fig.2).

Fig.2

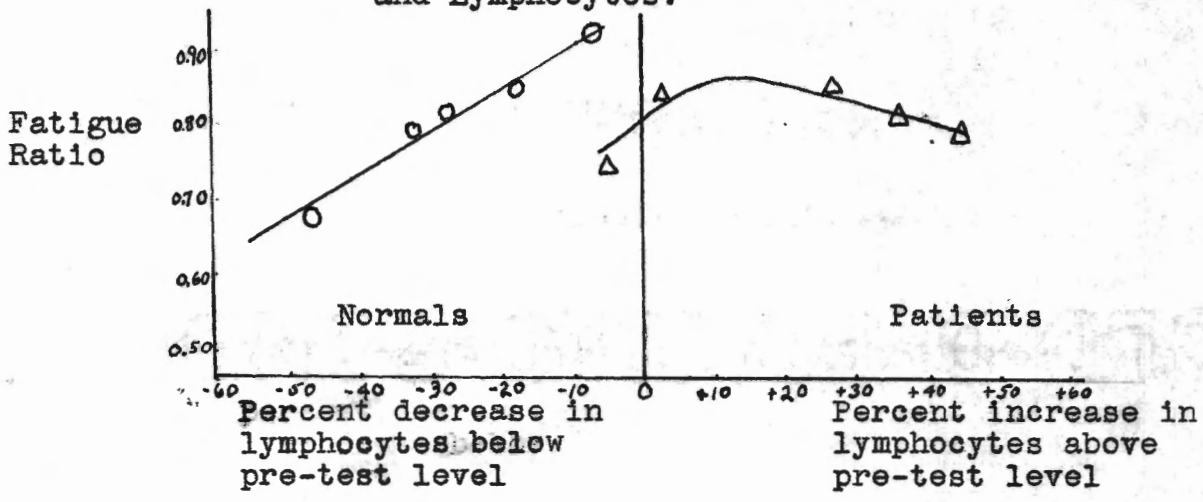
Effect of Stress on the Lymphocyte Count



Among the normal subjects there was also a good correlation between the fatigue ratio and the change in lymphocyte count. As mentioned previously the fatigue ratio diminishes as the degree of fatigue of the subject increases and his score diminishes during the last half of the experiment. It is at this time that he has to exert a greater effort, because of his fatigue, in order to perform the test. (Fig.3). The correlation between the fatigue ratio and the lymphocyte count was highly significant in the normal subjects ($P<0.01$) but was not significant in the schizophrenic group.

Fig. 3

Relationship Between the Fatigue Ratio and Lymphocytes.



A rather significant finding was made by Freeman and Elmadjian (41) in 1947 while observing the relationship between blood sugar curves and lymphocyte levels in normal and schizophrenic patients. These same authors had shown previously with laboratory animals that the lymphopenic response to glucose is abolished by adrenalectomy.

The normal subjects showed an inverse relationship between the rise in blood sugar during the Exton-Rose test and the change in lymphocyte count. Among the schizophrenics, 43% had an increase in the number of circulating lymphocytes with the rise in blood sugar and 57% had the normal inverse relationship. The latter as well as the normal subjects showed a rate of lymphocyte change of 25 lymphocytes per mg. rise in blood sugar while the 43% had a more "sluggish" lymphocyte change of 12 lymphocytes per mg. rise in blood sugar. When these two groups of patients

("abnormal" and "normal") were classified diagnostically it was found that while the majority of the "abnormal" reacting type fell into definite schizophrenic categories more or less easily, most of the "normal" reacting type had been classified in a wastebasket category of"Schizophrenia, other types", which was used to connote those who had a relative preservation of affect and who react in a rather appropriate manner to their environmental situation. Their symptomatology was of a more fluid nature. When the factors of age, duration of hospitalization, etc.were treated statistically the only significant difference that was found between these groups was the severity and duration of the illness. Here we see a rather close relationship between the physiologic defect and the psychiatric status. It is enlightening to recall at this point the experiment cited earlier which showed a close agreement between the patients who recovered from their illness and the ability to maintain adreno-sympathetic activity.

The most important contemporary study on the adrenal cortex and the pituitary-adrenal relationships in schizophrenia was published in 1949 by Pincus, Hoagland, Freeman and Elmadjian (42) and is one of the great milestones in the understanding of schizophrenia. As is due such an important work, it will be recorded in some detail.

These investigators studied 36 normal men and 34 schizophrenic men under various conditions of stress that would induce endogenous adrenocortical stimulation. In addition, in order to test the responsivity of the end-organs affected by the adrenocortical secretions, potent extracts of adrenal glands were admin-

istered and their effects noted. Blood and urine specimens were taken at timed intervals and were marked as pre-stress, stress and post-stress samples. The last was taken 3½ hours after the start of the particular experiment. The biologic measurements of adrenocortical activity during the three periods included lymphocyte count, 17-ketosteroid excretion, urinary potassium and sodium, urinary uric acid (the latter is increased when the lymphocytes are destroyed) and neutral reducing lipides of the urine (this contains a variety of adrenal cortical hormones). Also measured were the blood amino acids, sugar and inorganic phosphate. Urinary creatinine and phosphate were determined in addition. All results underwent a rigorous statistical scrutiny.

Before studying the ability of various stresses to stimulate adrenal cortical activity in schizophrenia, it had to be determined whether the patient responded to adrenal cortical hormones as did the normal subjects. Adrenal cortex extract in oil was administered to both groups. It was found that although the normal subjects showed on the average a somewhat greater increase in 17-ketosteroid, neutral reducing lipide and uric acid output than the patients, the differences were not statistically significant. There was also no statistical difference in the potassium excretion changes or in the stress sodium outputs. The normal post-stress sodium excretion was significantly less than the patients and the relative increase in the stress and post-stress inorganic phosphate differed significantly from the mean decrease in the normals. The blood lymphocyte count decreased about equally in

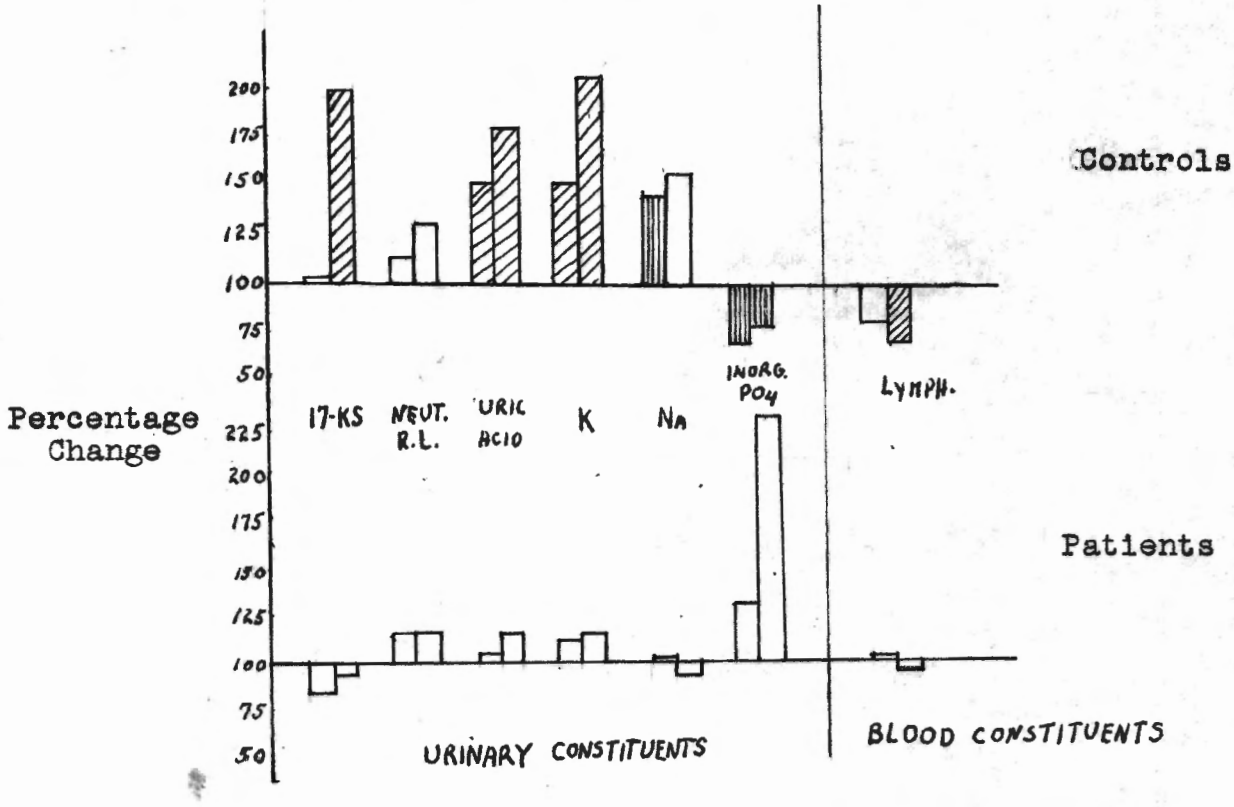
both groups. Thus, the uric acid, potassium, sodium and blood lymphocyte changes which represent the effects of adrenocortical steroids on various end-organs are not remarkably different in the two groups of subjects. Neither are the 17-ketosteroid and neutral reducing lipide changes which presumably indicate the metabolism of the administered steroids. The differences in the inorganic phosphate and sodium excretion in the two groups may represent a "normalizing" of the levels of these substances in the patients due to a diminished pre-existing endogenous adrenal cortical secretion. According to the chief indices of response to adrenocortical steroids, the patients are capable of normal or almost-normal response to these hormones.

When 25 mg. of pituitary adrenocorticotrophin (ACTH) were administered, a clear differentiation between the schizophrenic and normal subjects occurred which was statistically significant (Fig.4). In this diagram as in the others that follow the pre-stress value is taken as 100 and the changes that occur during the test are expressed as percent change from the pre-stress level. Cross-hatched areas indicate that the changes in the controls are highly statistically different from the patients ($P<0.01$) and the vertically-hatched areas are also statistically significant although somewhat less than the cross-hatched areas (i.e. $0.02<P<0.05$).

The first rectangle represents the stress period and the second rectangle the post-stress period.

Fig.4

The Effect of ACTH on the Urine and Blood Constituents Under the Control of Adrenal Steroids

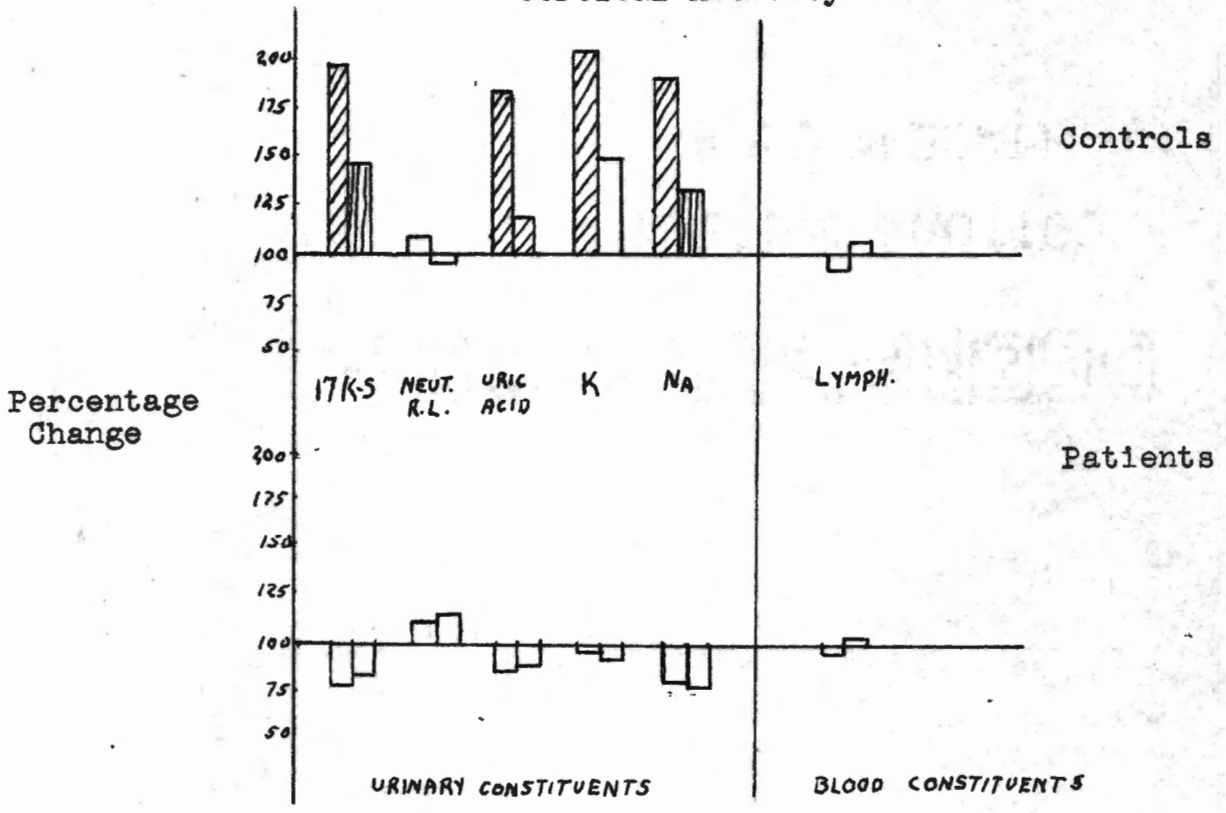


These data clearly show that adrenal cortex responsivity in the schizophrenic subjects is defective. Since the schizophrenics can respond to adrenal cortex hormones much like normal men (see last experiment), they either fail to produce such hormones in adequate amount on administration of ACTH or the latter is destroyed more radidly by the schizophrenics.

The investigators also used the pursuit-meter test, a psychomotor stress situation, to evoke adrenal cortical activity (see several pages back for explanation of this instrument). The results are plotted in Fig.5.

Fig.5

Effect of the Pursuit-Meter on Adrenal Cortical Activity



Of the five characteristic indices of adrenocortical activity, four (17-ketosteroid, potassium, sodium and uric acid) exhibit statistically significant differences between the two groups of subjects. The blood lymphocytopenia is not so marked in either group in these data and therefore does not serve to differentiate the two groups of subjects. As in the ACTH experiments it is again indicated here that endogenous adrenocortical secretion in response to stress is impaired in schizophrenic subjects.

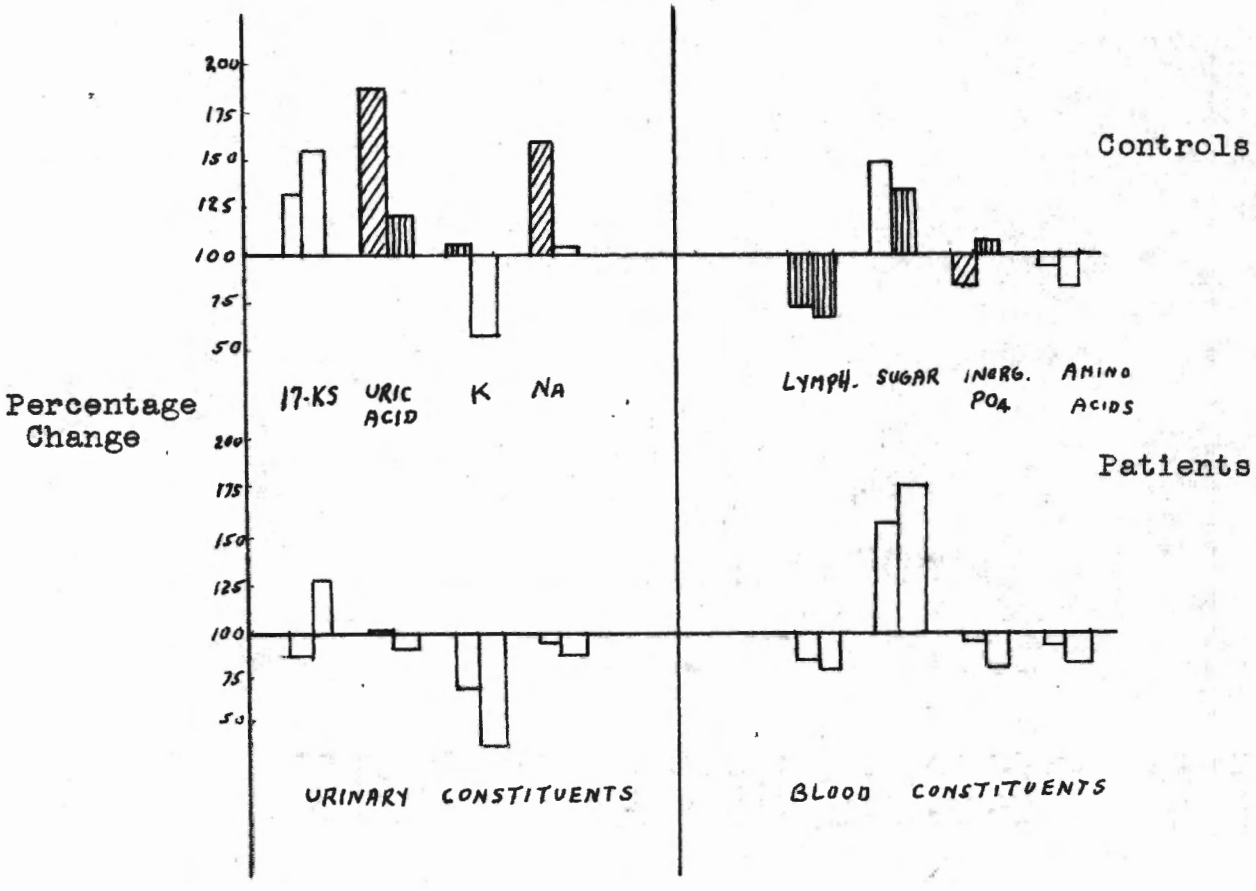
Using a targetball frustration test to create a psychological stress situation resulted in small increases in uric acid, potassium and sodium excretion in normal subjects indicating only

a mild effect on the pituitary-adrenal response mechanism. Therefore, there was no marked differentiation between the normal and patient groups.

The adrenocortical response to glucose administration in the form of an Exton-Rose tolerance test is shown in Fig.6.

Fig.6

Effect of Glucose on Adrenocortical Activity



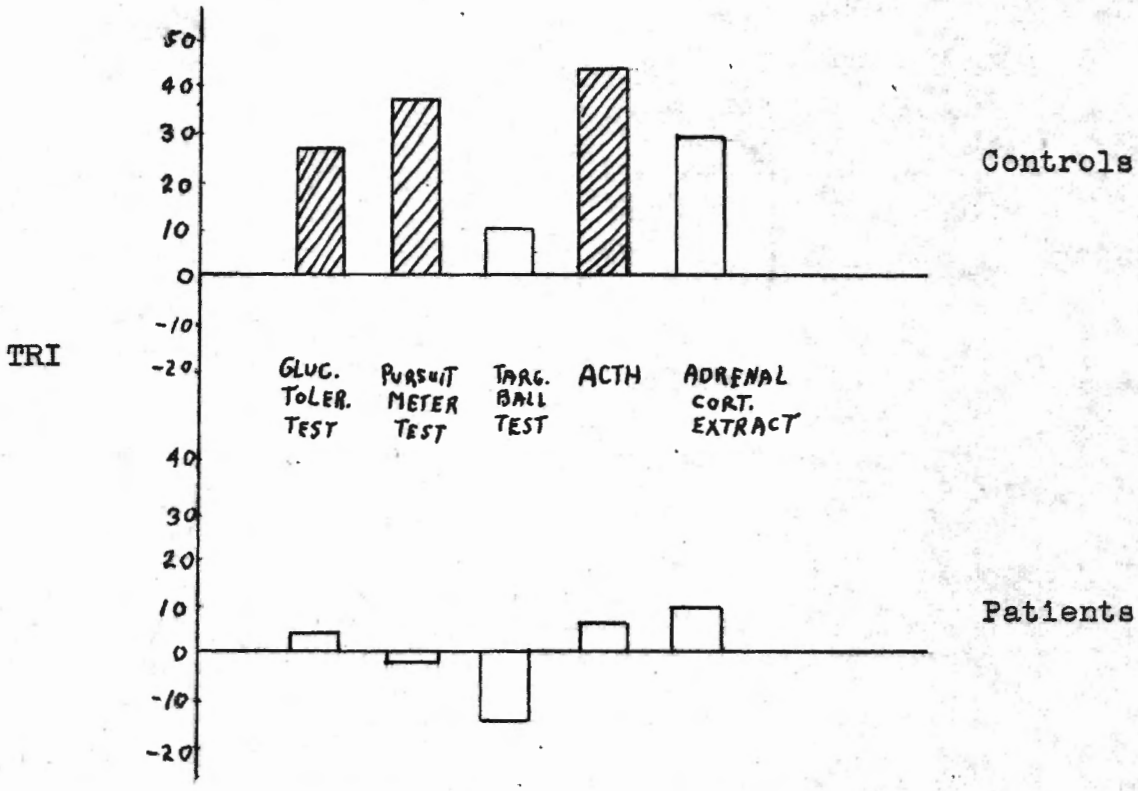
There is no significant difference in the excretion of urinary steroids, but there is a marked difference in the excretion of uric acid between the normals and schizophrenics. The normal subjects fail to show any increased excretion of potas-

sium but the marked stress decline in output shown by the patients cf differentiates their output change significantly from the nor-mals. A rise in stress sodium output among the normals is signi-ficantly different from the slight drop in the patient's mean val-ues. The lymphocytopenia is significantly greater in the normal subjects. The drop in blood amino acids is entirely similar inthe two groups and reflects similar insulin evocation. The schizo-phrenics had a "diabetic-like" blood sugar curve. A greater de-decrease in blood inorganic phosphate is observed initially in the normal subjects and this may be due to a more rapid phosphory-lation of the glucose. (Verzar and his co-workers (24) have ob-tained results from animal experimentation which indicated that this phosphorylation was controlled by the adrenal cortical se-cretions).

The data in the various experiments discussed above are expressed as the group mean values of different determinations which were done on many subjects i.e. it is a cross-sectional analysis. In order to obtain a picture of the distribution of individual responsivity the investigators devised an arbitrary "total response index" (TRI) which was determined for each individual. This was obtained by employing the data which represented the principle indices of adrenocortical activity, namely 17-keto-steroid and neutral reducing lipid outputs, the potassium, sodium and uric acid excretions and the blood, lymphocyte changes. The TRI was constructed for each individual by averaging the stress and post-stress percentage changes of these constituents. The mean TRI values for the five tests are shown in Fig.7.

Fig.7

Mean TRI Values of Adrenocortical Responsivity



It is seen from Fig.7 that all of the values for the control subjects are positive and are maximal in the ACTH test. Among the patients' data the largest positive value was obtained with the adrenal cortex extract administration and there is no statistically significant difference between the control and patient values both for this test and the targetball frustration test. The differentiation is significant in the remaining tests. These results clearly indicate that (a) the end-organs in schizophrenics can respond at a normal or almost-nowmal level to adrenocortical hormones, (b) a rather severe degree of unresponsivity of the adrenal cortex to ACTH in schizophrenia, (c) failure of indirect stimulation of the pituitary-adrenal mechanism in schizophrenics by glucose administration or pursuitmeter operation.

These experiments all indicate that the schizophrenic shows a peculiar type of hypoadrenalism which does not have the clinical and laboratory features of Addison's disease. Certain schizophrenics exhibit normal responsivity to one or more tests but in no single case did any patient show a normal response to every test. In considering the nature of the adrenocortical stress response there is seen a reason for diverse schizophrenic responsivities. The stress stimulus sets off the following sequence of events: stress → (a) central nervous stimulation → (b) pituitary activation → (c) adrenocortical secretion → (d) end-organ response. The data with the adrenal cortex extract show that (d) approximates the normal. The data on ACTH administration indicate that a real block occurs at (c) in most of the patients. However, one out of five schizophrenics exhibit normal responsivity at this level. The pursuitmeter test involves the whole sequence from (a) to (d) and those who showed a poor response with ACTH also had a poor response with this test. It is possible also that certain schizophrenics may have the block to adrenal cortical responsivity at (a) and (b) as well as at (c). Psychotics who respond to ACTH but not to psychomotor stress would be in this category.

In the light of these experiments we can now examine some of the studies that have been made on the effect of convulsive therapy on adrenal cortical activity. Ashby (43) studied the effects of electro-shock therapy on the excretion of various adrenal cortical steroids, namely, the sugar-active steroids, the reducing steroids and the 17-ketosteroids. It was found

that an increased excretion of the sugar-active and the reducing steroids occurred usually from one to seven days after convulsive treatment had started, at which time a peak excretion was present. She did not find an increase in the 17-ketosteroids too. The 14 subjects that were studied consisted of a mixed group of mental illnesses which included several schizophrenics. In attempting to correlate statistically the degree of psychiatric improvement with the occurrence of peaks in the excretion of the adrenal cortical steroids a P value between 0.016 and 0.10 was obtained, suggesting that increased steroid secretion and "good" clinical improvement tend to be associated. However, until a larger series of patients is studied this cannot be stated as positive fact. Altschule et.al. (44) observed a marked depression in the eosinophile count (these are also destroyed by the 11-oxysteroids) four hours after an electro-shock treatment was given to various types of psychotic patients. They believe that the beneficial effect of shock in involutional melancholia is over and above the effect on the adrenal cortex. Altschule and Tillotson (45,46) have suggested that their findings of an increase in extracellular fluids and a heightened diuretic response to water as well as an increased tissue storage of protein in psychotic patients receiving electro-shock therapy point to the action of evoked corticosteroids. Parsons et.al. (47) were impressed by the fact that the resting values of the blood sugar and lymphocytes were the same in the apathetic schizophrenic as when he was in a state of pathologic emotional behavior. This was unlike the great fluctuations which occur in the excited or depressed manic-depressive patients.

The physiologic concomitant of psychological stress was lacking in the schizophrenics. These authors state that the defect in schizophrenia is somewhere between the central nervous system and the endocrine glands, possibly a failure of pituitary activation.

At this stage of our knowledge it is impossible to give the specific relationship of the adrenal cortex to central nervous activity. However, that such an important relation does exist is now beyond dispute and that it is tied up in some way with cerebral malfunction is also unchallenged. It may be mentioned in passing that Grenell and McCauley (48) have shown that the administration of adrenal cortical extract to normal men causes definite changes in the EEG pattern, consisting primarily of remarkable increases in the amplitude of the brain waves.

D) Allergy and Schizophrenia

In view of the recently discovered beneficial effects of the adrenal cortical hormone cortisone (11-dehydro 17-hydroxycorticosterone) and ACTH in many diseases of allergic nature it is of interest to relate some of the clinical reports dealing with allergies in schizophrenia. Dougherty (49) has stated that it is almost impossible to immunize an adrenalectomized animal. McAllister and Hecker (50) made an elaborate study of the incidence of allergic conditions as well as past histories of allergies in over 1,300 schizophrenic patients. The control group consisted of 757 employees in the same hospital that the patients were housed. Both groups were studied at the same time of the year. The incidence of allergic histories in the control group was 21%, which agrees

well with the figures for the general population. Physical examination revealed that 13% had positive findings at this time. Among the schizophrenics a positive allergic history was present in only 5.7% and on physical examination only 2.9% showed any evidence of allergy. MacInnis (51) surveyed over 7,000 psychotic patients and found allergic symptoms in only 0.07%. Three of the patients showed an improvement or even a complete remission of the allergic symptoms while the mental disturbance was at its peak (low adrenal cortical activity?) and a return of allergic symptoms as the mental condition improved. Molholm (52) studied the cutaneous responses of 12 normal and 12 schizophrenic subjects to weekly intradermal injections of guinea pig serum by measuring the area of erythema that developed. Both groups became sensitized but the rate of development of sensitization as well as the intensity were significantly less in the schizophrenics than in the controls. As an example of this, the rate of increase in the area of erythema was 67 sq. mm./injection for the schizophrenics and 167 sq. mm./injection for the controls. Local vascular factors were not the cause for the differences between the groups since intradermal injection of histamine showed that they behaved alike to this substance.

E) Disturbances in the Somatic Nervous System in Schizophrenia

As a preface to the discussion of the following experiments it would be well to restate Freud's descriptive definition of anxiety. "The expectation of trauma, on the one hand, and, on the other, an attenuated repetition of it". We have seen how the very basic machinery for the survival of an organism in our

particular physical and chemical environment is seriously at fault in the schizophrenic individual. The mere act of living is indeed very traumatic for him.

Malmo and Shagass (53) made an elaborate study of several reacting systems in patients under a stressful situation which consisted of a thermal stimulation to the forehead. The subjects were 75 patients with various psychiatric diagnoses, who were classified into three groups. One group consisted of those who clinically showed much anxiety. Another was a mixed patient group consisting of depressions, psychopaths, alcoholics and others. The third group was made up of early schizophrenics. Normal subjects served as the control group. The order of anxiety in the groups, from greatest to least, was the anxiety patient group, the mixed patient group and the control group. The early schizophrenics were not rated as to anxiety. Simultaneous records of neck muscle potentials, head and finger movements (voluntary and involuntary) and respiration were taken. The involuntary finger movement scores for the different groups were: controls 15.7, mixed patient group 28.1, anxiety patient group 40.2 and schizophrenics 44.61 All intergroup differences were statistically significant except the anxiety and schizophrenic groups---showing a close analogy of the latter to the former since the degree of movement appeared to correspond closely to the degree of anxiety. Table V shows the group differences in the voluntary signaling of the experience or the expectation of pain.

Table V.

Voluntary Signaling of Pain of its Expectation

Group	Mean no. of signals	Median duration of signaling	Median latency period (between application of stimulus and start of signaling)
Control	2.9	0.86	2.76
Mixed	3.7	1.12	2.61
Anxiety	6.6	1.49	1.97
Schizophrenics	7.0	2.49	1.15

The greater the degree of anxiety the greater the frequency with which pain was signaled; and the signaling started sooner and kept up for a longer time. When the groups were compared at various intensities of pain stimulation a difference between the anxiety and schizophrenic patients did emerge. As the intensity of the stimulus was increased by steps it developed that the schizophrenics responded less discriminately than any other group when it came to signaling pain. The schizophrenics signaled to the most intense stimulus only 1.5 times as frequently as to the least intense, whereas the anxiety group increased its frequency 4.5 times. Therefore, the schizophrenics differ from the anxiety group in that their voluntary reactions tend to bear less relation to the physical characteristics of the stimulus.

Electrodes were attached to the neck of the subject to record the bursts of activity during the experiment. The neck muscle potential scores were: controls 8.9, mixed patient group 16.0, anxiety patient group 21.0 and schizophrenics 20.3. It was also demonstrated statistically that the only similar groups were the

anxiety and the schizophrenic patients---and the activity potential score was directly related to the degree of anxiety. Overt head movement scores led to similar conclusions. Respiratory irregularity is a measure of the immediate disturbing effect of a painful stimulation and again the anxiety and schizophrenic patients were the only groups that resembled each other.

Recalling Freud's definition of anxiety as "the expectation of trauma.....and.....an attenuated repitition of it" we may say that the early schizophrenic subject with his serious disturbance in fundamental homeostatic activity is an organism in "total retreat", putting up a strong but indiscriminate and exhaustive rear-guard action which further saps his "adaptation energy" and intensifies the internal biochemico-neural disorganization.

The last series of experiments to be examined deal with an homeostatic mechanism which literally subserves equilibrium, namely the vestibular apparatus. Testing the nystagmic reaction of a large number of schizophrenic and normal subjects to caloric and rotational stimulation Angyal and Blackman (54) found marked differences between these groups. After rotational stimulation the mean number of nystagmic beats for the patients was 44.9 and the frequency was 1.32/sec. The corresponding values for the normal subjects were 60.8 and 1.67. The differences between both sets of figures was of the highest statistical significance as witnessed by a $P<0.01$. Similar results were obtained by caloric stimulation; 60.2 mean nystagmic beats at a frequency of 0.82/sec. for the patients and 116.4 and 1.34 were the corresponding figures

for the normals. Statistical analysis again showed the differences to be significant with a $P<0.01$. One particular schizophrenic patient whose illness was marked by periodic stupors reflected his clinical course in the vestibular responsivity, which was good when he was in touch with environment and depressed when he returned to his stupor. Three successive trials at stimulation during one of these stuperous periods produced not even one nystagmic beat! The patients who manifested the least vestibular reactivity were characterized by an extreme degree of apathy, lack of initiative and poverty of mental content. All in all it is as if the chronic schizophrenic organism had retired to a state of physiological, intellectual and emotional hibernation i.e. a state which suits his low biologic adaptation energy.

Freeman and Rodnick (55) using a kymographic recording device were able to demonstrate that after rotational stimulation the postural steadiness was significantly greater in the normal subjects than in the schizophrenics. A similar study by Angyal and Sherman (56), also testing the interconnections of the vestibular apparatus with neuron nets other than those of the oculomoter centers, yielded similar and also highly significant differences in the postural behavior of blindfolded schizophrenic and normal subjects after caloric stimulation. After stimulation and with the blindfold still in place the subjects were told to mark time at a designated area and their tracking was noted. The normal subjects rotated 215.5^{o} from the position in which they were initially placed while the schizophrenics rotated only 73.3^{o} ($P<0.01$). Although the duration of the vestibular reaction was significantly

longer in the normals than in the schizophrenics, 108.0 seconds for the former as opposed to 45.0 seconds for the latter ($P<0.01$) the rate of rotation was still greater for the normals (50.2°/sec.) than for the schizophrenics (22.2°/30 sec.). Again the statistical P was less than 0.01.

The above experiments again disclose the presence of a low energy level in a fundamental homeostatic mechanism in the schizophrenic organism.

III Conclusion---Fact and Fantasy

We have seen the evidence which indicates that the schizophrenic is an organism with defective mechanisms for maintaining homeostasis. So fundamental a system as the hypothalamic-pituitary-adrenal cortical complex cannot be at fault without seriously incapacitating in some manner the activity of every living cell in the organism. The question that raises itself immediately is the causal direction of the psychologic and physiologic defects. The answer as to which comes first awaits further investigations, but one must not lose sight of the possibility of complementarity in this problem. However, this aspect of the subject has hardly been investigated, partly because it is exceedingly difficult to approach experimentally, but also because we are used to thinking in terms of cause and effect.

Although we can speak only in generalities at present, we, nevertheless, are to an extent on limited but firm experimental ground. The human organism besides being a self-controlling (homeostatic) system is peculiar in another physico-chemical respect in that it is able to exist at differnt levels of energy;

one example being the sleep and the waking states. The total energy of the system, and, more important, the rate of exchange of energy between the system and the environment is quantitatively different under both conditions. Similarly, different levels ~~of~~ of energy exist during the waking state depending on the demands of the environment at any particular instant. It is the second Law of Thermodynamics which states the manner in which any 2 systems at unequal energy levels, if allowed to act on each other, tend to equilibrate by a flow of energy from the high to the low energy system. It is this flow of energy which, if properly channeled, will do work. It is thus obvious that this phenomenon is basic in the many complex processes which are lumped together under the term--"living".

The total energy exchange between the "living" energy system and the only other energy system in relation to itself, namely, the environment (i.e. each organism "knows" only two energy systems--its own and the total environment) varies not only diurnally but also during the various stages of its lifetime. It is not simply that the infant is the species type of low-rate energy-exchange system but conversely--because it is a low-rate energy-exchange system it is an infant. What is called "development" of the infant is the progressive acquisition, in a genetically determined manner, of a higher-rate energy-exchange system. In this manner this "living" system is able to broaden its range of contact among the numerous sub-systems that compose the great environmental energy system.

The schizophrenic organism is thus viewed primarily as a

failure in "development" of a high-rate energy-exchange system. For some as yet unknown reason "maturation" stops at a stage which, although compatible for the energy exchange system at that particular age-environment, cannot maintain itself at a higer energy level. Gradually, as the organism finds it constantly "difficult to adjust" to the higher energy levels for which it has not developed a suitable energy-exchange system of its own, it drifts back to an energy-exchange level with which it is "compatible". Therefore, the extent of regression of a particular schizophrenic when viewed by the psychiatrist is an indication to what extent this organism has had to limit his contact with the environmental energy sub-systems. The theoretical limit approached is that of a single, isolated energy system---termed by the psychiatrist narcissism.

The questions to be answered in order to understand the neaning of schizophrenia are many and complex. What is the nature of the maturation process of the organism? What are its controls? What are the causes of its disturbance? To what extent and in what manner can this process be restimulated if it has ceased to function? Are its changes irrevocable?

BIBLIOGRAPHY

(1) McFarland,R.A., and Goldstein,H.
The biochemistry of dementia praecox.
Am. J. Psychiat. 93,1037,1937

(2) _____and___ ibid. 95,509,1938

(3) _____and_____ ibid. 96,21,1939

(4) Cannon,W.B.
The wisdom of the body.
W.W.Norton & Co.,Inc. New York, 1932

(5) Duval,A.M.
Symposium--various approaches to the schizophrenia problem.
Quart. Rev. Psychiat. and Neurol. 3,92,194

(6) Kanner,L.
The adrenalin blood pressure curves in dementia praecox and the emotional psychoses. Am. J. Psychiat. 85,75,1928

(7) Freeman,H., and Carmichael,H.T.
A pharmacodynamic investigation of the autonomic system in schizophrenia.
Arch. Neurol. and Psychiat. 33,342,1935

(8) Funkenstein,H.H.,Greenblatt,M. and Solomon,H.C.
Psychophysiological study of mentally ill patients.
Amer. J. Psychiat. 106,16,1949

(9) Hoskins,R.G.and Jellinek,E.M.
The schizophrenic personality with special regard to psychologic and organic concomitants.
A. Research Nerv. and Ment. Dis., Proc. 14,211,1933

(10) Gottlieb,J.S.
Relationship of systolic to diastolic blood pressure in schizophrenics.
Arch. Neurol. and Psychiat. 35,1256,1936

(11) Pfister,H.O.
Disturbances of the autonomic nervous system in schizophrenia and their relation to insulin, cardiazol and sleep treatments.
Am. J. Psychiat. Suppl. 94,109,1938

(12) Cameron,D.E. and Jellinek,E.M.
Physiological studies in insulin treatment of acute schizophrenia.
Endocrinol. 25,100,1939

(13) Rinkel,M.,Greenblatt,M.,Coon,G.P. and Solomon,H.C.
The effect of bilateral frontal lobotomy upon the autonomic nervous system.
Am. J. Psychiat. 104,81,1947-1948

(14) Dynes,J.B. and Tod,H.
The emotional and somatic response of schizophrenic patients and normal controls to adrenalin and doryl.
J. Neurol. and Psychiat. 3,1,1940

(15) Heilbrunn,Gert and Liebert,Erich
Observations on the adrenalin level in the blood serum during insulin hypoglycemia and after metrazol convulsions.
Endocrinol. 25,354,1939

(16) Tietz,E.B., Dornheggen,H. and Goldman,D.
Blood adrenalin levels during insulin shock treatments for schizophrenia.
Endocrinol. 26,641,1940

(17) Tietz,E.B. and Birnbaum,S.M.
Level of adreno-cortical substance in the blood during hypoglycemic treatment for schizophrenia.
Am. J. Psychiat. 99,75,1942

(18) Braceland,F.J., Meduna,L.J. and Vaichulis,J.A.
Delayed action of insulin in schizophren
Am. J. Psychiat. 102,108,1945

(19) Soskin,S. and Levine,R.
"Carbohydrate metabolism".
University of Chicago.Press. 1946

(20) Proctor,L.D., Dewan,J.G. and McNeel,B.H.
Variations in the glucose tolerance observations in schizophrenics before and after shock treatment.
Am. J. Psychiat. 100,652, 1943-1944

(21) Freeman,H. and Zaborenke,R.N.
Relation of changes in carbohydrate metabolism to psychotic states.
Arch. Neur. and Psychiat. 61,569,1949

(22) Paschkis,K.E. and Boyle,D.
Adrenal cortical hormone in blood.
J. Clin. Endocrinol. 9,658,1949

(23) Hoskins,R.G. Oxygen consumption in schizophrenia.
Arch. Neurol. and Psychiat. 28,1346,1932

(24) Advances In Enzymology. 4,264, 1944. Interscience Publishers, New York

(25) Golla,F., Mann,S.A. and Marsh,R.G.B.
Respiratory regulation in psychotic subjects.
J. Ment. Sc. 74,443,1928

(26) Hoskins,R.G. The biology of schizophrenia.
W.W. Norton & Co.
New York, 1946

(27) Cohen,L.H. and Fierman,J.H.
Metabolic, cardiovascular and biochemical changes associated with experimentally induced hyperthyroidism.
Endocrinol. 27,548,1938

(28) Hoskins,R.G. and Sleeper,F.H.
The thyroid factor in dementia praecox.
Am. J. Psychiat. 10,411,1930

(29) Rheingold,J.C. Autonomic integration in schizophrenia.
Psychosom. Med. 1,397,1939

(30) Neustadt,R. and Howard,L.G.
Fluctuation of blood iodine in cyclic psychoses.
Am. J. Psychiat. 99,130,1942

(31) Gottlieb,J.S. and Lindner,F.E.
Body temperatures of persons with schizophrenia and normal subjects.
Arch. Neurol. and Psychiat. 33,775

(32) Finkelman,I. and Stephens,W.M.
Heat regulation in dementia praecc
J. Neurol.and Psychopath.16,321,19

(33) Freeman,H. and Rodnick,E.H.
Autonomic and respiratory responses of schizophrenia and normal subjects to changes of intra-pulmonar atmosphere.
Psychosom. Med. 2,101,1940

(34) Freeman,H. Heat-regulatory mechanisms in normal and schizophrenic subjects under basal conditions and after the administration of dinitrophenc Arch. Neurol. and Psychiat. 43,456,1940

(35) Kerschbaumer,L. Endocrine maldevelopment in schizo phrenia. J. Nerv. and Ment. Dis. 98,521,194

(36) Freeman,H. and Hoskins,R.G. Comparative sensitiveness of schiz phrenic and normal subjects to glycerin extract of adrenal cortex Endocrinol. 18,576,1934

(37) Dougherty,T.F. and White,A. The influence of hormones on lymphoid tissue structure and function. Endocrinol. 35,1,1944

(38) Elmadjian,F. and Pincus,G. A study of the diurnal variation in circulating lymphocytes in nor- mal and schizophrenic subjects. J. Clin. Endocrinol. 6,287,1946

(39) Pincus,G. and Elmadjian,F. The lymphocyte response to heat stress in normal and psychotic subjects. J. Clin. Endocrinol. 6,295,1946

(40) Hoagland,H., Elmadjian,F. and Pincus,G. Stressful psychomotor performance and adrenal cortical function as indicated by the lymphocyte res- ponse. J. Clin. Endocrinol. 6,301,1946

(41) Freeman,H. and Elmadjian,F. The relationship between blood sugar and lymphocyte level in nor- mal and psychotic subjects. Psychosom. Med. 9,226,1947

(42) Pincus,G., Hoagland,H, Freeman,H. and Elmadjian,F. Adrenal function in mental disease Recent Progress in Hormone Res.Vol P.291. Academic Press, 1949

(43) Ashby,W.R. The effects of convulsive therapy on the excretion of cortins and ketosteroids. J. Ment. Sc. 95,275,1949

(44) Altschule,M.D., Parkhurst,B.S. and Tillotson. Decrease in blood eosinophilic leukocytes after electrically induced convulsions.in man. J. Clin. Endocrinol. 9,440,1949

(45) Altschule,M.D. and Tillotson,K.J. The effect of electroconvulsive therapy on water metabolism in psychotic patients. Am. J. Psychiat. 105,829,1948-49

(46) Altschule,M.D., Cline,J.E. and Tillotson,K.J. Fall in plasma protein level associated with rapid gain in weight during course of electroshock therapy. Arch. Neur. Psych. 59,476,1948

(47) Parsons,E.H., Gildea,E.F., Ronzone,E. and Hulbert,S.Z. Comparative lymphocytic and biochemical response of patients with schizophrenia and affective disorders to electroshock, insulin shock and epinephrine. Am. J. Psychiat. 105,573,1948-49

(48) Grenell,R.G. and McCauley,E.L. The effects of adrenal cortical extract on the EEG. Fed. Proc. 6,116,1947

(49) Dougherty,T. Recent progress in hormone researcl P.142,Vol.I,1947 Academic Press, New York

(50) McAllister,R.M. and Hecker,A.O. The incidence of allergy in Psychotic patients. Am. J. Psychiat. 105,843,1948-49

(51) MacInnis,K.B. Allergic symptoms in psychiatric patients. J. Allergy, 8,73,1936

(52) Molholm,K.B. Hyposensitivity to foreign protein in schizophrenic patients. Psychiat. Quart. 16,565,1942

(53) Malmo,R.B. and Shagass,C.
Physiologic studies in anxiety and early schizophrenia.
Psychosom. Med. 11,9,1949

(54) Angyal,A. and Blackman,N
Vestibular reactivity in schizophrenia
Arch. Neurol. and Psychiat.44,611,1940

(55) Freeman,H. and Rodnick,E.H.
Effect of rotation on postural steadiness in normal and schizophrenic subjects.
Arch. Neurol. and Psychiat.48,47,1942

(56) Angyal,A. and Sherman,M.A.
Postural reactions to vestibular stimulation in schizophrenics and normal subjects.
Am. J. Psychiat. 98,857,1942