THE RELATIONSHIP OF AUTONOMIC NERVOUS SYSTEM STIMULATION TO BEHAVIORAL ADJUSTMENT, CHANGE AND OUTCOME IN SCHIZOPHRENIA

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Ralph Hirschstein

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THESIS ABSTRACT

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THESIS ABSTRACT

The purpose of this study was to investigate the relationship between autonomic nervous system responses to the injection of adrenergic and cholinergic drugs, and the behavioral adjustment, change, and outcome of a group of schizophrenic patients.

The three hypotheses around which this study was structured were: 1. A significant relationship can be established between the quality of behavioral adjustment and the direction of blood pressure change after the injection of the adrenergic drug Epinephrine Hypochloride and the cholinergic drug Mecholyl Chloride. 2. A significant relationship can be established between spontaneous behavioral changes and the direction of blood pressure change after injection of the cholinergic drug Mecholyl Chloride. 3. The outcome of institutionalization can be related to the direction of blood pressure change after the injection of the cholinergic drug Mecholyl Chloride.

The tool used to investigate behavioral adjustment and change was the Gardner Behavior Chart, a five point scale, consisting of fifteen behavior categories. Behavior ratings were made by groups of nurses and attendants for a period of eight weeks.

Maximum blood pressure increases and decreases after the injection of the adrenergic and cholinergic drugs were used in the analysis of the results.

No significant relationship existed between the direction of blood pressure change after the injection of the adrenergic drug and behavioral adjustment. Significant relationships were established between blood pressure increase and poor behavioral adjustment, and blood pressure decrease and good behavioral adjustment, after the injection of the cholinergic drug.

Statistically significant results were obtained in an analysis of behavioral changes over an eight week observation period, after the injection of the cholinergic drug. Increase of blood pressure is associated with reduced adequacy of behavior. Decrease of blood pressure is associated with behavior improvement. A follow-up study five months after the initial experiment revealed a significant relationship between blood pressure change after injection of the cholinergic drug, and hospital status. Blood pressure decreases larger than increases were related to hospital release. Blood pressure increases larger than decreases were related to continuing hospitalization.

The blood pressure reaction to the injection of a cholinergic drug is a valuable tool in the diagnosis of adjustment, the prognosis of behavior change, and outcome of the disorder in schizophrenic patients.

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General Introduction to the Concept of Schizophrenia

Attempts to define the disorder known as schizophrenia have met with many difficulties. These difficulties are at least in part a function of the great variability of symptoms encountered in the schizophrenic patient. In studying the literature which deals with the problem of etiology and diagnosis of the schizophrenic, one is struck by the variability of judgments on the part of different authors regarding the origins, dynamics, and symptomatology of this disorder.

Those points of agreement amongst authors dealing with the problem of schizophrenia are that the patient said to suffer from a schizophrenic illness demonstrates such symptoms as inappropriate emotionality and speech, bizarre behavior, and thinking disorganization. We frequently find postulated a clash between the world of reality and the fantasied world of the patient, which is evidenced by the presence of delusions and hallucinations.

Attempts to define nosologically the schizophrenic process have met with much criticism. When sub-groups are established having in common similar symptoms, much depends on what the individual examiner will choose to stress in order

to arrive at a satisfactory classification. Frequently, the patients have symptoms that cut across several of the nosological categories. Bleuler (4) called attention to the fact that clear sensorium of vision, audition, touch, and smell differentiates non-recovering patients from those who recover quickly and completely. Patients in the acute state of schizophrenia whose sensory functions are much disturbed are usually those whose onset of illness was sudden and can be traced back to recent emotional stress. Patients, on the other hand, whose senses appear to be relatively well preserved but whose thinking processes are severely disrupted, are usually those whose onset of illness has been slow in developing and whose prognosis is poor. This observation has led a number of writers, such as Kantor, Wallner, and Winder (19), to investigate the schizophrenic disorder in terms of "process" and "reactive" types of the illness. The "process" type of schizophrenia might correspond to Bleuler's patients whose thinking appears much disturbed, but whose senses appear to be well preserved. The "reactive" type refers to patients whose sensory functions show much disturbance, and whose onset of illness can be traced back to considerable emotional stress. Kantor, Wallner and Winder (19) could successfully make a crude differentiation between "reactive" and "process" schizophrenia on the basis of Rorschach findings as well as clinical histories. In their study, each patient was classified as a "reactive" or "process" schizophrenic on the basis of

Rorschach protocols. Patients called "reactive" as determined by their history, tended to be called non-psychotic on the Rorschach protocol. As the authors pointed out, patients whose pre-schizophrenic personality was relatively normal, who had an acute onset of the disease which could be related to a specific precipitating factor, and whose sensorium was much disturbed at onset, manifest the "reactive" type.

Bellak (3) has pointed out that what is perhaps most impressive about the etiology of schizophrenia is the wide variety of factors reported. He goes on to conclude that:

(a) Schizophrenia is not a disease entity, but a syndrome or reaction type associated with a large variety of etiological factors. He refers to the reaction as a "deficit" reaction, implying the organism's inability to function properly.

(b) The syndrome may be hypothetically completely psychogenic in nature, or, it may be hypothetically completely somatic in nature. Between these two polarities, a continuum is assumed to exist.

(c) Predisposition to the reaction may be considered from a constitutional, somatic, or sociopsychological viewpoint. Factors interact differentially for different individuals.

Bellak also suggests that each case be considered on the following four-dimensional scheme: a, somatic predisposition, b, sociopsychological predisposition, c, psychological

precipitating causes, d, somatic precipitating causes. He feels that failure to understand the complexity of the schizophrenic process is a function of our inability to conceptualize multiplicity of causes.

Integrative Approaches to the Problem of Schizophrenia

A relatively recent and promising approach to the problem of schizophrenia has been an attempt to link psychogenic and somatogenic factors in the consideration of the schizophrenic process. Angyal, Freeman, and Hoskins (2) utilize the concept of "withdrawal" and incorporate in it a large number of physiological and psychological characteristics encountered in the schizophrenic patient. "Withdrawal" on the psychological level implies a reduction in intensity and quantity of relations between the person and his environment. This partial break in relationships to the outside world results in an increasing impoverishment of living, and is reflected by the indifference, emotional blunting, and lack of interests encountered in schizophrenics. On the psychological level, an impoverishment of a large number of body processes is likewise noted. Hoskins et al (18) have performed a vast number of experiments involving general metabolism as well as functions of the central and autonomic nervous systems.

A similar integrative approach to the problem of schizophrenia, likewise using factors of physiological and psychological concomitance, is one that uses the concept of

"stress" as an explanatory tool. By "stress" is implied a disruption of the organism-environment relationship (28). This disruption may be viewed as a function of three types of situations. One situation may occur when the organism is exposed to an external stimulus for which there is no adequate adjustive response available. Another kind of situation occurs when the organism attempts to satisfy two equally strong needs aroused by the environment. A third type of situation is the one in which the environment lacks adequate structure in order to satisfy an aroused motive on the part of the organism.

Selye's experiments (28) with animals have shown a number of alarm reactions as a function of situations involving "stress". He points out that all organisms respond to "stress" producing situations, and that basic reaction patterns of a behavioral, physiological and psychological kind result, irrespective of the agent producing the stress (28). LeVay (20) comments upon failures to adapt to "stress" producing situations, and calls such failures "diseases of adaptation". Such failures are reflected at all levels of the organism's existence. As a "stress" producing situation evolves, the organism is called upon to respond to it in an integrative fashion. In this attempt, not only do psychological changes occur, but internal physiological changes likewise are a part of the evolving attempt to deal with the "stress" producing situation. The anterior pituitary gland

is stimulated, effecting release of the adrenal corticotrophic hormone ACTH. This in turn stimulates the adrenal cortex, the corticoid hormones of which produce widespread effects on target organs. Since conditioning patterns may considerably alter the reaction pattern to "stress" on a psychological level, diverse symptomatology results. Individuals who are suffering from schizophrenia have evidenced a lack of ability to cope with situations. We are thus confronted by a vast number of symptoms in which the schizophrenic gives evidence of this lack of adjustive ability.

It is quite apparent that concepts such as "stress" and "withdrawal" have in common an increased emphasis upon an integrated approach to our understanding of the schizophrenic process. There is no evidence that the schizophrenic process is caused by either biological or psychological factors working alone. The value of these concepts rests upon their attempts toward a unified approach to the problem. The assumption of a psycho-biological disturbance not only helps to clarify our conception of schizophrenia as a disorder of the total person, but furthermore helps to cut across the nosology of either a psychologically or organically biased approach. It makes a distinct difference with regard to the type of problems investigated.

Some Physiological Aspects of Schizophrenia

The literature in the field of physiological aspects of schizophrenia is voluminous. No attempt will be

made to include in this survey more than a brief representative sampling. Inasmuch as the present study will deal more specifically with autonomic nervous system functions, these will be described under a separate section.

The present investigator has been impressed by the many physiological investigations which are ill supported by factual data and lack statistical correctness. Many studies have a tendency to sound conclusive, but upon closer analysis are unsupportable because repeat investigations show negative results. Few of them yield more than promising trends at best. A notable exception are the studies that, for a good number of years, have been carried out by the Worcester State Hospital Research Service (16, 24, 25).

These studies encompass the areas of metabolic reactivity, central nervous system reactivity, and autonomic nervous system functions in schizophrenic subjects. The overall impression one gains from these investigations is that the schizophrenic patient suffers from a hypo-reactivity of these body processes. Upon administration of metabolic stimulants, such as desiccated thyroid substance, investigators found a strong resistance to the expected increase of metabolic functioning (6, 17). Administration of the autonomic nervous system stimulant, Epinephrine, by Freeman (10) produced less response in oxygen consumption,

cutaneous temperatures, and perspiration rate in twenty schizophrenic subjects than in control subjects. Studies of central nervous system reactions likewise tend to support the assumption of hypo-reactivity in schizophrenic patients. Angyal and Blackman (1) discovered that vestibular activity to caloric and rotatory stimulation in a group of fifty-eight schizophrenic subjects was markedly reduced, when compared to a control group. Rubin (26) found that, upon hyper-ventilation in a group of schizophrenic subjects, only a 52% increase of slow waves as measured by the EEG will occur, when compared to a group of normal subjects. This latter study emphasizes the inability of the schizophrenic to cope with the metabolic problem inherent in the hyper-oxidation of brain tissue. The schizophrenic is apparently unable to absorb excess oxygen in his central nervous system.

Hoskins (13, p. 159), in summing up the total of physiological studies, states: "The schizophrenic is marked by numerous defects of adaptive efficiency, leading to inadequate and uneconomical organic response to changing stimuli. Obviously, in the human mechanism, failure of integration might be due to functional imbalance arising in a variety of ways, including conditioning in the broadest of terms. It would seem that the prodigality of effort required for organic adaptation leaves the patient with but inadequate energy for successful adaptation in the social

field. Bellak (3) comments upon this by stating that all these observed changes are but different levels of expression of an overall disturbance.

The Autonomic Nervous System in its Relation to Schizophrenia

This study attempts to relate the reaction sensitivity of the autonomic nervous system to the behavioral adjustment of schizophrenic patients. The following discussion aims therefore to present briefly autonomic nervous system functions, and a series of studies that investigate their relationship to the schizophrenic process.

The autonomic nervous system consists of nerves, ganglia, and plexuses which provide innervation to the heart, blood vessels, glands, viscera, and smooth muscles. It is, therefore, a widely distributed system and controls autonomic or vegetative functions (15). This system can be divided into two divisions which serve roughly different functions. The sympathetic nervous system is not essential to life, and animals deprived of it can continue a fairly normal existence within the laboratory. This division frequently discharges as a unit, which results in heart acceleration, red blood cell increase in the circulation, blood sugar rise, pupil dilation, and, in general, changes that prepare the organism for fight or flight. The parasympathetic system, on the other hand, is essential to life, and is organized for discrete and localized discharge. In its function as

conserver and restorer, it tends to slow the heart action, lowers blood pressure, stimulates gastro-intestinal movements, aids absorption, protects retinae from excess light, and empties bladder and rectum.

Greatly enhanced by the effects of sympathetic stimulation, the adrenal cortex secretes Adrenin, which in turn reinforces the sympathetic stimulation. Nerves instrumental in the release of Adrenin are known as adrenergic nerves. It furthermore appears that mainly upon parasympathetic stimulation, a substance known as Acetylcholine is secreted, enhancing the effects of this autonomic division. While the actual method of production of this substance in the body is not fully understood, it appears that it is secreted at the nerve endings of parasympathetic as well as some sympathetic nerves. These nerves are known as cholinergic nerves (15). The synthetic production of Adrenin and Acetylcholine has enabled investigators to study in more detail the reaction sensitivity of the autonomic nervous system.

Investigations of autonomic nervous system processes in their relation to the schizophrenic process have primarily dealt with the efficiency of organs responsible for the secretion of the substances Adrenin and Acetylcholine.

Hoagland (16) has shown that, in a study of one hundred schizophrenics, two-thirds of this group was subnormal in its adreno-cortical responses. This adrenal activity is a function of autonomic nervous system stimulation. Adrenal stereoids have far-reaching metabolic repercussions on tissue metabolism, including that of the brain. Thus, there are mechanisms which might modify brain functioning in the direction of producing the distortion of affect and association processes associated with the schizophrenic process (16). It is well to remember that there is no implication here regarding the cause of the schizophrenic process. The significance of these findings rests upon the observation of psycho-physiological changes in the organism, once the failure to adapt has commenced. Although the organism is regarded as functioning in a holistic framework, in which a breakdown of autonomic nervous system processes is an indication of failure to relate adequately to the environment, the origin of this adaptation failure remains multicausal.

Investigations concerned with the functions of autonomic nervous system processes have devoted much attention to the thalamic centers. A considerable body of evidence shows that the hypothalamus is of prime importance when one considers the effects of the autonomic nervous system in schizophrenics. Cannon's (5) pioneering work in relating the functions of the thalamic center to the emotional

life of the organism is much supported by recent studies concerned with the functions of the autonomic nervous system. Pincus et al (24, 25), in a series of studies have shown that hypo-activity of the adrenal cortex is found when disturbed schizophrenics are subjected to situations involving a sudden threat to the organism, such as loud noises. A confirmation of this finding comes from a similar study conducted by Hoagland (16), who likewise finds consistent hypo-active adreno-cortical responsivity in situations of psychological stress. Freeman (8, 9, 10) suggests that the schizophrenic reaches a stable balance at the cost of losing contact with his environment. The behavioral picture of the chronic schizophrenic emerges as being non-discriminating, non-adaptive, and inflexible. This state is likewise reflected in the schizophrenic's autonomic nervous system sluggishness, as indicated by defective adreno-cortical functioning.

Primary control of autonomic functioning is lodged in the hypothalamus. The distinctive importance of the hypothalamus is its integrative effects upon autonomic discharges (15). These integrative functions are derived from its relationship to the various neural and endocrine mechanisms regulating the internal environment of the organism. Nuclei contained in the hypothalamus can be divided into two main groups: a) the posterior and lateral nuclei, and b) the medial and anterior nuclei. When stimulating the former,

one obtains all the effects of sympathetic discharge, including pupil dilation, blood pressure elevation, and heart acceleration. When stimulating the latter, one obtains the effects of parasympathetic discharge, including blood pressure drop, heart deceleration and pupil contraction.

Emotional arousal changes the chemical and endocrine balance of the blood. Release of Adrenalin from the medulla of the adrenal glands, activated by hypothalamic activity, results in the effects associated with sympathetic discharge. Nerve fibers associated with the parasympathetic system release acetylcholine which has effects similar to parasympathetic enervation. Release of this substance has similar effects to those produced by electrically stimulating the medial and anterior nuclei of the hypothalamus.

Research in this area points to the fact that apparently we do find unusual reactions of the autonomic nervous system which are associated with the schizophrenic process. This is to be expected, if we regard schizophrenia as a disease process in which communication between the individual and the environment has become severely disrupted. Schizophrenics react to sensations which are not in accord with the real world. This leads one to suspect that the mechanism whose function it is to cope with sensations would likewise reflect this impairment. If one were to investigate

the extent of such an impairment, one might obtain an indicator not only of the present state of the schizophrenic disease process, but also of its prognostic implications. Adrenin, or its synthetic equivalent Epinephrine Hypochloride, and Acetylcholine, or its synthetic equivalent Mecholyl Chloride, appear to be the energizing substances secreted by the organism under stress.

The Autonomic Nervous System Test

Funkenstein et al (11, 12, 13) have shown that a significant relationship exists, in a group of mentally ill patients, between reaction to the injection of autonomic nervous system stimulants, and the reaction to electric shock therapy (ECT) and insulin coma therapy (ICT*).

The Funkenstein test of the autonomic nervous system was administered as follows: With the patient at rest, blood pressure measurements were obtained until constant for a period of five minutes. One cc. of saline solution was then administered intravenously, and systolic blood pressure measurements obtained for a period of thirty seconds. This had as its object the elimination of any patients in whom the suggestive element of the needle might account for the blood pressure changes. On the second day, a solution of .05 mg. of Epinephrine Hypochloride was injected intravenously within one second, in order to raise blood

* Henceforth, the above abbreviations will be used.

pressure. Systolic blood pressure measurements were obtained every fifteen seconds, beginning at thirty seconds after injection time, until a return to basal pressure was recorded, and remained constant for five minutes. A solution of 10 mg. of Mecholyl Chloride was given intramuscularly on the third day, in order to lower blood pressure. Systolic pressure measurements were obtained every thirty seconds for a total of six minutes, and once every minute thereafter for nineteen minutes, until a total of twenty-five minutes had elapsed, at which time all patients' blood pressure had returned to basal pressure.

Results of blood pressure reactions to these drugs were recorded for each patient. Patients were subsequently divided into seven groupings, differing from each other according to their blood pressure reactions, as described by Funkenstein (11). Since this original study, however, it has been found by Meadow and Funkenstein (22) that these seven groupings can be conveniently re-combined into three distinct groups that yield distinctly different blood pressure reactions. These groups can be differentiated from each other by using the following criteria:

(a) basal blood pressure

(b) height of blood pressure rise after Epinephrine injection

(c) immediate fall of blood pressure after Mecholyl injection

(d) possible delayed rise after Mecholyl injection

(e) return to basal blood pressure (homeostasis)

The description of these groups is as follows:

"Group A

Epinephrine: Marked strong rise in systolic pressure above 50 mm. of mercury, with return to pre-injection level within 3-7 minutes.
Mecholyl: Slight fall in systolic pressure with early rise above pre-injection level, and no return to homeostasis within 25 minutes.

Group B

Epinephrine: Marked or moderate rise in systolic pressure, not above 50 mm. of mercury, with return to basal pressure within 3-7 minutes.
Mecholyl: Moderate fall in systolic pressure with or without slight rise above pre-injection level, but return to homeostasis within 25 minutes.

Group C

Epinephrine: Moderate or marked rise in systolic pressure, not above 50 mm. of mercury, with return to pre-injection level within 3-7 minutes.
Mecholyl: Marked fall in pressure with failure to reach pre-injection level within 25 minute observation period" (22, p. 135).

The following interpretations are offered, in an effort to explain these strikingly different reactions to the injected drugs. Meadow and Funkenstein (22) point out that Group A type reactions represent a sympathetic release phenomenon similar to that observed in sympathetic denervation. Evidence for this is based upon the extremely marked rise of systolic blood pressure, exceeding 50 mm. of mercury rise, in response to Epinephrine injections shown by patients

in this group. Results of a long series of experiments indicate that sympathetic denervation produces a heightened reaction to Epinephrine (22). It thus appears warranted to state that the sympathetic nervous system of group A patients does not react to physiologically induced stress in a normal fashion. Funkenstein (11) has demonstrated that this group shows the least improvement after ECT, while Meadow and Funkenstein (22) have shown that this group suffers from the most significant loss in abstraction ability.

Group C patients includes those patients who evidenced marked anxiety before, during, and after the injection of the drugs. All cases of severe chill after the Mecholyl injection were found in this group. Group B patients did not show marked anxiety reactions. It was furthermore reported that Group B patients, while evidencing severe emotional disturbances before and after the actual experiment, did not evidence any marked rise in blood pressure during these disturbances.

Group B patients, who show no particular autonomic system disturbance, yield only a fair prognostic picture after ECT and ICT. Although these patients are apparently under considerable psychological stress, as indicated by their extreme disturbances in associations and affectivity, the autonomic system is apparently not integrated with the rest of the organism. This is shown by the virtual lack of

blood pressure change when under violent mood spells severe enough to warrant seclusion rooms.

Group C patients show a heightened reaction of their autonomic nervous system to the autonomic nervous system stimulant. This group has an excellent prognosis following ECT and ICT, while their abstraction ability is least impaired (21). The prognosis of group B patients following ECT and ICT, is better than that of Group A patients in whom the reaction actually reflects denervation. It is only group C, however, in which physiological stressors, in conjunction with the psychological stress under which the schizophrenic usually operates, produce heightened sympathetic activity, that appears to be the most favorable sign for improvement following ECT and ICT.

Studies that have attempted to relate psychological tests to the above discussed physiological stress reactions have been relatively few. Meadow et al (21, 23) attempted to discover to what extent anxiety level related to specific autonomic groupings. The Wechsler-Bellevue digit span and arithmetic subtests, and the Rorschach sum shading and turning scores, were used in an effort to investigate anxiety level in fifty-eight schizophrenic patients. Hypotheses stated that a high anxiety level would relate to autonomic group C, while a low anxiety level would relate to groups A and B. These hypotheses were not confirmed. The

authors felt that the questionable reliability and validity of the anxiety measures were to be held accountable for the negative findings. Meadow and Funkenstein (22), in an investigation designed to relate the extent of abstraction ability in a group of fifty-eight schizophrenic patients to autonomic groupings, utilized the Wechsler-Bellevue similarities and block design subtests, the object sorting tests, and the Benjamin Proverbs tests. Highest loss of abstraction ability was encountered in patients belonging to the prognostically poorest autonomic group A. Highest abstraction ability was significantly related to group C reactions.

Ficca (7) attempted to relate Wechsler-Bellevue clinical patterns as well as Rorschach scores and signs to the Funkenstein autonomic groups. His subjects were comprised of twenty-eight schizophrenic, thirty-one neurotic, and seven psychopathic patients. No statistically significant relationship could be established between autonomic grouping and Wechsler-Bellevue pattern. It appears, according to the author, that attainment and scatter measures seem characteristic of the hospital population as a whole, rather than of autonomic groupings. Rorschach scoring categories, locations, popular responses, and sum of color were used as a further basis of comparison. Significant relationships could be established between the number of human and inanimate movement responses and specific autonomic groupings. Movement responses were significantly higher in the

autonomic groupings that is related to a favorable prognosis. The number of schizophrenic "signs" appeared to be significantly related to the autonomic groupings. The prognostically more favorable autonomic group contained patients who had less schizophrenic "signs" in their Rorschach protocols. The author admits, however, that the number of subjects for each group were so small that the findings do not warrant any definite conclusions. The author furthermore utilized Funkenstein's original seven group breakdown, a method that, since Ficca's study, has been found to be not reliable, and which furthermore requires very large groups of patients.

The investigations discussed so far have attempted to discover relationships between physiologically induced autonomic nervous system reactions, psychological test findings, and progress of the schizophrenic disorder after, or before, electric and insulin shock treatments. No attempt has been made to investigate the possible relationship between autonomic nervous system reactions to physiologically induced stress, level of current adjustment, and trends of behavioral change in untreated schizophrenic patients.

The importance of a study designed to investigate the relationship between autonomic reaction patterns and spontaneous improvement rests upon its consequent predictive value regarding the outcome of illness. It has become a

standard procedure to utilize shock treatment techniques almost immediately upon hospitalization of a schizophrenic patient. The effects of such techniques, while beneficial in some cases, are relatively uncontrolled, and furthermore not understood. Patients who give a favorable autonomic response to the Funkenstein test (11) would conceivably be spared from the possible undesirable side effects of indiscriminate shock treatments. The theoretical implications from such an investigation are likewise of great interest. Our conception of the etiology and progress of the schizophrenic illness has become so overwhelmed by personality dynamics and direct observations of the patient's behavior, that body processes are by-passed. It is felt that the type of investigation proposed is an important step in the direction of viewing illness as a total process.

STATEMENT OF THE PROBLEM AND HYPOTHESES

This study is an attempt to relate observed behavioral adjustment of institutionalized schizophrenic patients to blood pressure changes following the injection of the adrenergic drug Epinephrine Hypochloride and the cholinergic drug, Mecholyl Chloride. This study furthermore is an attempt to relate behavioral changes observed over a two months time span to characteristic blood pressure changes following the injection of the drugs, Epinephrine Hypochloride, and Mecholyl Chloride.

The objective in this particular study rests upon the need to possess a clinical tool that can be used as a possible prognostic instrument to predict whether or not a patient suffering from a schizophrenic break will recover without the interference of shock treatments. Shock treatment may be regarded as possessing chiefly an ameliorative value, especially when viewed as a tool to calm the disturbed patient or to elevate the mood of the depressed patient. The choice between the use of barbiturates and shock treatment in calming the patient has become in many instances a highly arbitrary one. It is no exaggeration to state that in many state hospital settings, uses of ECT and ICT have become a standard procedure. The indiscriminate use of such treatment appears to be highly undesirable as a general policy, since neither improvement nor failure to improve after

shock treatment can be explained nor accurately predicted. While it is quite true that shock treatments frequently do have beneficial effects, it appears highly desirable to this investigator, to predict a patient's behavioral adjustment more accurately before subjecting him to a series of shocks. It is with this consideration in mind that the present study was developed.

As Funkenstein, Greenblatt, and Solomon (14) have indicated, success or failure of ECT and ICT can be significantly predicted on the basis of characteristic blood pressure reactions to the adrenergic drug, Mecholyl Chloride. It appeared to this investigator that it would be highly desirable to investigate the behavioral changes of schizophrenic patients, after first having obtained their characteristic blood pressure reactions following the injection of Epinephrine and Mecholyl Chloride, without any shock treatments at all to be administered during the observation period. In other words, can one significantly predict behavioral changes without shock interference, using blood pressure reactions to these two drugs as a criterion? If using these drugs results in significantly accurate prediction, we would have a prognostic measurement of considerable value in deciding who is and who is not to receive shock treatment.

It would, furthermore, be of great value to know

whether characteristic blood pressure reactions following the injection of Mecholyl Chloride could be used as a prognostic device in predicting what patients would be discharged after a certain period of hospitalization.

The problem may be stated in the following hypotheses:

1) The quality of behavioral adjustment in a group of schizophrenic patients is significantly related to a characteristic autonomic nervous system reaction, as defined by the direction of blood pressure change, induced by the adrenergic drug, Epinephrine Hypochloride, and the cholinergic drug, Mecholyl Chloride.
   a) Decrease of blood pressure following the injection of Epinephrine Hypochloride is related to unfavorable behavioral adjustment.
   b) Increase of blood pressure following the injection of Epinephrine Hypochloride is related to favorable behavioral adjustment.
   c) Decrease of blood pressure following the injection of Mecholyl Chloride is related to favorable behavioral adjustment.
   d) Increase of blood pressure following the injection of Mecholyl Chloride is related to unfavorable behavioral adjustment.

2) The trend of spontaneous behavioral adjustment changes over an eight week observation period in a group of schizophrenic patients is significantly related to the direction of blood pressure changes following the injection of Mecholyl Chloride.

   a) Decrease of blood pressure following the injection of Mecholyl Chloride is related to favorable behavioral adjustment changes over an eight week observation period.

   b) Increase of blood pressure following the injection of Mecholyl Chloride is related to unfavorable behavioral adjustment changes over an eight week observation period.

3) Discharge from the Traverse City State Hospital is significantly related to blood pressure changes following the injection of Mecholyl Chloride in a group of schizophrenic patients.

   a) Decrease of blood pressure following the injection of Mecholyl Chloride is related to hospital discharge within a five months period after admission of a group of schizophrenic subjects.

   b) Increase of blood pressure following the injection of Mecholyl Chloride is related to continued hospital confinement beyond a five months period in a group of schizophrenic patients.

Funkenstein (11) reports that the characteristic reaction in patients who are more apt to improve following shock treatment is a gradual decrease in blood pressure following the injection of Mecholyl Chloride, with the blood pressure remaining below the individual's normal pressure for an approximate twenty-five minute observation period. Most characteristic of poor prognosis following shock treatment is a blood pressure reaction that, while often indicating a short fall in blood pressure, is quickly followed by a large increase of blood pressure. This is considered an abnormal reaction. Administration of a cholinergic drug should normally energize the parasympathetic system with resultant blood pressure decrease. These two most characteristic reactions to Mecholyl Chloride injections will be used in an analysis of their significance in relation to behavioral adjustment, behavioral change, and discharge from the institution.

Funkenstein's results with Epinephrine have been less conclusive. He reports frequent abnormal blood pressure changes in patients who react most poorly to shock treatment (11). He found that the subjective evaluation of manifest anxiety was the most significant indicator of a good prognosis following shock treatment. In this investigation, the attempt will be made to evaluate blood pressure reaction to Epinephrine in terms of abnormal increase as well as

decrease of blood pressure, although this latter phenomenon has not been previously dealt with. Can such an abnormal blood pressure reaction to Epinephrine be related to behavior adjustment in a manner similar to one which utilizes the parasympathetic stimulant Mecholyl Chloride? It was not felt that the evaluation of "manifest anxiety", however, could be used as a valid and reliable criterion, due to the inherent difficulties in such a subjective evaluation.

METHODOLOGY

Selection of the Subjects

The subjects selected for this study consisted of sixty patients, diagnosed unequivocally as suffering from a schizophrenic disorder. These subjects were obtained at the Traverse City State Hospital. Care was taken to utilize only patients free from the following disorders: heart disease, thyroid disorder, tuberculosis, diabetes, hypertension, or any organic disorder involving central or peripheral nerve mechanisms. Inasmuch as the drugs Epinephrine and Mecholyl Chloride constitute some threat to the organism when administered, it was felt that any complication arising from using the drugs would be minimized in this manner.

The age range of the subjects extended from age nineteen to forty-one years, with a mean of 28.7. An attempt was made in this study to avoid older subjects, since the use of the drugs can constitute a possible health hazard, especially for the older patient. With the exception of the senile groups at the institution, the age group utilized well represents the average age of the patients at the hospital.

While it was not felt that the range of intelligence had to be considered as a possible factor to be

controlled, care was taken not to utilize any patients who were found to be mentally deficient. This was felt to be a further safeguard in avoiding any subjects who might conceivably be suffering from a central nervous system disturbance.

One of the objectives in this study was to investigate spontaneous behavior changes over a two month time span in patients suffering from schizophrenia, without the administration of any of the physical therapies. This proved to be one of the most difficult aspects to control. While ICT was not difficult to control since during the time of study, it was not administered; ECT was administered as standard procedure. The original sample of eighty-seven patients was reduced to a total of sixty, primarily due to the administration of ECT at some time during the observation period. None of the patients received any psychotherapy during the time of this study. Some of the patients did receive hydrotherapy. It was not felt that the effects of this therapy have any more far-reaching effects than the general environmental change that occurs when a patient is admitted to the hospital surroundings.

The original aim had been to utilize a sample of patients totally comprised of recent first admissions to the receiving hospital. However, sample controls as described above necessitated the use of a sample of schizophrenic patients who had been institutionalized for a period not

exceeding three years. While the majority of subjects had been institutionalized less than one year (70%), none of the subjects used had received any ECT. The sample thus includes sub-acute as well as acute schizophrenics. Care was taken to include only subjects who had not previously been institutionalized. This was deemed to be important, since frequently the record accompanying the patient neglects to include possible therapy the patient might have obtained.

Although the sex of the patient did not appear to have any bearing on the results of the study, it developed by chance that the population of sixty was divided evenly into thirty males and thirty females.

Procedure in the Administration of Drugs

The drugs, Epinephrine Hypochloride, a synthetic equivalent of the adrenergic hormone adrenaline, and Mecholyl Chloride, the synthetic equivalent of acetylcholine, were administered to all sixty subjects.

The injection of Epinephrine Hypochloride was performed by medical personnel, since due to its rapid disintegration, it has to be administered intravenously. A dosage of .05 mg. of Epinephrine Hypochloride was administered, according to Funkenstein (11). Prior to the

intravenous injection of the drug, the subject was subjected to an intravenous injection of saline solution, the purpose of which was to control the possible psychological effects which may cause great fluctuations in blood pressure. Any subject fluctuating more than ten points from his resting blood pressure was eliminated from the sample.

After each patient had recovered from the Epinephrine Hypochloride injection, as indicated by blood pressure return to normal, Mecholyl Chloride was administered intramuscularly. A dosage of 10 mg. of Mecholyl Chloride was administered, following Funkenstein (11). It is to be noted that this procedure differs from Funkenstein's, insofar as the Mecholyl Chloride injections were administered on the same day as the Epinephrine Hypochloride injections. This was done in an effort to avoid the considerable upset of patients when they are transferred to different surroundings, required in order to administer the drugs. The fact that Mecholyl Chloride was administered after basal blood pressure measures had been obtained for a minimum of five minutes, indicates that the injections of Epinephrine Hypochloride had been neutralized by the organism.

Procedure in the Evaluation of Blood Pressure Changes

The critical aspect of this study involved the accuracy of blood pressure measurements prior to, during, and

following the administration of the drugs. The instrument used was the reliable arm cuff manometer. Great care was taken to instruct student nurse personnel in the accurate measurement of blood pressure, since careless use of the measuring instrument could seriously impair the accuracy of readings. According to Dunkenstein, only systolic readings were recorded (11). Speed and accuracy of measurement were of prime importance in the evaluation of extremely rapid blood pressure changes.

At the beginning of the experiment, patients were kept in a supine position for a minimum of fifteen minutes. During this time, a minimum of three blood pressure readings were obtained. Following this resting period, the saline solution was administered and an additional three blood pressure readings were obtained. Out of this minimum total of six readings, average systolic pressure was obtained. After the administration of Epinephrine Hydrochloride, blood pressure readings were obtained every fifteen seconds, for a period of seven minutes.

After blood pressure had returned to normal, usually within a fifteen minute period, the drug, Mecholyl Chloride, was administered. Blood pressure readings were obtained every thirty seconds for a period of six minutes, followed by readings every sixty seconds, until a total of twenty-five minutes had elapsed since injection time. During

both Epinephrine Hypochloride and Mecholyl Chloride reactions, blood pressure readings were stopped when a subject yielded a minimum of three readings in succession of equal pressure.

Using normal blood pressure as a base line, increases and decreases of blood pressure were carefully recorded. The maximum amounts of blood pressure increase and of blood pressure decrease were used as the critical figures in this study.

The reliability of blood pressure reactions to the drugs administered was considered to be of great importance. Will the obtained maximum blood pressure reactions to these drugs be fairly stable? While it is generally accepted that normal blood pressure remains very stable over long time periods, it was of great concern in this investigation to have some knowledge regarding the reliability of the drug reactions. Funkenstein, Greenblatt, and Solomon (14) report on such a reliability investigation, in which they found no significant differences between groups of twenty-one, sixty-four and fifty-five subjects run in two trials.

Procedure in the Evaluation of Behavioral Adjustment

The instrument used in the evaluation of

behavioral adjustment and of changes in behavioral adjustment was the Gardner Behavior Chart (30). This chart was developed as an aid in obtaining such a record in the patients' behavior, so as to allow a running commentary on behavioral adjustment as well as changes in adjustment. The following categories are used in determining behavioral adjustment: attention to personal appearance, sleep, appetite, sociability, activity control, care of property, self-entertainment, cooperation on routine, work capacity, work initiative when alone, work initiative when supervised, willingness to follow directions. Under each category five brief phrases characterize the degree of adjustment for the specific behavior segment. The numerical evaluation for these five phrases runs from 0- none, 1- poor, 2- fair, 3-good, and 4-extra good. (See Appendix). In this manner, a possible maximum mean score of four, and a possible minimum mean score of zero can be obtained.

The Gardner Behavior Chart appears to be well suited for behavioral evaluations. It utilizes a number of questions designed to elicit direct information that appears to be inherently valid, since these questions deal concretely with those aspects of behavior that demand a direct answer. The wording of the questions appears to be of such a nature as to allow little if any misconception on the part of nurses and attendants who supply the

information. In a study of post-operative changes in a group of lobotomized patients, the Gardner Behavior Chart was used extensively. Schrader and Robinson (27) point out that these scores make possible the quantitative consideration of group averages, as well as affording convenient indices for judging the status of individual patients. In their particular study, it was of great value inasmuch as it significantly indicated critical differences between pre- and post-operative scores.

Patients in the sample were rated twice weekly for a period of eight weeks. Each weekly rating was obtained twice on the same day from two different shifts of nurses and attendants. This was done for the following reasons: one was that practical circumstances required different attendants and nurses due to frequent shift in personnel; another was that possible halo and anchoring effects were avoided; and a third was that double ratings could be used in a reliability estimation of the instrument. Observation over a period of eight weeks was felt to be a minimum in order to discover any trends of behavioral change in the group of patients.

No previous study had investigated the reliability of the Gardner Behavior Chart. It was felt that knowledge concerning its reliability as a clinical instrument

was essential if one were to use it as a criterion measure for behavioral adjustment. In order to arrive at an estimate of reliability, the judgments of two independent sets of judges, consisting of nurses and attendants, were analyzed. These two sets of judges had rated each of sixty patients. Judgments during the eighth week of behavioral observation were utilized, and a Pearson r was computed. A correlation of .83 ≠ .030 was obtained. This relationship is considered significant at well below the one percent level of confidence. This finding supports the assumption that the Gardner Behavior Chart is a reliable instrument for the evaluation of behavioral categories.

Procedure in the Evaluation of Hospital Status Five Months after Investigation

The sixty patients were classified as to status five months after the drug injections. This classification was as follows: paroled from hospital, in hospital, and on indeterminate status (such as home visit or family care). Only the first two groups were used in the evaluation of status and its relationship to drug reactions. These first categories represent clearly definable status. The last category represents a poorly definable status, and was not used in the evaluation. In this manner, fifty-one subjects could be used in this investigation.

RESULTS

Method of Analysis

The following data were obtained for each of sixty subjects used in this investigation; blood pressure measurement when at rest, blood pressure measurement after intravenous saline injection, blood pressure measurement after intravenous Epinephrine injection, blood pressure measurement after intramuscular Mecholyl Chloride injection, weekly behavior chart ratings for eight weeks, and hospital status five months after the initial experiment.

After the resting blood pressure recordings had been obtained, maximum increase and maximum decrease of blood pressure after the injection of Epinephrine and Mecholyl Chloride were recorded. This procedure differed from Funkenstein's original procedure(11). Funkenstein had recorded the total number of pressure readings, on the basis of which he assigned patients to seven groups differing from each other in their blood pressure recovery rates . He was forced to eliminate two groups due to their unreliability, reducing the total to five groups. Meadow(21), in a similar kind of investigation, had been forced to reduce these groups further into three separate groups . He followed this procedure due to the extremely small number of subjects he had been able to obtain for the eliminated two groups. This investigator was struck by the very large

decreases or increases after the injection of the drugs. It was therefore felt that two groups which could simply be regarded as blood pressure increase and blood pressure decrease groups, would most adequately indicate the grossly different reactions. A further consideration had been the number of subjects that were available for this study. In order to attempt to obtain sufficiently large groups, a much larger number of patients would have been necessary. Analysis of the data revealed furthermore that the tendency amongst the patients was to either decrease, or increase their blood pressure; fluctuations in both directions were usually small or did not occur at all.

In order to discover the strength of relationship between maximum blood pressure increase and maximum blood pressure decrease, and the injection of Epinephrine and Mecholyl Chloride, Pearson r co-efficients were computed between these blood pressure peaks and the behavior rating mean scores.

In order to arrive at an estimate of the difference between first week and eighth week behavioral observations, and its relationship to maximum increase and maximum decrease of blood pressure following the Mecholyl injections, the significance of the difference between behavior rating means was computed. Inspection of the data

indicated that selection of the fifteen largest blood pressure increases and fifteen largest blood pressure decreases would most succinctly show the predicted trend.

In order to discover the extent of relationship between hospital status five months after administration of the drugs, and the increase or decrease of blood pressure as a function of the administered drugs, Chi Square analysis was utilized.

Results with Epinephrine Hypochloride

It had been predicted that significant relationships could be obtained between good behavioral adjustment and an increase of blood pressure after the administration of Epinephrine Hypochloride. Conversely, it was predicted that a significant relationship could be obtained between poor behavioral adjustment and a fall in blood pressure following the administration of Epinephrine Hypochloride. The concepts of "good" and "poor" behavioral adjustment are a function of the relative standing of the Gardner Behavior Chart mean score for each patient. A maximum "good" adjustment would be reflected by a mean score of four and a maximum "poor" adjustment by a mean score of 0. In other words, "good" and "poor" indicate high and low scores on the Gardner Behavior Chart, and are a function of the total sample used in this investigation.

Using Pearson r co-efficients in order to investigate these predictions, no significant relationship could be established(Table 1). One cannot distinguish between a favorable and an unfavorable adjustment on the part of schizophrenic patients when the drug Epinephrine Hypochloride is used. Blood pressure changes as a result of the use of this drug will not discriminate between patients on the basis of their behavioral adjustment. This is in partial agreement with Funkenstein's findings(11), in which he stresses the point that only a subjective evaluation of anxiety could be used as a dependable criterion for differential reactions to the drug Epinephrine Hypochloride.

Results with Mecholyl Chloride

The hypothesis formulated predicted that a significant relationship could be established between good behavioral adjustment and a fall in blood pressure after the administration of Mecholyl Chloride. Conversely, the hypothesis had predicted that an increase in blood pressure after the administration of Mecholyl Chloride would be significantly related to poor behavioral adjustment.

Using Pearson r co-efficients in order to investigate these two hypotheses, significant relationships were established(Table 1). This leads one to the conclusion that the reaction a schizophrenic patient will manifest

TABLE 1

PEARSON r CORRELATIONS BETWEEN BLOOD PRESSURE CHANGES AS A FUNCTION OF EPINEPHRINE HYDROCHLORIDE AND MECHOLYL CHLORIDE INJECTIONS AND GARDNER BEHAVIOR CHART MEAN SCORES FOR SIXTY SCHIZOPHRENIC PATIENTS.

N=60	Gardner Behavior Chart Mean Scores
Blood Pressure Rise After Epinephrine Injection	r .13*
	S.E. r .115
Blood Pressure Fall After Epinephrine Injection	r .06*
	S.E. r .128
Blood Pressure Rise After Mecholyl Injection	r -.52**
	S.E. r .094
Blood Pressure Fall After Mecholyl Injection	r .43**
	S.E. r .107

*Correlation non-significant.

**Correlation significant at the one percent level or less.

following the injection of Mecholyl Chloride is of considerable prognostic importance. Blood pressure changes as a result of injection of this drug will significantly discriminate between patients on the basis of their behavioral adjustment.

Results with Mecholyl Chloride in an Investigation Concerned with Behavior Changes

The hypothesis had been advanced that trends of behavioral improvement over an eight week time span will be significantly related to the blood pressure reaction to Mecholyl Chloride. It had been predicted that maximum blood pressure fall would significantly relate to significant behavioral improvement , as shown by a rise in behavior ratings during the eight week observation period. Conversely , maximum blood pressure rise would significantly relate to behavioral deterioration as reflected by a fall in behavior ratings during the eight week observation period. Analysis of the significance of difference of behavioral rating means between the first and the eighth week of observation revealed the following: For the group of fifteen patients who had shown maximum rises of blood pressure following the injection of the cholinergic drug Mecholyl Chloride, a significant difference between behavior rating means for the first week of observation and for the eighth week of observation could be established. The significance of this difference between behavior rating means occurs in the direction of decrement. This difference is significant

at below the .01 level of confidence in the direction of behavioral deterioration (Table 2). For the fifteen patients who showed a maximum fall of blood pressure following the injection of Mecholyl Chloride, analysis of the significance of difference between first and eighth week behavior rating means revealed significance at the .05 level of confidence in the direction of behavioral improvement (Table 2). These findings support the hypothesis: Behavioral deterioration over an eight week time span is significantly related to maximum blood pressure rise following the injection of Mecholyl Chloride, in a group of fifteen patients who evidenced maximum blood pressure increase out of a total group of sixty schizophrenic patients. Fall in blood pressure after the administration of Mecholyl Chloride is significantly related to behavioral improvement over an eight week time span, in a group of fifteen patients that evidenced maximum blood pressure fall out of a total group of sixty schizophrenic patients (Table 2).

Results with Mecholyl Chloride in an Investigation Concerned with Patient Status Five Months After Drug Injection.

The object of this follow-up study was to determine whether blood pressure reactions to the injection of Mecholyl Chloride could be related to the future status of patients at the hospital. The patient was considered cured if he had

TABLE 2

TESTS FOR THE SIGNIFICANCE OF DIFFERENCE OF GARDNER BEHAVIOR CHART MEANS BETWEEN THE FIRST AND THE EIGHTH WEEK OF OBSERVATION, FOR THE FIFTEEN SUBJECTS HAVING LARGEST INCREASES AND THE FIFTEEN SUBJECTS HAVING LARGEST DECREASES OF BLOOD PRESSURE FOLLOWING MECHOLYL CHLORIDE INJECTION.

Group	N=15	Gardner Behavior Chart		
		Mean	Mean Difference	t
Blood Pressure Increase				
First Week		1.95		
Eighth Week		1.68	.27	3.068**
Blood Pressure Decrease				
First Week		2.54		
Eighth Week		2.74	.20	1.818*

** Significant at below the one percent level.

* Significant at the five percent level.

been returned to his home; he was considered institutionalized if still at the hospital five months after the initial experiment. Out of the group of sixty patients, fifty-one were either paroled to their home, or were still institutionalized. The remaining nine patients were of an indeterminate status, due to their placement in family care or temporary home visit. A Chi Square analysis showed a significant relationship between greater fall than rise in blood pressure after the injection of Mecholyl Chloride, and release from the hospital within five months after the initial experiment. Conversely, a larger rise than fall of blood pressure could be related to continuing hospitalization five months after the initial investigation. These findings were significant at the one to two percent levels of confidence (Table 3).

It had not been possible to control for the non-administration of ECT after the initial eight week observation period. Approximately one-third of the sample did receive ECT at some time after this initial observation period because of the difficulty in convincing medical personnel to refrain from ECT during this period. The statistical findings therefore reflect the dependability of prognosis of schizophrenic patients, regardless of whether or not they receive shock treatment. In this manner, the finding supports Funkenstein's original contribution, as well as the ability to predict spontaneous improvement in relation to the reaction to Mecholyl Chloride, inherent in this investigation.

TABLE 3

CHI SQUARE ANALYSIS OF RELEASE OR INSTITUTIONALIZATION FIVE MONTHS AFTER THE INITIAL INVESTIGATION, AND BLOOD PRESSURE REACTIONS FOLLOWING THE ADMINISTRATION OF MECHOLYL CHLORIDE.

	Blood Pressure Increase	Blood Pressure Decrease
Release	5	14
Institutionalization	20	12

N 51

X^2= 5.68** (Yates' Correction)

** Significant at between the one percent and two percent levels of confidence.

DISCUSSION

Practical Implications

The need for a broader base and greater usefulness of our clinical understanding cannot be sufficiently stressed. Useful as the psychodiagnosis of the schizophrenic disorder is, it is not enough if we hope to be able to appraise the total functioning organism. One of the primary problems that confronts us in the appraisal of the schizophrenic disorder is the extent of physiological imbalance which accompanies an existing or incipient schizophrenic withdrawal. It is felt that this study emphasizes the importance that one must assign to the influence of the autonomic nervous system in the etiology and prognosis of schizophrenia. While this investigation did not deal with etiological considerations, it was concerned with the prognostic implications that a knowledge of autonomic nervous system sensitivity would entail. Further research will have to determine whether autonomic nervous system imbalance can be viewed as a causative, a concomitant, or a predisposing agent in the development of schizophrenia. It may not be unlikely that all three possible influences of the autonomic nervous system must be considered in the evaluation or the individual case.

The motivation that led to the present investigation had been to inquire into the prognostic significance of the Funkenstein autonomic nervous system test(11) as related to

behavioral adjustment, change, and outcome of untreated schizophrenic patients. Funkenstein(11) had been able to predict whether a patient would, or, would not, recover from schizophrenia when treated with ECT or ICT. He had been able to distinguish between patients who recover from ECT and patients who recover from ICT, on the basis of characteristically different blood pressure reactions as a function of the injection of adrenergic and cholinergic drugs. What is so particularly remarkable about this finding is that no adequate theory has been offered to explain the curative aspects of either ECT or ICT. It must furthermore be noted that no actual theoretical formulation has been offered to explain these characteristically different blood pressure reactions. It is a case in point in which empirical application is ahead of any satisfactory theoretical body of knowledge. Autonomic nervous system activity is still very much of a puzzle, a fact which the literature reflects(15).

This author has been much concerned with the empirical application of shock treatments to schizophrenic patients. We find here another example of empirical application without theoretical support. One of the most frequent questions arising in a state hospital setting is " should one attempt shock treatment?" The answer to such a question, while peripherally involving such considerations as suicidal risk, uncontrollable violence, or age factor, requires largely an intuitive affirmation or rejection. Extent of custodial care

available, and the dynamics of the personality of the physician will often be the crucial factors in such a decision. It is quite readily apparent that such shock methods as ECT, ICT,camphor injections,ammonia injections,metrazol and triazol injections, acetylcholine shock,pure nitrogen inhalation, and extended sedation therapy, all constitute severe trauma to the organism. It is unknown to what extent different organisms will differ in their reaction sensitivity to such treatments. It is not even known to what extent organisms will react in a like manner to such shock treatments as a function of the shock proper(3). If one were able to predict more accurately which patients will improve spontaneously without intervening shock treatment, such a hit-and-miss application would be reduced to patients who react unfavorably to the procedure used in this investigation. While Funkenstein's autonomic nervous system test(11) had been successful in predicting success or failure of shock treatment, it appeared to be highly desirable to utilize this test in an effort to investigate the course of illness without shock treatment.

Results of the study support the considerable prognostic significance of patients' reaction sensitivity to the cholinergic drug Mecholyl Chloride. Favorable blood pressure reaction, indicated by a blood pressure fall, was related significantly to spontaneous improvement. It was furthermore shown that, five months after the initial experiment, a significantly larger number of patients who had responded favorably to the

cholinergic drug injection, had been discharged from the hospital. Practical application of this finding appears self-evident. The actual time consumed in administering the test takes approximately one half-hour. The test can be administered by a nurse without direct medical supervision. Results of the test can easily be entered routinely into the patient's medical chart. It is a measure that will help the physician in his decision whether or not to attempt shock treatment.

This investigation could not establish any dependable relationship between reaction to the adrenergic drug Epinephrine and behavioral adjustment. Funkenstein's findings have likewise been less conclusive in this respect(11). He stresses the important element of subjectively experienced anxiety reported by schizophrenic patients when subjected to Epinephrine injections. In cases of extremely large blood pressure increase after Epinephrine injection, prognosis following shock treatment was reported as poor(11). This investigator saw no adequate way to measure the subjective elements of the patient's reaction to epinephrine. In only three subjects out of the total group of sixty, did the patient express verbally a feeling of dread. Nevertheless, a routine injection of Epinephrine to newly admitted schizophrenic patients may be valuable as a further help in predicting reaction to shock treatment, provided anxiety is evidenced. Lack of such anxiety, however, cannot be assumed to be contra-indicative to spontaneous improvement, since this investigation could not establish a satisfactory relationship be-

tween the blood pressure reaction to Epinephrine and behavioral adjustment.

Theoretical Considerations

The literature does not offer a satisfactory explanation of the autonomic nervous system test's prognostic significance. Observations of the hypoactivity often encountered in the schizophrenic, emphasizing the inability of the organism to cope with physiological and psychological stressors, actually lack a theoretical structure. The closest approximation to a theoretical structure underlying autonomic nervous system reactivity, comes from the writings of Angyal, Freeman, and Hoskins(2). Their concept of "withdrawal", based upon physiological and psychological sluggishness of reaction in schizophrenics, does not give, however, a theoretical formulation beyond the observational data.

Results of this investigation revealed that while no dependable reaction difference could be obtained between re - covering and non-recovering patients when injected with the adrenergic drug Epinephrine, dependable differences could be obtained when injected with the cholinergic drug Mecholyl Chloride. It is indeed difficult to offer a theoretical formulation for this partial failure, due to the fact that no satisfactory theoretical formulation has been encountered that deals with this problem. While acetylcholine, or its synthetic equivalent Mecholyl Chloride, is associated with parasympathetic

activity, and is held responsible for the synaptic transmission of nerve currents , hypotheses offered to explain its precise functioning are contradictory.One hypothesis suggests a chemical basis for the transmission of nerve currents across the released acetylcholine at the synapse; another hypothesis assumes that the production of acetylcholine is a function of electrotonic spread at the synapse(15).

It is most generally accepted that acetylcholine,in its release and subsequent resynthesis, is directly responsible for the conduction of nerve currents. Synthesis and breakdown of the cholinergic stimulant, after a nerve current has passed, is considered part of the metabolic cycle underlying the maintenance and recovery of nerves. Acetylcholine thus plays a central role in the choline metabolism of the nerve. The conduction of impulses and the synaptic transmission of them involves either chemical or electrotonic spread. It would appear that an abnormal reaction of the organism to an injected cholinergic agent is related to a faulty metabolic reaction most likely at the nerve synapses. The assumed synthesis and breakdown of the cholinergic agent in the normal organism apparently malfunctions in schizophrenics who do not recover spontaneously.

Irrespective of whether chemical or electrolytic agents are responsible for release of acetylcholine at the synapse, authorities are agreed that release of acetylcholine results in parasympathetic stimulation(15). It has been shown that

injection of the synthetic equivalent of acetylcholine will result in similar effects. The sluggishness of body activities, associated with cholinergic stimulation, apparently does not occur in schizophrenics who have a poor prognosis. The question arises why this may be so. It is generally agreed that physiological reactions on the part of the schizophrenic are either more variable or underactive. As the synthetic equivalent of acetylcholine is injected into the schizophrenic with poor prognosis, an overreaction on part of the organism occurs. It may secrete an adrenaline like substance to counteract the agent which would ordinarily aggravate hypoactivity. Thus, increase of blood pressure is a function of the organism's attempt to counteract the aggravating action of the cholinergic stimulant. Future research will have to determine whether such an adrenaline like substance is actually secreted by patients that suffer from schizophrenia and who are not spontaneously improving.

Another possible explanation of the action of Mecholyl Chloride is that in certain patients the effects of such stimulation may imitate the adrenergic pattern. As the organism attempts to meet optimal internal conditions, its reaction sensitivity undergoes a change in the direction of reducing stress that cholinergic hypoactivity would entail.

It is felt that the approach used by Funkenstein(11), and extended in the present investigation, contains implications which may produce substantial changes in our conception

of the behavioral disorders. It appears to cut across behavioral symptom categories, and may represent a more fundamental psychobiological orientation. It brings about a change in our thinking with regard to pathological reaction types, a recasting of our concepts in the direction of stress and anxiety as related not only to psychodynamic, but also to physiodynamic frames of reference. Psychologists and physiologists will have to work in closer harmony, in order to coordinate research projects designed to investigate the processes involved in behavior malfunctioning.

Implications for Further Research

A coordinated psychophysiological approach to the problems inherent in adjustment patterns appears to be most desirable. This approach can be conveniently subdivided into four major areas: a) The investigation of reaction types. While this will for some time to come require the assumptions of psychiatric classification, it is felt that it ultimately will cut across symptom classification inherent in present day thinking. b) Investigations designed to ascertain the changes that occur in body chemistry as a function of adrenergic and cholinergic stimulation. It may well be that upon such findings will rest the ultimate explanation of why some patients react adrenergically to cholinergic stimulation. Is it a function of an adrenaline like substance increase in the organism, or a function of the cholinergic drug effecting adrenergic like

reactions? c) Investigations of central nervous system reactions to stimulation of the autonomic nervous system. Will electroencephalographic changes occur as a function of autonomic nervous system stimulation, and will these changes differ in relation to the patient's specific autonomic nervous system reaction? This investigator is at present attempting such a research project at the Traverse City State Hospital, in coordination with members of the electroencephalographic research team. d) Additional attempts to relate specific physiological reactions, such as blood pressure change as a function of autonomic nervous system stimulants, to a series of psychological tests. These attempts should be specifically directed at the prognostic implications inherent in projective techniques, and their relationship to physiological factors.

SUMMARY

Recent investigations have disclosed that a specific autonomic nervous system reaction, blood pressure change after the injection of adrenergic and cholinergic drugs, is related to success or failure of shock treatments of schizophrenic patients(11,12,13,14).

The purpose of this study was to investigate the relationship between autonomic nervous system responses after the injection of adrenergic and cholinergic drugs, and the behavioral adjustment, change, and outcome of a group of schizophrenic patients. It was felt that this should help to reduce part of the arbitrariness in the selection of patients for shock treatment.

The three general hypotheses around which this study was structured were:

1. A significant relationship can be established between the quality of behavioral adjustment in schizophrenic patients, and characteristic blood pressure changes after injection of the adrenergic drug Epinephrine Hypochloride, and the cholinergic drug Mecholyl Chloride.

2. A significant relationship can be established between spontaneous behavioral changes and characteristic blood pressure changes following Mecholyl Chloride injection.

3. A significant relationship can be shown between

characteristic blood pressure changes after the injection of Mecholyl Chloride and outcome of institutionalization.

Sixty schizophrenic patients, first admissions to the Traverse City State Hospital, were selected on the basis of an undisputed diagnosis of schizophrenia, without organic disturbances and without mental deficiency. These patients did not receive any shock treatment during a two months period of behavioral observation.

The tool used to investigate behavioral adjustment was the Gardner Behavior Chart, a five point scale instrument, that possesses face validity and good reliability. Behavior ratings were obtained weekly for eight weeks by two shifts of nurses and attendants.

Blood pressure readings were obtained in the following manner: 1. Determination of basal blood pressure by having patients rest in a supine position for a period of fifteen minutes. 2. Blood pressure readings after an intravenous injection of a saline solution in order to determine possible fluctuations due to psychological stress.3. Blood pressure readings every fifteen seconds for a period of seven to eight minutes following intravenous Epinephrine injections.4. Blood pressure readings every thirty seconds for six minutes, followed by readings every one minute for a total of twenty-five minutes after intramuscular injection of Mecholyl Chloride. The maximum

increase and decrease of blood pressure as a function of the injections were recorded.

The relationship of blood pressure reactions to the adrenergic drug Epinephrine Hypochloride and behavioral adjustment was not found to be statistically significant.

Findings with regard to the cholinergic drug Mecholyl Chloride supported the three major hypotheses. A significant relationship was established between increase of blood pressure following Mecholyl Chloride injection and poor behavioral adjustment, with an r of -.527. A significant relationship between decrease of blood pressure following Mecholyl Chloride injection and good behavioral adjustment was established, with an r of .425. Using t tests, mean differences were determined between first and eighth week behavior ratings for those subjects with the fifteen highest and fifteen lowest blood pressure reactions to Mecholyl Chloride. A t of 3.068, significant at the less than one percent level of confidence in the direction of behavioral decrement was obtained for the fifteen highest blood pressure increases. A t of 1.818, significant at the less than five percent level of confidence in the direction of behavioral improvement was obtained for the fifteen largest blood pressure decreases. Behavior ratings were significantly different for the first week and eighth week of behavioral observation, for the fifteen largest blood pressure increases and decreases.These differences were in the expected direction.

A follow-up study, five months after the initial experiment, revealed that out of the original group of sixty patients, thirty-two had been discharged on parole, while nineteen were institutionalized; nine were of indeterminate status and were not included. The relationship between hospital status and blood pressure reaction after the injection of Mecholyl Chloride was investigated by a Chi Square analysis. A Chi Square of 5.68 was obtained and found to be significant at the .01 - .02 levels of confidence. Prolonged institutionalization is related to an abnormal blood pressure reaction after the injection of Mecholyl Chloride, while a normal reaction tends to be associated with early hospital discharge.

It has been demonstrated that reaction sensitivity of the autonomic nervous system, as indicated by blood pressure changes after the injection of a cholinergic drug, is a valuable tool in the prediction of behavioral adjustment and spontaneous behavioral changes. It also helps in predicting the status of patients with regard to prolonged hospitalization versus early hospital discharge.

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APPENDIX

Name of Institution

GARDNER BEHAVIOR CHART

Last Name *First Name*

This behavior chart was developed in a state hospital for mental diseases and is particularly applicable to the periodic behavior analysis of the continued care cases. The period rated at one time usually should not be less than 24 hours nor more than 6 months. A conscientious nurse with a little supervision at the start can rate a patient fairly reliably if she consults her colleagues regarding those aspects of the patient's behavior which she is not in a position to observe herself.

Key to Ratings

In rating the patient's work consider the characteristics in relation to the particular task or tasks at which he is now occupied. If in doubt, put a question mark and add explanatory comments. Make use of all information available.

1. Attention to Personal Appearance.

-1 — *Untidy* — Wets or soils or both. Indicate which.
0 — *None* — Slobbers his clothes and neither washes nor changes his clothes unless forced to.
1 — *Poor* — Does not slobber, but is untidy in general appearance and is physically rather dirty.
2 — *Fair* — Washes up an average amount and keeps his clothes tidy.
3 — *Good* — Keeps himself clean and neat most of the time. Takes some pride in his appearance.
4 — *Extra Good* — Very particular about being physically clean and about having his clothes clean and neat, and if possible, pressed.

2. Sleep.

0 — *None* — Seems to be awake day and night.
1 — *Poor* — Awake frequently during night, sleeps very lightly.
2 — *Fair* — Usually sleeps most of the night, but is occasionally restless.
3 — *Good* — Sleeps soundly all night, unless there is considerable commotion.
4 — *Extra Good* — A heavy sleeper, seldom disturbed by noises.

3. Appetite.

0 — *None* — Has to be tube fed.
1 — *Poor* — Eats very little, but will eat more when spoon fed.
2 — *Fair* — Eats a moderate amount when encouraged — usually leaves food on his plate after one helping.
3 — *Good* — Eats one large serving regularly.
4 — *Extra Good* — Usually asks for second or third helpings.

4. Sociability.

0 — *None* — Never talks or plays with others. Always seclusive.
1 — *Poor* — Almost always seclusive, will occasionally speak to others, but never joins in games.
2 — *Fair* — Converses with others a fair amount and may occasionally join in games.
3 — *Good* — Usually found talking or playing with others.
4 — *Extra Good* — Takes an active interest in others. Talks and plays freely with both patients and employees as opportunity arises.

5. Activity Control.

0 — *None* — Acutely restless. Stays in bed or in a chair scarcely five minutes at a time, or has prolonged periods of running to and fro.
1 — *Poor* — Quite restless. Prolonged restlessness, though will stay in bed or in a chair for half hour periods. Stirred up by newcomers in the room or by commotion.
2 — *Fair* — Restless. Frequently moving about but does not run about. Will stay in bed or in a chair frequently for considerable periods.
3 — *Good* — Slightly restless at times but most of the time moves about only according to the demands of the situation.
4 — *Extra Good* — Not restless. No excess unnecessary activity.
x — *Underactive* — Slow and sometimes motionless.
y — *Motionless* — Frequently and for considerable periods motionless.

6. Noise Disturbance Control.

0 — *None* — Acutely disturbed, noisy most of the time, shouting, banging doors, etc.
1 — *Poor* — Rather noisy at times or a little noisy most of the time.
2 — *Fair* — Quiet most of the time, but moderately noisy occasionally, or frequent low mutterings.
3 — *Good* — Never causes noisy disturbance.
4 — *Extra Good* — Very quiet.

P. H. W. 9-'38 Ref.: Wilcox, Paul H.: The Gardner Behavior Chart, Am. J. Psychiat., 98:874-880, May 1942. Hatton Press, Inc., Gardner, Mass.

BEHAVIOR CHART

Last Name	*First Name*	*No.*	*Age on Adm.*	*Date of Adm.*

Date Rated	Period Covered	Ward	Occupation and Comments	Hours of Work, Daily

BEHAVIOR CHART

Date Rated	1 Appearance	2 Sleep	3 Appetite	4 Sociability	5 Activity Control	6 Noise Control	7 Temper Control	8 Combativeness Control	9 Care of Property	10 Self Entertainment	11 Cooperation in Routine	12 Work Capacity	13 Initiative, Alone	14 Initiative, Supervised	15 Directability	16	17	18	19	20	21	22	Scorer's Name

Key to Ratings (continued)

7. Temper Control.

0 — *None* — Flies off the handle at every little thing.
1 — *Poor* — Loses temper easily, but can be handled, if done with care.
2 — *Fair* — Usually controls his temper, but has spells of irritability.
3 — *Good* — Seldom loses his temper, except occasionally when bothered.
4 — *Extra Good* — Very seldom loses temper, even with provocation.

8. Combativeness Control.

0 — *None* — Is continually violent, attacking or fighting. Must be restrained or under sedation to protect others.
1 — *Poor* — Assaults patients and/or nurses nearly every day.
2 — *Fair* — Occasionally assaultive.
3 — *Good* — Never strikes except in self-defence.
4 — *Extra Good* — If attacked, attempts to protect self without hurting the attacker.

9. Care of Property.

0 — *None* — Destructive of furniture and clothing much of the time, or steals constantly.
1 — *Poor* — Occasionally destructive of furniture and clothing, or will sometimes steal.
2 — *Fair* — Usually takes care of clothes, never destroys furniture, but will occasionally do minor damage to clothing, e. g. pulls buttons off, or occasionally steals food.
3 — *Good* — Never intentionally damages furniture or clothing. Makes no petty thefts.
4 — *Extra Good* — Always very careful about furniture, clothing, etc. Will assist in protecting property when asked.

10. Self-entertainment, including reading, writing, handicraft, or solitaire. Score and insert letters indicating the entertainment, r, w, h, and s.

0 — *None* — Absolutely idle or destructively occupied when not forced to work or play.
1 — *Poor* — Only occasionally entertains self constructively except when urged to.
2 — *Fair* — Entertains self of his own accord a moderate amount, but content to be absolutely idle for considerable periods.
3 — *Good* — Usually entertains self in spare moments, but occasionally allows himself to be idle.
4 — *Extra Good* — Always entertaining himself constructively when not working or mingling with others.

11. Cooperation in Routine.

0 — *None* — Is resistive to all routine procedures. Must be dressed and undressed and bathed by the nurses.
1 — *Poor* — Will not move in routine unless the nurse takes him by the arm, when he will go without special resistance. Never responds to calls.
2 — *Fair* — Will move to meals or to bed or bathe, etc., if called individually, but not when the group is called.
3 — *Good* — Moves according to the group routine when others take the initiative.
4 — *Extra Good* — Fits in with the routine very well. Goes to bed or to meals or bathes promptly on schedule without waiting for the rest of the crowd to lead the way.

12. Work Capacity.

0 — *None* — Entirely unable to learn this type of work, even after repeated instruction and demonstration.
1 — *Poor* — Learns this type of work with difficulty and never is able to do it well.
2 — *Fair* — Learns rather slowly, but in time gains considerable skill.
3 — *Good* — Gets the idea quickly, and acquires skill quickly.
4 — *Extra Good* — Gets the idea quickly without detailed instructions and does the task well from the start.

13. Work Initiative When Alone.

0 — *None* — Stops immediately, unless continually supervised or with other patients.
1 — *Poor* — Makes only a little effort when not continually supervised or with other patients.
2 — *Fair* — Makes an average effort when alone, but must be started.
3 — *Good* — Can be expected to work well when not closely watched but may require starting.
4 — *Extra Good* — Takes full interest and drives his work when alone. Needs but a minimum of supervision.

14. Work Initiative When Closely Supervised.

0 — *None* — Refuses to work while closely supervised or while with other patients.
1 — *Poor* — Makes little effort when closely supervised or while with other patients.
2 — *Fair* — Does fairly well when closely supervised or while with other patients.
3 — *Good* — Works well while closely supervised or while with other patients.
4 — *Extra Good* — Takes full interest, drives his work when closely supervised or with other patients.

15. Willingness to Follow Directions.

0 — *None* — Refuses to do the task assigned.
1 — *Poor* — Does task assigned, but insists on doing it his own way.
2 — *Fair* — Does task assigned, prefers to do it his own way, but does it as directed if closely supervised.
3 — *Good* — Gladly (or willingly) does task as directed.
4 — *Extra Good* — Very careful to do a task just as directed, and if in doubt, asks for further instructions.

ROOM USE ONLY