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Foundations of Biochemical Psychiatry

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Foundations of Biochemical Psychiatry

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Preface

Although most of the psychiatric world has not yet acknowledged it, the age of clinical application of behavioral biology is upon us. Basic discoveries in the laboratories of neuropharmacologists and neurobiologists are now being taken to research wards for application to humans in a brief matter of months or years. Complex human traits such as sensitivity, passivity, aggressiveness, and sexuality, previously conceived of as metaphysical, are now being examined by behavioral biologists and suitably oriented psychiatrists as the influence of their chemical understanding of the human body expands.

There are reasons this trend is being resisted by many schools of human behavior. First is the fact that previous scientific promises to the psychiatrically ill have been disappointing. Lobotomy produced a patient who was shallow and irresponsible. High doses of sedatives proved toxic and ineffective in the treatment of psychoses. Electroshock was predictably useful only for a subgroup of depressives. Recently, even the phenothiazines have been shown to produce severe toxic side effects. Perhaps only in the area of the affective disorders are we gaining some everyday clinical credibility, through the use of tricyclic antidepressants, monoamine oxidase inhibitors, and lithium.

A second factor that has led to resistance among clinically or behaviorally oriented theorists and practitioners has been the gap between the dependent variables of experiments (eg, leucine incorporation, inhibitory postsynaptic potential, amine turnover) and the phenomenology of humans (eg, desire, envy, love, contempt). I've heard it said that successful efforts to close this gap will lead humans to lose their specialness, the soul. It is particularly frightening to the older generation to have human traits described as genetically and chemically determined. "What will the world be coming to when I can take a pill to alter my personness? Who am I, then, after all?"

The historical sequence in psychiatry has been almost circular with regard to reductionism. When psychodynamic and psychoanalytic thinkers began to derive the highest forms of human functioning from "baser" instincts, they were accused of denying the person's unique self-determination and choice. Now, when behavioral biologists name and characterize the central mechanisms underlying instinctual life (the music behind the words of living), they are seen as still worse offenders of the idea of human specialness. Interestingly, the strongest formal objections came from neo-Freudian philosophers

who focus on the human being's cognitive ability as having originated from "neutralized" instinctual energy. As a group they have moved as far as possible from biological determinants of behavior. They feel that human nature is beyond comprehension in biological terms. The psychoanalyst who saw the animal in all of us is uneasy about seeing the animal's brain in all of us. Hopefully, like all resistance to valid scientific advance, the present cultural and intellectual inertia in psychiatry will pass.

From an epistemological point of view, textbooks represent organized defenses of the status quo. They arrive relatively late during periods of scientific transition, and are frequently oversimplified (and therefore inaccurate) summaries of how things *were*. When a field is in a state of rapid flux, textbook writing is almost impossible. In its place come collections of papers, which have the advantage of freshness. There have recently been a few such compendiums in biological psychiatry. However, all of them, although of good quality, lack continuity. They lack the informal discussions that create holistic impressions.

It seems to me that Drs. Segal, Yager, and Sullivan have taken on the challenge of creating a textbook in a field of rapid flux with the best possible result. From an active, ever-changing, and currently revolutionary field, they have chosen representative and important original work. Their discussions provide continuity. They have fleshed out the chemical bones of biological psychiatry with well-chosen clinical material, and they have done all this without assuming a political posture. Most importantly, they have made available to a wide range of readers the kind of material that certainly will be part of the liberal arts education of the future. They are to be congratulated on a difficult job well done. I hope the reader will enjoy the book as much as I have.

ARNOLD J. MANDELL

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1. Introduction to Fundamental Concepts

Biochemical psychiatry has emerged over the past 25 years as an important conceptual and experimental approach to understanding mental illness. Although various physical techniques used in the treatment of mental illness since the 19th century reflect an early biological orientation in psychiatry, the major impetus to the development of biochemical psychiatry came in the early 1950s with the introduction of pharmacological agents that proved effective in the treatment of schizophrenia and depression.

The past 25 years have also been characterized by rapid technological growth in experimental psychopharmacology, neurochemistry, neurophysiology, and genetics. Antidepressant and antipsychotic drug effects and familial patterns of mental illness have become focal points of experimental investigation into the biological foundations of psychiatric disease. Neurochemical, neurophysiological, and behavioral data from animal studies have provided insight into the mechanisms of action of drugs that affect the functioning of the central nervous system and understanding of the dynamics of synaptic transmission. Carefully controlled genetic studies of psychiatric populations have afforded provocative evidence regarding genetic transmission of psychiatric illness, particularly schizophrenia and disorders of mood.

The primary objective of this text is to provide, through discussion and readings, an overview of the contributions made by biochemical psychiatry to the understanding of mental illness. The readings selected bear directly and indirectly on biochemistry; they include biochemical studies of psychiatric patients before and after pharmacological intervention and genetic studies which imply that yet largely unknown but critically important biochemical events play a major role in these disorders. The readings include both review articles that provide broad overviews of several areas of research, as well as original studies that demonstrate specific research methods in high-power focus. Since many of the selections assume that the reader is familiar with basic concepts of abnormal behavior and brain function, we will introduce and define those that are most fundamental. In addition, some of the more frequently used research strategies are presented to acquaint the reader with the values and limitations of current experimental procedures.

Abnormal Behavior

We all have a common sense idea of what kinds of behavior we consider normal. These ideas usually stem from the mores and values that we have learned to accept as appropriate in our society. However, mores and values may differ not only among individuals, but for the same individual at different times in his or her life. It should not be surprising, therefore, that there is great difficulty finding definitions of normality and abnormality that have universal agreement. Most attempts at defining normal and abnormal behavior have involved either a statistical or a relativistic approach.

According to the statistical view, any behavior that deviates from the mean may be considered abnormal. Although at first glance this definition might appear adequate, there are several difficulties with it. First, how extreme or divergent must the behavior be before it is considered pathological? The length of time that behavior must remain divergent for the individual to be classified as abnormal is also arbitrary: should the person who infrequently exhibits divergent behavior be considered abnormal? Finally, *which* divergent behaviors should be considered pathological? For example, individuals who are continuously depressed depart from the mean, but so do those who are exceptionally intelligent or creative. It is not possible to find universal agreement as to which behavioral dimensions are relevant for the diagnosis of psychopathology.

According to the relativistic approach, the behavior of an individual should be evaluated on the basis of the culture or group with which he or she is associated (the reference group). The proponents of this view point to the fact, for example, that aggressive behavior is quite normal in some cultures, but frowned upon in others; thus it is necessary to avoid the untenable conclusion that all the members of a particular culture are abnormal because they differ from the mean of the total population. However, this definition is subject to most of the difficulties that limit the statistical definition of abnormality; it also deals with deviance from a mean, in this case the mean of the reference group. In addition, there is the problem of determining the appropriate group to use as a reference. Such a choice could be made on the basis of any of a number of criteria, including culture, sex, age, or socioeconomic level.

In fact, the issue of normality is not necessarily relevant to research dealing with the biochemical basis of behavior. That is, the appropriateness of a behavior and whether or not it requires alteration is not essential to the question of what biochemical mechanisms subserve that behavior. Rather, the primary focus is on what neurochemical processes are involved in the elaboration of a behavior and the extent to which alterations in those processes are responsible for behavioral differences. Within the content of biochemical psychiatry the specific behaviors of interest are those that represent the distinguishing characteristics of syndromes such as schizophrenia and depression.

Psychiatric Classification. Attempts at classification are in general subject to a number of difficulties. Often there is greater variability between individuals within the same diagnostic category than there is between individuals in different diagnostic categories. Symptoms exhibited by an individual may depend on experiential and situational factors. Moreover, individuals placed in a particular category might be only superficially similar; that is, comparable symptoms might have very different causes.

In spite of these and other limitations, most behavioral scientists agree that a distinc-

tion between neurosis and psychosis is useful. While a protracted neurosis can be more debilitating to an individual than a temporary psychotic state, in general the neuroses interfere less with social functioning than the psychoses do. An individual having some form of neurosis is usually able to function at least moderately well in many social situations. In fact, neurosis might be undetectable, particularly by casual acquaintances. On the other hand, psychoses, even if transient, often affect behavior to such an extent that social functioning is markedly impaired. The differences between neuroses and psychoses are not always apparent; in patients classified as severe neurotics some symptoms may be quite similar to those usually attributed to the psychotic. It is, however, generally believed that neuroses do not usually develop into "true" psychoses.

Neurosis. The term neurosis commonly refers to any one of a group of conditions in which there is a chronic or repetitive pattern of thoughts, moods, or behaviors usually seen as undesirable by the afflicted individual. The onset of significant symptoms is usually abrupt and frequently associated with a stressful event. Anxiety is so frequently a part of neurosis that many believe it to be central to these conditions. The ability to distinguish reality from fantasy is usually preserved, and the person may recognize that the troubling symptoms are of irrational origin. Biochemical factors may play an important role in determining the susceptibility of an individual to neurotic disorders, but few biochemical theories of neurosis have been formulated.

In spite of the emphasis on experiential or psychodynamic factors, several families of drugs, especially the so-called antianxiety agents, have been used with some degree of success in the treatment of neuroses. For example, chlordiazepoxide (Librium®) and diazepam (Valium®) have both proved to be clinically effective in the reduction of anxiety.[1] Although the mechanisms by which these drugs exert their clinical effects are unclear, knowledge of these mechanisms may eventually provide us with insight into biochemical factors that influence neurotic behavior.

Psychosis. The term psychosis refers to any one of a group of conditions in which reality testing is impaired. Reality testing refers to the ability of the individual to discriminate the source and significance of perceptions, thoughts, and feelings and to validate these with external experiences. As a consequence of impaired reality testing, the behavior of psychotics often appears inappropriate and bizarre.

Two of the main classifications of psychoses are schizophrenia, in which the prominent disorder involves an impairment of thinking or cognition, and affective disease, in which the prominent disorder involves extremes of mood or affect. It should be recognized that, although either thinking or mood disorder may be prominent, both are usually present to some extent in all psychotics, and that differentiations between schizophrenia and affective disorder are sometimes ambiguous. More complete descriptions of schizophrenia and affective disorders are presented in the introduction to Sections 2 and 3, respectively.

Biochemical Considerations

A growing body of evidence indicates that biochemical factors play an important role in the etiology of at least some forms of psychotic behavior. The evidence includes

the observation that behavioral syndromes resembling functional psychoses accompany certain metabolic defects, infectious disorders, and toxic states in humans. Examples of such conditions are described briefly below.

Inherited Metabolic Defects. Many inborn errors of metabolism have been described in which behavioral features are prominent. One example is Hartnup's disease, a rare familial condition in which abnormalities occur in the absorption and metabolism of certain amino acids. As a result of these abnormalities, a large amount of the amino acid tryptophan is converted to unusual metabolites by bacteria in the intestine. The effect of these metabolites on the brain is believed to be responsible for the psychiatric features of Hartnup's disease, which range from emotional instability to delirium and may include vivid hallucinations and bizarre delusions.

Another example of an inborn metabolic defect is the Lesch-Nyhan syndrome. In this disorder the specific biochemical defect is inactivity of the enzyme hypoxanthine-guanine phosphoribosyl-transferase (HG-PRT), which results in increased intracellular production of phosphoribosyl pyrophosphate and in excessive production of uric acid. This rare inherited disease is characterized by mental retardation, cerebral palsy, and self-mutilation. Between the ages of 1 year and 18 months afflicted children begin such compulsive self-destructive behavior as biting lips, fingers, and other body parts, causing evident pain and severely damaging the tissues.

Other examples of familial disorders with important behavioral components are Wilson's disease and Huntington's chorea. In Wilson's disease, in which there is a defect in the metabolism of the copper-transporting plasma protein ceruplasmin, a condition similar to paranoid schizophrenia is frequently seen. In Huntington's chorea, an inherited disorder in which the specific biochemical lesion has not yet been elucidated, a psychosis similar to schizophrenia is frequently the first sign of illness.

Vitamin Deficiencies and Other Metabolic Defects. Pellagra is a syndrome that results from the dietary deficiency of niacin (nicotinic acid) or its amine (nicotinamide) and other B vitamins. The psychological symptoms of this condition develop insidiously; they include depression, anxiety, difficulty in concentration, and loss of recent memory. Subsequently clouding of consciousness, hallucinations, delusions, and other psychotic behaviors may be seen. Similar behavioral changes are frequently encountered with such other metabolic disturbances as hyper- and hypothyroidism, hyper- and hypoadrenal states, and the porphyrias (disorders of porphyrin metabolism).

Infectious Disorders. Not long ago, 10% of all admissions to mental hospitals were for syphilitic infections of the central nervous system (general paresis of the insane). Widespread damage to brain tissue may lead to bizarre delusions, hallucinations, and general deterioration of mental functions. Many other infectious processes can result in delirium, a psychotic behavioral syndrome characterized by disorientation, hallucinations, delusions, and shifting levels of consciousness. For example, viral encephalitis, inflammation of brain tissue, may at times produce a behavioral syndrome indistinguishable from certain psychoses.[2]

Toxins and Drugs. Throughout recorded history people have been aware of the ability of certain substances to bring about behavioral change. Alcohol is a notable ex-

ample. The various behavioral syndromes attributable to alcohol range from simple drunkenness to the schizophrenic-like syndromes of alcoholic hallucinosis and alcoholic paranoia.

Inhalants such as ether, nitrous oxide, and substances containing petroleum distillates (eg, glue) have been used by individuals to alter their subjective experiences. Psychotic behavior frequently accompanies the use of these inhalants. The effects of such substances as amphetamines, psychotomimetic drugs, and other pharmacological agents will be discussed in greater detail in later sections.

The occurrence of psychotic-like behavior accompanying specific biochemical defects suggests that biochemical alterations may contribute to the etiology of many psychiatric disorders. In attempts to uncover relationships between psychiatric disorders and underlying biochemical factors, researchers have employed various strategies of investigation, the most prevalent of which are outlined below.

Research Strategies

Epidemiological Research. Information about the incidence, prevalence, and distribution of cases within a population may provide useful clues about the etiology and pathogenesis of a psychiatric disorder. Incidence refers to the rate of appearance of new cases, and prevalence refers to the total number of cases present in a population. Certain patterns of distribution strongly suggest that environmental factors may be important, for example, the limitation of new cases of a disorder to one neighborhood sharing a common water supply. On the other hand, genetic factors may be suspected when cases are found only among biological relatives of afflicted individuals.

Epidemiological data can be obtained in several ways. Information about the incidence and prevalence of a disorder may be obtained through reviews of hospital, clinic, and other public records, as well as from private physicians' offices. Door-to-door surveys of the population may reveal additional cases never seen by physicians. Each of these methods will yield different figures for incidence and prevalence, and each has certain limitations.

Hospital surveys may reflect only the most severe cases of the disorder, those that require hospital care. The reporting of cases from clinics and private physicians' offices is often incomplete because of differences in record keeping. In population surveys great care must be taken to ensure that the subsample studied is representative of the whole population. Adequate attention must be given to such factors as age, sex, education, socioeconomic class, and ethnic background, among others.

Several methodological considerations are relevant to all epidemiological studies. The criteria accepted as evidence for the presence of the disorder in question are of central importance. Some investigators simply accept the diagnosis of the hospital or clinic records; others may require that cases meet specific diagnostic criteria. Since the criteria used to define such disorders as schizophrenia and depression vary widely from study to study, attempts to compare the results of different investigators must take the specific definitions used in each study into account.

The "age of risk" concept is also important. This refers to the ages during which susceptible individuals may be expected to develop the disorder in question. In schizophrenia, for example, the age of risk may extend from the teens until the late thirties; rarely will new cases be found that occur later in life. Therefore, when surveys are con-

ducted of populations or relatives of afflicted individuals who have not yet passed through the age of risk, the prevalence of the disorder may be underestimated unless this factor is taken into account.

Family studies have been especially important for elucidating the role of genetic factors in psychiatric disorders. When carefully designed, these studies will allow genetic and environmental contributions to a disorder to be teased apart. Examples of such studies are presented and discussed in several sections of this book. Investigators have pursued such information with varying degrees of vigor, depth, and success. In some instances, the only available data are the word of mouth histories provided by patients about their relatives. However, some investigators have been particularly adept at locating and arranging personal interviews and examinations with all known relatives and have, in addition, made extensive use of public case registers and hospital records. Such studies have been conducted most readily in such places as Scandinavia, where the population has been geographically stable and where good public case registers and hospital records have been maintained for many years.

Most epidemiologic studies have been retrospective; events are documented after the fact. Of course, information obtained retrospectively may be inaccurate because it is partly forgotten or distorted. Also, statements of causal relationships are difficult to make since correlated events may occur in the wake of the disorder rather than antecedent to it. For example, an association between low socioeconomic class and schizophrenia may imply *not* that poor socioeconomic conditions lead to schizophrenia, but that schizophrenics, unable to function adequately in society, drift to the lower socioeconomic classes.

Prospective studies are designed to bypass these difficulties. Groups of individuals especially at risk to develop a disorder are studied before the disorder appears and are followed through the age of risk. Attempts are made to identify environmental and biological markers that may signal an individual's susceptibility (although they are not necessarily pathogenetically important in themselves) and to uncover etiologic and pathogenetic mechanisms in the process of development; as yet unaffected children and siblings of persons with a disorder may be studied in this fashion. Prospective studies are costly and require a great deal of time, practical impediments that explain why so few have been conducted.

Clinical Research. Clinical studies consist of behavioral and biological observations of patients and appropriate control subjects. Attempts have been made to correlate behavioral and biological phenomena, the effects of biological manipulations upon behavior, and the effects of behavioral manipulations upon biological functions. In some clinical studies subjects can serve as their own controls; observations are made before, during, and subsequent to a given experimental or therapeutic intervention.

Social behaviors, mood, affect, and cognitive symptoms can be measured. For example, it is possible to document the type and frequency of social interactions initiated by a patient (friendly or angry) or the frequency with which hallucinations and delusional thoughts appear to interfere with a patient's functioning. Behavioral ratings are made at varied time intervals, which range from hourly to weekly depending on the nature of the study.

In some studies self-rating scales are used, where patients or subjects are asked to judge their own behavior on standardized rating forms. The Minnesota Multiphasic Personality Inventory (MMPI), used with tens of thousands of individuals in a variety of

studies, and the Zung Rating Scale for Depression, widely used in outpatient medical practice, are examples of self-rating scales. The self-rating scales have several limitations, including the obvious fact that severely psychotic patients are not able to cooperate sufficiently to fill out the forms, while other people misrepresent themselves in order to convey a desired impression to the examiner.

More frequently, behavioral ratings are made by trained personnel, usually psychiatrists, psychologists, nurses, or psychiatric technicians. A large variety of scales is available, including the Present State Exam (PSE), the Brief Psychiatric Rating Scale (BPRS), and the Nurses' Observation Scale for Inpatient Evaluation (NOSIE). These are widely used and data obtained can be processed by computer so that quantitative statements about psychiatric symptoms can be made.

In the development of these scales increasing attention has been given to the need to define observable behavior precisely and to avoid inferences about behavior, so that observers can better agree about what they see. Still, rating scale methods have limited reliability and validity. For ratings to be made reliably, observers require training in the use of the scale; in a given study there must be agreement about the range of behavior rated at a specified level (eg, severe versus moderate depression). With regard to validity, it has been demonstrated that trained raters often perceive symptoms differently, according to their theoretical orientation. For example, given the same pattern of behavior, some raters may "see" schizophrenia while others "see" depression. For these reasons, videotape is being increasingly employed to "capture" segments of behavior to serve as references and to facilitate communication between researchers about the specific symptoms and syndromes being considered.

Repeated measurements are necessary in order to separate findings that are due to the "trait" from those due to the "state" of an individual. Trait refers to a feature that remains more or less constant over a long period of time, such as the high level of anxiety or high autonomic nervous system arousal that would characterize a chronically anxious person. Such traits may be related to constitutional temperament. State-related features are those that appear largely as a consequence of internal or external influences of the moment, which can be expected to change as these influences change, for example, a burst of anxiety that follows a nearly fatal accident.

Numerous biological functions have been monitored, including blood pressure, heart rate, galvanic skin resistance, and electrical activity of the brain. Biochemical measurements have been made of all accessible body fluids; urine, blood, cerebrospinal fluid and even saliva have been analyzed for the presence and amount of various chemical substances.

Clinical studies abound with methodological difficulties and, as a consequence, interpretation of results is often severely limited. Experimenters must attend to so large a number of possible confounding influences that few studies withstand critical scrutiny. These difficulties are explored at length and representative studies are discussed in the paper by Dr. Wyatt and his colleagues in the section on schizophrenia. The study by Dr. Goodwin and his coworkers presented in the affective disorders section is an example of how a clinical investigation can be designed to minimize the effects of potentially confounding variables.

Animal Research. Prior to the early 1950s there were few effective treatments for psychotic behavior. Psychotics were usually institutionalized and, as a consequence, there

was a large patient population in mental hospitals. However, with the advent of certain drugs, the trend has been dramatically reversed.

In addition to their obvious practical contribution, these drugs serve as tools to study the relationship between biochemistry and behavior. This strategy of research, frequently referred to as the pharmacological bridge, relies on the observation that certain drugs (such as the phenothiazines and tricyclic antidepressants) are effective in the treatment of various types of psychoses, while other drugs (such as reserpine or amphetamine) produce patterns of behavior in some individuals that are, in many respects, indistinguishable from naturally occurring psychoses. It is reasoned, therefore, that if we understood the way in which such drugs affected brain chemistry, we might gain insight into the pathogenesis of psychiatric disease. Pharmacology thus is used as a bridge connecting neurochemistry to clinical psychiatry. However, since the human brain is inaccessible to this kind of biochemical analysis, most research involves the examination of the effect of psychotropic drugs on the brain chemistry of animals. It is assumed that these effects are similar enough to those that occur in people to justify generalizing the results of animal research to humans.

Many of the studies employing the pharmacological bridge have implicated the process of neurochemical transmission in the etiology of psychiatric disorders. Some investigators have suggested that an excess or deficiency of one or more transmitter substances may be responsible for a specific disorder. It has also been suggested that an endogenously synthesized substance that resembles a neurochemical transmitter may accumulate and produce anomalous patterns of neural activity.

A biochemical defect might be acquired genetically and expressed behaviorally when the affected neural pathways are activated by certain environmental conditions. Effective therapeutic treatments (eg, drugs) are presumed to compensate for the defect by altering the production of the relevant transmitter substance or by appropriately modifying its accessibility to receptor sites. Norepinephrine, dopamine, and 5-hydroxytryptamine are transmitter substances that have been extensively studied in this regard. In the subsequent sections there will be frequent reference to each of these transmitter substances as playing a potential role in one or more of the psychiatric disorders discussed.

We can now turn our attention to several specific areas of contemporary psychiatry that have been approached from a biochemical perspective. The two major groups of psychiatric diseases, schizophrenia and affective disorders, are considered in the next two sections of the book. The subsequent sections deal with evidence supporting a biochemical basis for such diverse conditions as neurosis, behavioral disturbances of childhood, and alcoholism. The final section focuses on behavior-neuroendocrine relationships.

2. Schizophrenia

Although there is no universally accepted definition of schizophrenia, there is some agreement that the primary disturbance is an impairment of logical thought processes. It is still unclear as to whether schizophrenia is a single disorder or group of disorders. For example, some behavioral scientists believe that schizophrenia is a clinical syndrome with multiple etiologies. There are numerous examples of such syndromes in clinical medicine, including pneumonia and heart failure. However, it is also conceivable that the diversity of symptoms associated with schizophrenia is not due to multiple defects, but instead results from various modifying factors that influence the expression of a specific genetic predisposition. For example, the severity, frequency, and/or type of stressful events may determine the overt symptomatology of a schizophrenic illness.

Since the etiology(ies) of schizophrenia is unknown, our present system of diagnostic classification is primarily descriptive in nature. Nevertheless, we can still make some useful statements about the clinical characteristics of schizophrenia, including common symptoms, subtypes, and natural history.

Clinical Description

Symptoms

Thought Disorder. The disturbance of thinking seen in schizophrenia is the most characteristic feature of the disorder. Often the logical flow of ideas is lost, and speech may become bizarre and confused. Some schizophrenics report that a blocking of their thought processes feels as if thoughts are being "robbed" from them. Thoughts that are usually only remotely connected emerge in close association. For example, a schizophrenic might describe his or her recent work history as "scattered—about five weeks—for I was weak and couldn't stick to the envelope." With mild thought disorder the speech is vague and difficult to follow. In more extreme cases language may be totally incomprehensible, a jumble of associations referred to as word salad.

Disturbances of Affect. Both flattened and inappropriate affect (emotional response) are frequently observed in schizophrenics. The flatness or impoverishment of affect

may appear as an indifference to thoughts or events that would usually be expected to elicit an observable emotional reaction. At times, inappropriate affect may be more prominent than emotional apathy. In such instances feelings seem to be unrelated to the specific circumstances that elicited them. A schizophrenic might laugh when describing the death of a close family member or weep in response to a joke.

Autism. Autism, a prominent feature of schizophrenia, refers to withdrawal from involvement with the external world through private or self-centered behavior or thought. Daydreaming is one type of autistic activity; but, in contrast to the daydreaming in which each of us engages, schizophrenics' preoccupation with fantasy impairs their ability to deal effectively with the external environment. Another example of an autistic process is the schizophrenic's creation of new words (neologisms), whose meaning can be so private and obscure that they have no communicative value.

Ambivalence. Ambivalence refers to the coexistence of opposite feelings about a particular person, situation, or idea. Although each of us experiences mixed feelings, schizophrenic ambivalence is greater in magnitude. For example, a schizophrenic may have equal feelings of love and hate toward a spouse. In its extreme form, schizophrenic ambivalence can lead to a paralysis of decision-making or to rapid and dramatic changes in behavior.

Stereotypy. Stereotypy refers to continuous repetition of the same behavior. For example, repetition in conversation and writing is often observed in schizophrenics. In addition, some schizophrenics will maintain the same body position for long periods of times, a feat which would be both unnatural and uncomfortable for most others. This phenomenon, called catalepsy, is one of the most prominent features in catatonic schizophrenia.

Delusions. Delusions are persistent beliefs that are contrary to fact or logical reason. Although delusions are not unique to schizophrenia, certain types are frequently associated with this disorder. These include delusions of influence, in which individuals believe that their thoughts or actions are controlled by mysterious external forces. Also common in schizophrenia are ideas of reference, in which the person feels that certain remarks or events are special communications directed to or about her or him, when, in fact, they are not. An example of an idea of reference is a false belief that the newspaper headline is a personal message. Other delusions characteristic of schizophrenia include a conviction that one can read other people's minds and the belief that one's thoughts are being broadcast telepathically.

Hallucinations. Hallucinations are perceptions that have no obvious corresponding external stimulus. They occur in many psychiatric conditions, and any of the senses may be involved. In schizophrenia these inner perceptions are usually auditory and are interpreted by the patient as "hearing voices." These auditory hallucinations may involve long sentences and complex instructions (command hallucinations). In contrast, auditory hallucinations associated with other mental disorders are usually brief, perhaps only one or two words long.

Subtypes

Schizophrenia is frequently divided into subtypes that are determined by the predominant symptoms. Because the clinical manifestations of schizophrenia can change over time, many individuals are included in several subtypes during the course of their illness.

Paranoid Type. Paranoid schizophrenia is characterized by delusions of persecution and/or grandeur, often accompanied by terrifying hallucinations. In general, behavior tends to correspond to the delusional thoughts. The paranoid schizophrenic is often fearful, hostile, suspicious, or aggressive. For example, in a paranoid delusion the schizophrenic may become fearful because he believes that he is the target of an international conspiracy. Loosening of associations is often not as prominent in paranoid schizophrenia as in the other subtypes.

Catatonic Type. Grossly abnormal behavior, either in the form of excitement or withdrawal, distinguishes catatonic schizophrenia from the other types. Catatonic excitement is marked by hyperactivity which can be violent or dangerously exhausting. In catatonic withdrawal (stupor) the patient is mute and passively uncooperative. If left undisturbed, the patient may stay in one position for extended periods of time (catalepsy).

Hebephrenic Type. Hebephrenic schizophrenia is characterized by pronounced thought disorder and by markedly inappropriate emotional responses. Strange juxtapositions of thought and neologisms are prevalent. Behavior is often silly or childlike and may include giggling and odd mannerisms. Hallucinations and delusions are often present.

Schizoaffective Type. In this subtype either pronounced elation or depression accompanies the thought disorder. Whether schizoaffective psychosis should be considered a form of schizophrenia or affective disorder or as an entirely separate group is unresolved.

Simple Type. Patients with simple schizophrenia usually manage a marginal existence at the fringes of society. They are noted for their lack of drive, impoverished social relationships, and unusual personal idiosyncrasies. There is rarely deterioration of mental functioning over time. Hallucinations and delusions, when present, are transient and are usually related to stressful events.

Undifferentiated Type. This subtype includes individuals who do not readily fit into any of the categories described, but who manifest definite schizophrenic thought, affect, or behavioral disturbances.

Natural History

Overt psychotic symptoms usually first appear in adolescence or early adulthood. The onset of symptoms can be abrupt or insidious. Following the appearance of symptoms, some patients show a progressive deterioration of mental functioning while others experience recurrent psychotic episodes, usually lasting weeks to months. In some cases recovery from an acute episode appears to be permanent.

Disorders with an abrupt onset (reactive schizophrenia) are thought to have a better prognosis than those that start insidiously (process schizophrenia). Some European psychiatrists have suggested that schizophrenic-like psychoses, which begin abruptly and remit within a few weeks, should be called psychogenic psychoses and differentiated from "true" schizophrenia.

In summary, schizophrenia is primarily a disturbance of logical thought processes in which the severity and expression of symptoms can be quite variable. It should be noted that present classification systems, including the subtypes we have discussed, are based on descriptive accounts of the more commonly observed behavioral manifestations of schizophrenia. We must stress that a more meaningful classification awaits better understanding of the cause or causes of schizophrenia. Such an understanding is one of the major goals of contemporary psychiatric research.

Treatment

The great strides that have been made in the treatment of schizophrenia over the past two decades have been due largely to the development of several classes of antipsychotic medication. The most important of these are the phenothiazines such as chlorpromazine (Thorazine®) and fluphenazine (Proloxin®), thioxanthenes such as thiothixene (Navane®), and butyrophenones such as haloperidol (Haldol®). Unlike sedatives or minor tranquilizers, these drugs appear to have specific antipsychotic properties. A large number of schizophrenic patients receiving these drugs experience a significant decrease in anxiety and agitation, an improvement in the thinking disorder, a diminution of hallucinations and delusional thoughts, and an improvement in social behavior. Medications can be taken orally each day or can be given in long-lasting "depot" injections as infrequently as once every two to four weeks.

Although some patients can be taken off medication after clinical improvement, others require medication indefinitely. Studies have shown that the incidence of rehospitalization is greater when medication is discontinued. Nevertheless, there is a significant risk of neurological disturbance (that is, tardive dyskinesia) among patients who take high doses of phenothiazines over long periods of time. Tardive dyskinesia is characterized most frequently by abnormal movements of the jaw, repetitive protrusions of the tongue, and sometimes by tremors in the hands and stepping movements of the feet. The treatment of tardive dyskinesia remains problematic.

In addition to medications, the concomitant use of psychotherapy and therapeutic environment can be of value in the treatment of schizophrenics. Psychosocial therapies include individual, family, or group psychotherapy. Rehabilitative activities such as social, vocational, or educational programs that have been specifically structured to suit each patient are also useful. A variety of changes in living situations, work, or school may be appropriate. Electroconvulsive therapy is occasionally of value, particularly in the management of severe catatonic schizophrenia. As with diabetes, the treatment of schizophrenia may be a lifelong endeavor, with the specific methods of treatment varying over time, depending upon the patient's changing symptoms and problems.

Reading Selections

The articles included in this section represent current research efforts to elucidate the biochemical origins of schizophrenia. In the first paper *The Genetics of Schizophrenia and*

Schizoid Disease, Heston discusses evidence that relatives of schizophrenics have a greater incidence of schizophrenia and other forms of psychopathology than does the general population. A major problem with the family study approach is in separating the effects of genetic from psychosocial factors. In addition to having common genetic traits, family members who live in close contact with one another are also likely to be exposed to similar environmental influences.

In order to separate the relative contribution of these two factors, several research strategies have been employed, including investigation of half-siblings, identical twins, and individuals adopted in infancy. Such studies indicate that adoptees from biological families with a history of schizophrenia are more likely to be afflicted with schizophrenia or related forms of psychopathology than are adoptees with no biological family history of schizophrenia. This evidence provides support for a genetic contribution to schizophrenia.[3]

Wyatt and his colleagues have used another approach for identifying a genetic contribution to schizophrenia.[4] These investigators have identified an enzymatic abnormality, a reduction in the activity of blood platelet monoamine oxidase (MAO), in many of the chronic schizophrenics they studied. Monoamine oxidase is a degradative enzyme that metabolizes a variety of amines, including the putative central nervous system (CNS) neurotransmitters dopamine (DA), norepinephrine (NE), and serotonin (5HT). Additionally, because platelet MAO activity is decreased in nonmedicated chronic schizophrenics,[5] it is unlikely that antipsychotic medications alone are the cause of the decreased enzyme activity. The fact that monozygotic (identical) twins discordant for chronic schizophrenia are concordant for low platelet MAO suggests that this enzyme may be a genetic marker for vulnerability to schizophrenia. However, Murphy and Weiss[6] have also reported that platelet MAO activity is lowered in bipolar affective disease. Therefore, it is uncertain whether MAO activity can be used as a specific marker for schizophrenia.

The evidence for a genetic factor in schizophrenia does not necessarily imply that experiential and environmental factors are unimportant in the etiology of schizophrenia. In fact, the variability in expression of this disorder may result from the influence of both factors. As Heston points out, monozygotic twins may be discordant for schizophrenia. Since such individuals are genetically identical, experiential differences, including those stemming from the intrauterine environment which has been shown to be different for monozygotic twins, may account for this discordance.

Genetic studies have demonstrated that at least some forms of schizophrenia are inheritable, which necessarily implies a biochemical aberration that leads to the expression of schizophrenic traits. However, elucidation of the specific biochemical mechanisms involved requires the use of other research strategies.

The second article, entitled *Biochemical and Sleep Studies of Schizophrenia: A Review of the Literature, 1960–1970* by Wyatt, Termini, and Davis, focuses primarily on clinical studies dealing with the possible formation of endogenous hallucinogens (the transmethylation hypothesis) and with other biochemical aberrations alleged to be present in schizophrenics. One aspect of the transmethylation hypothesis which has received a considerable amount of attention recently is the search for amine methylating enzymes capable of converting neurotransmitters into psychotomimetic substances. This work is reviewed by Wyatt et al, and more recent findings are described by Snyder et al (see page 117).

Wyatt and his colleagues point out that despite the arduous labors of many investigators, much of the clinical data has been confusing and contradictory. This is due largely to methodological problems, particularly those involving the control of extraneous fac-

tors. To allow for accurate interpretations, groups studied should be the same in all respects except for the variable(s) under examination. For example, when hospital and outpatient populations are compared, differences in body chemistry may be related to environmental rather than to psychiatric differences between the two groups.

It is also possible that frequent failures to replicate experimental results in patient populations that appear to be alike symptomatically are due to the fact that schizophrenia may be a group of heterogeneous disorders, each with a different biochemical defect. Thus, the search for a single biochemical aberration invariably associated with schizophrenia may be futile.

It should also be kept in mind that the demonstration of a biochemical abnormality in a population of schizophrenics does not necessarily imply that this abnormality has caused schizophrenia. Rather, such biochemical alterations may be consequences of being afflicted with schizophrenia. For example, stress is known to produce marked changes in body chemistry. Since they may inappropriately perceive certain situations as threatening or stressful, schizophrenics may appear to be biochemically different from nonschizophrenics under those conditions. The conflicting results obtained in different studies could thus be explained on the basis of different environmental conditions to which patient populations are exposed.

A great deal of research involves the study of neurochemical effects of drugs that are either effective in the treatment of schizophrenia or produce schizophrenia-like patterns of behavior. One drug that has received considerable attention is amphetamine which, especially when administered in chronic high doses, produces a behavioral state in humans indistinguishable in many respects from paranoid schizophrenia. In fact, individuals with amphetamine psychosis have frequently been misdiagnosed and treated as paranoid schizophrenics and, therefore, many investigators have suggested that amphetamine psychosis may represent a "model" schizophrenia. The behavioral characteristics of amphetamine psychosis and the factors influencing its expression are described in the article entitled *Amphetamine Psychosis: A Multi-Dimensional Process* by Ellinwood.

Although there is general consensus that amphetamine can produce a state of paranoia with ideas of reference, delusions of persecution, and visual and auditory hallucinations, in some studies amphetamine psychosis has been found to differ from clinical schizophrenia with respect to its relatively high incidence of visual hallucinations (as opposed to the auditory hallucinations typical of schizophrenia) and the absence of both thought disorder and affective disturbance. However, as discussed in the article by Snyder and his colleagues (see page 106), these differences are more apparent after acute injection of amphetamine. Following chronic high doses (comparable to the dosage schedules used by amphetamine addicts), amphetamine has been reported to produce typically schizophrenic auditory hallucinations, thought disorders, and affective disturbances. Thus the neurochemical state produced by amphetamine may not be substantially different from that present in paranoid schizophrenia. However, the neurochemical alteration, whether drug-induced or naturally occurring, may have to persist for relatively long periods of time before many of the symptoms associated with chronic schizophrenia develop.

Since research on the effects of amphetamine in humans is limited, much emphasis has been placed on the study of experimental animals. Extrapolation of results from animal studies to humans is justified to some extent because a primary feature of amphetamine intoxication in both humans and lower animals is the elicitation of stereotyped behaviors (repetitive behavioral sequences). Although the particular behaviors mani-

fested are species-specific, the compulsive nature of this behavior is apparent in all animals. In fact, Ellinwood has suggested that in humans stereotypy may be an invariable concomitant of amphetamine psychosis. Therefore, elucidation of the biochemical mechanisms underlying stereotyped behavior may provide insight into the neurochemical processes responsible for the psychosis.

A dopaminergic model for the etiology of schizophrenia is discussed in the article by Snyder and his coworkers entitled *Drugs, Neurotransmitters, and Schizophrenia.* This model is partially based on evidence obtained from the study of behavioral and biochemical changes produced by amphetamine in experimental animals. Additional support stems from the research by these authors and other investigators on the biochemical action of neuroleptics (phenothiazines, butyrophenones, and thioxanthenes), drugs effective in the treatment of schizophrenia and the best-known antidotes for amphetamine psychosis.

The therapeutic efficacy of the neuroleptics appears to be due to a selective antischizophrenic action rather than to a general sedative or antianxiety effect. And although these drugs are known to have a multiplicity of neurochemical effects, there appears to be a relatively strong correlation between their DA-blocking and antipsychotic potencies. The relative potencies of neuroleptic agents may be related to their ability to assume a DA-like structural conformation.

The behavioral effects of amphetamine, especially stereotypy, appear to be due to the release of DA or the blockade of its inactivation. Therefore, on the basis of evidence obtained from the study of neuroleptics and amphetamine, it has been postulated that at least some forms of schizophrenia may be attributed to an excess of dopaminergic activity. However, as Snyder et al indicate, this interpretation is at best tenuous "since the effects of drugs could well be exerted at a locus extraneous to the fundamental schizophrenic abnormality."

In addition to their discussion of drug-related research strategies, Snyder and his colleagues also discuss some recent research pointing to the existence of amine methylating enzymes in the brain. Such enzymes are potentially capable of converting neurotransmitters, like the catecholamines and indoleamines, into psychotomimetic substances. This evidence is consonant with the transmethylation hypothesis described in the article by Wyatt et al.

Several criticisms are frequently levied against theories of schizophrenia that postulate the endogenous formation of hallucinogenic or psychotomimetic substances. One is that hallucinogenic drugs produce only accessory and not fundamental symptoms of schizophrenia. However, as previously described (see page 14 and Snyder article), behavioral differences between naturally occurring and drug-induced psychoses may be attributable to such factors as persistence of neurochemical change.

A second criticism, based on the results obtained in some studies, is that tolerance would ultimately develop to the effects of any endogenously formed hallucinogen, presumably ruling out the possibility that the presence of such a substance could be the cause underlying chronic schizophrenia. However, recent reports indicate that tolerance does not necessarily develop to all the effects of all psychotomimetic agents. For example, in one study cats were not found to exhibit tolerance to some of the effects of *N,N*-dimethyltryptamine (DMT), a potent hallucinogen in humans.[7] Furthermore, tolerance does not appear to develop to some of the behavioral effects of amphetamine; long-term administration of amphetamine in rats has been reported to produce a progressive augmentation of amphetamine-induced increases in both locomotor activity and stereotypy.[8,9]

These results are consistent with the hypothesis that schizophrenia may be produced by the excessive formation of an endogenous psychotomimetic.

Much the same argument can be directed against the "excess DA activation" hypothesis. Dopaminergic synaptic transmission is subject to regulation by a number of mechanisms, including neurotransmitter formation, feedback control of neural activity and transmitter release, and receptor sensitivity. These mechanisms appear to act in concert or sequentially to maintain synaptic activity within relatively restricted limits, analogous in many respects to the homeostatic control of body temperature. Thus, for example, a prolonged excessive release of DA and corresponding increased activation of DA receptors might be expected to result in a desensitization of those receptors and an eventual return to the normal range of dopaminergic synaptic activity. Whether, with a disorder like schizophrenia, enhanced DA activation would exceed the limits of available homeostatic or compensatory mechanisms remains to be determined.

Still, other kinds of biochemical mechanisms may be involved in the etiology of schizophrenia. In their paper entitled *Possible Etiology of Schizophrenia: Progressive Damage to the Noradrenergic Reward System by 6-Hydroxydopamine,* Stein and Wise propose a theory based on their research with the neurotoxin 6-hydroxydopamine (6-HD) in experimental animals. They demonstrate that this neurotoxin, which is believed to selectively destroy catecholamine neurons in the brain, significantly reduces intracranial self-stimulation by rats, and they suggest that such experimentally induced changes in rewarded or goal-directed behavior are fundamentally analogous to the anhedonia and the impairment of thought processes seen in schizophrenia. That is, the primary defect in schizophrenia may be a loss in the behavior organizing action of pleasure or reward. Their finding that the neuroleptic drug chlorpromazine protects experimental animals from the effect of 6-HD is consonant with this hypothesis.

Stein and Wise postulate that a specific metabolic defect causes an accumulation of 6-HD in NE neurons and that the resulting damage to these brain cells is expressed behaviorally as schizophrenia. The therapeutic effect of chlorpromazine is presumed related to its inhibition of a cellular mechanism necessary for the accumulation of 6-HD.

To determine if noradrenergic "reward" pathways are damaged in schizophrenics, Wise and Stein[10] performed postmortem examinations on brain specimens from schizophrenic and control patients. The relative activity of dopamine-β-hydroxylase (DBH), the enzyme that mediates the last step in NE biosynthesis, was used as an estimate of damage to NE neurons. The activity of this enzyme was found to be significantly reduced in schizophrenics. However, more recently Wyatt et al[11], using similar procedures, were unable to confirm these findings.

In addition to the research implicating catecholamines, Wyatt et al and Snyder et al discuss some evidence of a possible role for serotonin (5HT) in the etiology of schizophrenia. Thus, for example, some schizophrenic patients display certain electrophysiological aberrations during sleep which can to some extent be produced in experimental animals and humans with the administration of *p*-chlorophenylalanine, an inhibitor of 5HT biosynthesis[12] (see Wyatt et al article).

With respect to drug models of psychosis, some evidence suggests that hallucinogenic substances may exert their effects by reducing the activity of 5HT neurons in the brain.[13] Furthermore, hallucinogenic drug effects in animals and humans have been reported to diminish when 5HT levels are increased and to be enhanced with reduction in brain 5HT. As discussed by Snyder et al, there is some reason to believe that hallu-

cinogenic substances, some of which are 5HT derivatives, can be produced endogenously.

In more direct studies 5HT or its primary metabolite 5-hydroxyindoleacetic acid (5HIAA) has been reported to be reduced in some schizophrenics,[4] but the significance of this finding is unclear because low levels of 5HIAA are also associated with other disease states. Finally, Wyatt and his coworkers[11] have recently shown that patients with some forms of schizophrenia improved with the administration of the 5HT precursor L-5-hydroxytryptophan (5HTP). These results must also be interpreted with caution because the therapeutic action of 5HTP could have been produced by some nonserotonergic effect. However, in spite of the absence of strong direct support, converging evidence does indicate that there may be some disruption of 5HT functioning in schizophrenia.

The Genetics of Schizophrenic and Schizoid Disease

Leonard L. Heston, MD

The contribution of genetic factors to the etiology of schizophrenia has been confirmed decisively. Because the investigations that have led to this result have uncovered questions cutting across several fields of inquiry, a fresh look at some central aspects of the schizophrenia problem is warranted. These questions and the factual background underlying them are the main concerns of this article. Because emphasis is placed on formulating testable hypotheses, the evidence is organized in support of a particular genetic theory.

The Basic Evidence

During the first half of this century, systematic family studies demonstrated that the distribution of schizophrenia is that of a genetic disease. Relatives of schizophrenics were found to be afflicted with the illness much more frequently than members of the general population. The child of a schizophrenic parent, for example, was found to have a risk of schizophrenia about 15 times that of a member of the population at large. It was found that, among all classes of relatives, the closer the genetic relationship to a schizophrenic proband (or index case) is, the greater is the likelihood of schizophrenia in the relative. Finally, and most telling of all, monozygotic twins were found to be concordant with respect to schizophrenia about four times as often as dizygotic twins. Several authorities have critically reviewed these basic data (*1, 2*). But, despite the supporting evidence, a genetic etiology for schizophrenia was not widely accepted, especially in this country. It was pointed out that the investigators did not pay enough attention to important procedural matters, such as providing sampling safeguards and insuring against bias on the part of the investigator. But the paramount objection to a genetic interpretation of the evidence was the objection that the whole research strategy was faulty. The results of these studies, it was held, were just as compatible with transmission of schizophrenia through the social environment as with transmission through genes. The closer the genetic relationship, the closer the social relationship. Were genes or was noxious social learning responsible for the familial clustering of schizophrenia?

Recently, several studies have been aimed at closing those methodological and conceptual gaps. In these newer studies diagnoses either were made by raters who

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did not know the genetic background of the subjects or were taken unchanged from medical records. Care was taken to remove sampling biases, and, most importantly, control groups were used. The strategy permitted separation of the effects of genes from the effects of social environment through the use, as subjects, of children reared in adoptive or foster homes.

The results of one such study are shown in Table 1 (*3*). The experimental subjects were individuals born to schizophrenic mothers, and the controls were individuals born to parents who had no record of psychiatric disturbance. The members of both groups had been permanently separated from their biological mothers in the first month of life and reared mainly in foster or adoptive homes. The subjects, as adults, were assessed through psychiatric interviews and review of every available record —for example, school, police, Veterans Administration, and medical—and then evaluated by a team of clinicians. The significant excess of schizophrenia found among those subjects whose biological mothers were schizophrenic seems impossible to explain except on a genetic basis. Moreover, among those same experimental subjects, and thus also linked to schizophrenia by the evidence, was an even greater excess of various apparently nonschizophrenic disorders. The latter finding, which is reflected in nearly every entry in Table 1, is a central concern throughout this article.

The preliminary results from a very similar study which stressed exemplary investigative safeguards were much the same. Rosenthal *et al.* (*4*) reported that biological children of schizophrenics reared in adoptive homes exhibited "schizophrenic spectrum" disorders in significant excess over similarly reared controls. The "schizophrenic spectrum"—an expression coined in a quite reasonable attempt to find a term that would encompass the various disorders seen among biological relatives of schizophrenics—included schizophrenia, possible schizophrenia, borderline states, certain paranoid disorders, schizoid disorders, and the condition known as inadequate personality.

Karlsson (*5*), as one result of his study of schizophrenia in Icelandic families, found that 6 of 29 persons, some of them siblings, born to a schizophrenic parent but reared in foster homes developed schizophrenia. None of their 28 foster sibs who were reared in the same homes developed schizophrenia. This difference, too, is significant. Karlsson did not ascertain any disorders other than typical schizophrenia among his subjects.

In two ingeniously designed research projects, adopted individuals served as the starting point. Wender *et al.* (*6*) studied the biological and adoptive parents of ten adopted schizophrenics and the adoptive parents of ten normal persons. The biological parents of the schizophrenics were found to exhibit significantly more psychopathology than either group of adoptive parents. In a similar but wider-ranging study conducted by Kety *et al.* (*7*), psychopathology, again reported as "schizophrenic spectrum" disorders, was found to be concentrated in significant excess among the biological relatives of adopted schizophrenics. The adoptive families of schizophrenics were indistinguishable from the adoptive and biological families of adopted controls. Since the psychopathology found in these studies was significantly greater among the group of biological relatives of the schizophrenic probands than among the adoptive relatives who actually lived with them, this evidence too strongly favors genetic over social transmission of schizophrenia.

The results of the studies of adopted and foster children—results which are strikingly consistent from study to study, considering the vagaries of research in this area—pre-

sent seemingly insurmountable difficulties for adherents of environmental theories of schizophrenia. The evidence must surely compel acknowledgment of a genetic contribution to schizophrenia, and probably to related disorders as well. To go further, however, requires information on other types of genetic relationships and larger numbers of subjects. Happily, the older family studies can now meet these needs. For perhaps the most important contribution of the recent studies of adopted and foster children is the fact that they have confirmed the results of the older studies in all material respects. The familial clustering of psychopathology that had been documented in such detail has been linked to one critical variable, a genetic relationship to schizophrenia.

The Schizoid

The presence of so much psychopathology other than typical schizophrenia among relatives of schizophrenics was first noticed by physicians on visiting days in the earliest asylums. Isaac Ray, writing in 1863, gave a good description (*8*). Because the relatives' disabilities resembled schizophrenia, investigators associated with the Munich school called these disabilities "schizoid" (schizophrenic-like). Describing the schizoid individual, delimiting schizoid from psychiatric and general populations, and placing the schizoid in relation to the schizophrenic were central concerns of the psychiatry of that day. After perhaps the longest detour in the modern history of science, we have come full circle in returning to the same concerns. Meanwhile, problems of nomenclature have developed.

To me, "schizoid" and "schizophrenic spectrum" seem to denote precisely the same disabilities, except that the latter term also includes schizophrenia. One consideration that may have led Kety (*7*), Rosenthal (*4*), Wender (*6*), and their coworkers to coin the new term is the obvious danger of confusing "schizoid" with "schizoid personality." The latter term, a diagnosis in the American Psychiatric Association and World Health Organization nomenclature, although descended from descriptions of the abnormal relatives of schizophrenics, has evolved and changed in meaning so that it is no longer applicable to most of those relatives. For example, it was not often applied to relatives of schizophrenics by the rating clinicians in the studies of adopted and foster children. But other diagnoses currently considered applicable to such individuals also fit these relatives imperfectly, so no formal categorization is now available. Because of a central trait of the schizoid—his clinical resemblance to the schizophrenic—and because of the desirability of maintaining continuity with older studies, I use the term "schizoid" as a name for the schizophrenic-like disabilities seen in relatives of schizophrenics, or for the individual manifesting such disabilities.

Nearly all observers of the schizoid have noted his clinical resemblance to the schizophrenic, but clinical criteria adequate to reliably distinguish the schizoid from members of a general or a psychiatric population or even from other kinds of abnormal persons with a coincidental genealogical connection to a schizophrenic are most imperfect (*9*). Though unsatisfactory, the only means of identifying many—perhaps most—schizoids remains genealogical, and a clinical understanding of the schizoid can best be gained by reading descriptions of abnormal relatives of schizophrenics (see *10–13* for good examples). The circularity thus introduced is regrettable but inescapable. The schizoid exists, and he sometimes shows as much impairment psychiatrically as a typical schizophrenic.

Several problematical behaviors have been associated with the schizoid. Among males, antisocial behavior has been found

Table 1. Results of a study of individuals born to schizophrenic mothers and reared in adoptive or foster homes, and of controls born to normal parents and similarly reared.

Item	Control	Experimental	Exact probability (Fisher's test)
Number of subjects	50	47	
Number of males	33	30	
Age, mean (years)	36.3	35.8	
Number adopted	19	22	
MHSRS, means*	80.1	65.2	0.0006
Number with schizophrenia	0	5	.024
Number with mental deficiency (I.Q. < 70)†	0	4	.052
Number with antisocial personalities	2	9	.017
Number with neurotic personality disorder‡	7	13	.052
Persons spending more than 1 year in penal or psychiatric institution			
Number	2	11	.006
Total years incarcerated	15	112	
Number of felons	2	7	.054
Number serving in armed forces	17	21	
Number discharged from armed forces on psychiatric or behavioral grounds	1	8	.021
Social group, first home, mean§	4.2	4.5	
Social group, present, mean§	4.7	5.4	
I.Q., mean	103.7	94.0	
Years in school, mean	12.4	11.6	
Number of children, total	84	71	
Number of divorces, total	7	6	
Number never married, > 30 years of age	4	9	

* The MHSRS is a global rating of psychopathology moving from 0 to 100 with decreasing psychopathology. Total group mean, 72.8; S.D., 18.4. † One mental defective was also schizophrenic; another had antisocial personality. ‡ Considerable duplication occurs in the entries under "neurotic personality disorder"; this designation includes subjects diagnosed as having various types of personality disorder and neurosis whose psychiatric disability was judged to be a significant handicap. § Group 1, highest social class; group 7, lowest.

commonly enough to warrant the older subdesignation "schizoid psychopath." Entries in the police records of the schizoid psychopaths in my study reflected impulsive, seemingly illogical crime such as arson, unreasoning assault, and poorly planned theft (*3*). Social isolation, heavy intake of alcohol, and sexual deviance have been noted frequently. Other schizoids, both male and female, have been described as eccentric, suspicion-ridden recluses. The main disability of still other schizoids, mostly females, has been found to be incapacitating attacks of panic or unreasoning fear in response to ordinary social challenges.

On a more technical level the resemblance to schizophrenia is more apparent. Rigidity of thinking, blunting of affect, anhedonia, exquisite sensitivity, suspiciousness, and a relative poverty of ideas—in variable combinations and intensities—characterize both the schizoid and the schizophrenic, though such characteristics are less prominent in the former. Though schizoids do not show a well-marked thought disorder, delusions, and hallucinations, descriptions of some of the behavioral lapses of schizoids, especially the schizoid psychopath, are bizarre enough to suggest micropsychotic episodes.

Slater took a different approach. He listed a series of explicatives, partially reproduced in Table 2, used by relatives of schizophrenics when describing their abnormal but nonschizophrenic relatives (*13*). Slater went on to say (*13*, p. 83) that "the same or similar words or phrases occur in descriptions of abnormal personalities from other kinds of families, but much less frequently, not in such concentrated form, and they are usually submerged by descriptions of a very different tone."

Table 2. Explicatives used by relatives of schizophrenics in describing their schizoid relatives. [After Slater (*13*)].

Paranoid eccentricities: suspicious, sensitive, sullen, touchy, grouchy, morose, resentful, unforgiving, difficult, quarrelsome, self-conscious, jealous, litigious, critical, and others.
Eccentricities: giggly, opinionated, pedantic, narrow-minded, meticulous, obstinate, humorless, rigid, little-minded, spiritualists, and many others.
Lack of feeling: passive, cruel, calculating, placid, hard and stingy, unsympathetic, cold, withdrawn, little-feeling, and others.
Reserve: shy, serious, haughty, snobbish, studious, unforthcoming, taciturn, unsociable, seeks solitude, and so on.
Anergic: dependent, tired, slack, unreliable, subservient, and so on.

Because Kallmann's investigations of the families of schizophrenics were by far the most extensive that have been made, his concept of the schizoid is of critical importance (*11*). From his description (*11*, p. 102) it is clear that he relied heavily on the schizoid's clinical resemblance to the schizophrenic. Kallmann regarded the distinguishing features of the schizoid to be the "fundamental symptoms of schizophrenia in the milder form of characterological abnormalities . . . dominating the personality of the individual in question." Kallmann also looked analytically at traits other than those obviously associated with schizophrenia or schizoidia that seemed to occur in excess among relatives of schizophrenics, with the aim of including or excluding them from the group of schizoid traits. On various grounds he excluded all the traits that he considered.

One of the traits which Kallmann considered and rejected, mental deficiency, perhaps deserves another look. About 6 to 10 percent of schizophrenics (see *14*) and their first-degree relatives (see *3*, *11*) are mentally subnormal, as compared with 3 percent of the general population. The expected reciprocal relationship, an excess of schizophrenics among mental defectives or their relatives, was found by Penrose (*15*) and Böök (*16*) among mental defectives but not by Reed and Reed (*17*) in their monumental survey of the relatives of mental defectives. Also, Kallmann found a much higher rate of mental deficiency (10.8 percent) among relatives of simple schizophrenics, where there is a clinical commonality of sorts, than among relatives of other subtypes in the Kraepelinian classification. The evidence for or against an association between schizophrenia and mental deficiency is inconclusive, and more data are needed before the matter can be decided.

Obviously there is much yet to be learned before we can describe and delimit schizoidia. However, the same thing can be said of schizophrenia itself, and in this regard study of the schizoid may lighten some dark corners. Schizophrenia is defined operationally, not etiologically. It is the clinician who determines whether schizophrenia is present. But of course the limits of the clinical entity may not correspond to those of the etiological entity. In fact the linking of schizoidia to schizophrenia by genetic evidence raises serious questions about the etiological reality of the clinical definition of schizophrenia. There has always been a fuzzy border about schizophrenia along which several named entries, including abortive, ambulatory, borderline, latent, pseudoneurotic, pseudopsychopathic, and reactive schizophrenia and the "schizotype" of Meehl (*18*) have seemed to lie.

These terms may best be viewed as attempts to cope with an operationally defined border between schizoidia and schizophrenia that is clinically imprecise because it is biologically unreal.

Table 3. Data on monozygotic twins of schizophrenics.

Investigator	Pairs (No.)	Schizophrenia (No.)	Other significant abnormality* (No.)	Normal, or mild abnormality (No.)
Essen-Möller (*19*)	9	0	8	1
Slater (*13*)	37	18	11	8
Tienari (*41*)	16	1	12	3
Kringlen (*12*)	45	14	17	14
Inouye (*42*)	53	20	29	4
Gottesman and Shields (*23*)	24	10	8	6
Kallmann† (*43*)	174	103	62	9
Totals	358	166 (46.4%)	147 (41.1%)	45 (12.6%)

* Investigators' diagnoses: ? schizophrenia, schizophreniform, transient schizophrenia, reactive psychosis, borderline state, schizoid, suicide, psychopathic, neurosis, and variations of these diagnoses. † From Shields, Gottesman, and Slater (*44*).

Quantitative Aspects

Given a schizophrenic who has a monozygotic twin, the empirical probability that his twin will also be schizophrenic has been found to be about 0.46 (Table 3). Most of the remaining 54 percent of monozygotic twins of schizophrenics have also been found to be abnormal. From clinical description included in five studies (*12, 13, 19–21*) it appears that nearly all of the abnormal though nonschizophrenic co-twins were schizoid. Overall, only about 13 percent of the monozygotic twins of schizophrenics have been regarded as normal or nearly normal, and, because most of the errors inherent in this sort of research tend to increase the proportion of apparent normals, this is surely an overestimate. But, while a critic could easily quibble about any of the proportions in Table 3, a crude but critical conclusion is inescapable: monozygotic twins of schizophrenics are about as likely to be schizoid as schizophrenic. What then is inherited? These considerations led Essen-Möller (*19*) to regard schizoidia as the basic inherited trait, and Kringlen, in a careful and sensitive analysis of twin research, including his own major study, seems to have reached a similar conclusion, although he regarded the predisposition as less specific (*12*). At the very least a prima facie case has been made for considering the whole group of schizoid and schizophrenic disorders as alternative expressions of a single genotype. Moreover, because monozygotic twins are identical genetically, there is presumptive evidence that the range of variability within pairs can in principle be accounted for by environmental factors. The genes allow a range of outcomes.

A critical point to be established is the proportion of schizoids or schizophrenics among the first-degree relatives (parents, sibs, children) of schizophrenics. Table 4 gives Kallmann's results. No one else has investigated so many relatives of schizophrenics, and few others have conducted field studies intensive enough to identify schizoids. The more intensive modern studies have tended to show somewhat larger proportions of afflicted relatives (*3, 10, 22*). So did Slater among dizygotic twins of schizophrenics (*13*). The proportions found by Gottesman and Shields (*23*) and by Ödegard (*24*) were somewhat smaller. Kallmann's values may be taken as fair average estimates of the proportion of schizoids or schizophrenics among first-degree relatives of schizophrenics.

Table 4 also shows the results of four studies of the children of two schizo-

Table 4. Percentages of first-degree relatives found to be schizophrenic or schizoid.

Relationship	Number of individuals	Schizophrenia* (%)	Schizoid (%)	Total: schizoid plus schizophrenic (%)
Children†	1000	16.4	32.6	49.0
Siblings‡	1191	14.3	31.5	45.8
Parents‡	2741	9.2	34.8	44.0
Children of two schizophrenics§	171	33.9	32.2	66.1

* Age-corrected rates. † From (*11*). ‡ From (*43*). § From Kallmann (*11*), Kahn (*45*), Schulz (*46*), and Elsässer (*47*).

phrenics. An estimated 66 percent of the children of these matings were schizoid or schizophrenic, again, this is surely an underestimate because the subjects were still quite young. The results of one such study, that of Lewis (*25*), was not included. Lewis did not give ages, and he stated that his follow-up was incomplete. Rosenthal has recently reviewed these studies (*26*).

An important unknown must now be considered. There is no adequate estimate of the proportion of schizoids in the general population. Then, is the clustering of schizoids among relatives of schizophrenics greater than might occur by chance? Although the proportion of schizoids found in families of schizophrenics is surely greater than that expected by even the most pessimistic observer of the general population, a better answer is that neither the relatives of other kinds of psychiatric patients nor the controls used in psychiatric studies have been found to be afflicted in significant numbers with disorders of a schizoid character or with any kind of behavioral disorder to the extent seen in relatives of schizophrenics. Further evidence—the small proportion of schizoids found among descendants of normal relatives of schizophrenics—is discussed below.

While the lack of data for the general population and the related lack of data for the families of schizoid probands preclude estimates of gene frequency, it should be noted that schizoid disorders surely afflict a large proportion of the population. With only isolated exceptions, schizophrenia afflicts about 1 percent of any population. If each schizophrenic has five living first-degree relatives (about the number in Kallmann's study), a simple extrapolation yields an estimate of 4 percent for the proportion of schizoids plus schizophrenics in the general population. This crude estimate can only make the point that any population, and especially any psychiatric population (persons identified because they came to psychiatric clinics or hospitals), is likely to contain large numbers of schizoids. One of the most neutral implications of this conclusion has an obvious application to the choosing of control groups for research in schizophrenia.

Genetic Hypothesis

The most parsimonious explanation of the data is given by the hypothesis that a defect in a single autosomal gene accounts for the genetic contribution to both schizoid and schizophrenic disease (the "dominance hypothesis"). By including schizoid disease (schizoidia), this hypothesis extends that of Slater (*27*). The view that schizoidia and schizophrenia are a single disease genetically is supported by their clinical similarity and is virtually required by the finding that the disorders occur with equal probability in monozygotic twins of schizophrenics. Further support for the hypothesis is presented in Fig. 1. The proportions of affected first-degree relatives fit

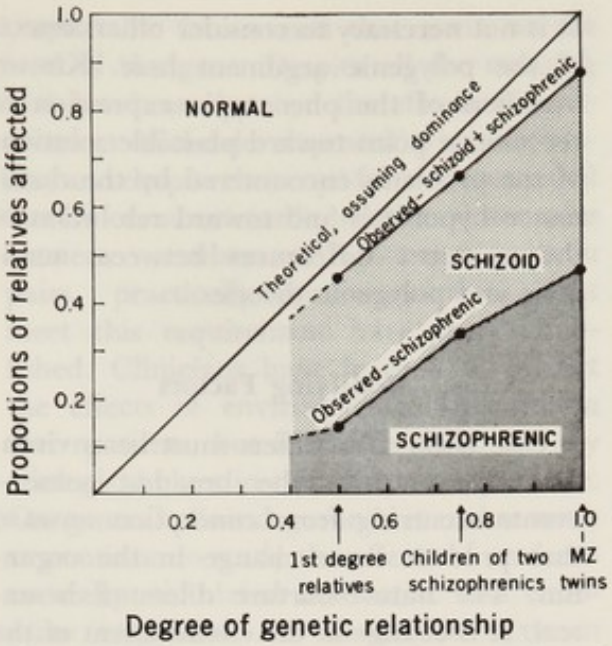

Figure 1. Observed and expected proportion of schizoids and schizophrenics.

reasonably well with the theoretical proportions expected under the dominance hypothesis.

Kallmann presented some data on second-degree relatives (*11*). Among 822 grandchildren of his schizophrenic probands he found 4.3 percent to be schizophrenic and 22.8 percent to be schizoid. The corresponding rates for nephews and nieces were considerably lower (3.9 and 6.2 percent). However, Kallmann pointed out that the normal sibs of his schizophrenic probands contributed many more nephews and nieces than the schizoid or schizophrenic sibs did. While the total of 27.1 percent for affected grandchildren is certainly close to the 25 percent expected under the dominance hypothesis, the proportions of affected nephews and nieces may or may not be compatible with that hypothesis.

The segregation of schizophrenia and schizoidia within families fits well with the dominance hypothesis. In Kallmann's study, which included three generations, the normal children of his schizophrenic probands produced few schizophrenic or schizoid children (1.8 and 2.6 percent, respectively), no more than might be expected in a general population. This is in contrast to the corresponding values of 13.7 and 33.4 percent for the children of the schizoid or schizophrenic children of Kallmann's schizophrenic probands (*11*).

The matter cannot be so simple, of course. The mechanisms involved in a disease like schizoidia-schizophrenia will surely be found to be extremely complex. Even phenylketonuria, which only a few years ago provided a prototype of rigorous simplicity for behavioral genetics, has turned out to be enormously complicated by secondary biochemical effects and by other, mostly unknown, factors (*28*). Heterogeneity is also likely. Probably the most completely known genetic disease in humans, glucose-6-phosphate dehydrogenase deficiency, occurs in at least 18 variants, each one presumably due to an amino acid substitution at a different place in the same enzyme (*29*). But research must proceed from hypotheses based on present understanding. From that viewpoint, and for practical purposes, it is not at all unreasonable to proceed on the working assumption that most schizoidia-schizophrenia is associated with defects in a single basic biochemical or physiological pathway, transmitted by a single mode of inheritance. It matters little that new research will no doubt turn up complexities that cannot even be imagined today.

Apart from insights gained from analogies to other diseases, there are factual reasons for expecting that many elements in addition to a single main gene go into the mix that results in schizoidia-schizophrenia. First of all, there remain small deviations from the theoretical expectations under the dominance hypothesis, deviations which have been cited by Shields (*2*). These mainly take the form of a greater resemblance between relatives than can be explained by simple dominance.

For example, the monozygotic twin of a severely afflicted individual is more likely to be schizophrenic than the twin of a mildly affected individual. If only a single gene were involved one would expect the risk of schizophrenia for a monozygotic twin of any schizophrenic to be equal to that of any other. Likewise, the larger the proportion of schizophrenic relatives is, the greater is the risk of schizophrenia for any given individual. Another sort of problem is that of accounting for the variability seen among schizophrenics; this becomes more difficult when schizoids are included. Although there are no grounds for expecting any particular degree of resemblance between affected persons, it has often been argued that, if only one gene were involved, the range of observable phenotypes should be smaller than is the case. And the persistence of schizophrenia presents a problem. Before the introduction of antipsychotic drugs, schizophrenics reproduced at a rate 30 percent lower (*16*), and schizoids at a rate 22 percent lower (*11*), than the rate for the general population. Such reproductive deficits should have lowered the rates of occurrence of a disorder due to a main gene of large effect far below the presently observed rates for schizophrenia.

Attempts to account for such findings have led to widespread espousal of polygenic theories of schizophrenia (*12, 24, 30*). As Gottesman and Shields have pointed out (*31*), the facts are explained adequately by polygenic theory. Most polygenic theorists have regarded schizophrenia as a threshold trait. But clinically schizoidia and schizophrenia seem to form a continuum of psychopathology, much as first described by Kretschmer (*32*). If there is a threshold it probably falls between the schizoid and the normal condition, but it seems that any such "threshold" is as likely to be a function of lack of diagnostic precision as a function of the disease. It is not necessary to consider other aspects of the polygenic argument here. Known modifiers of the phenotypic expression of the disease point toward plausible solutions of the problems encountered by the dominance hypothesis and toward resolution of the apparent differences between main-gene and polygenic theories.

Modifying Factors

One class of modifiers must be environmental events in the broadest sense—events occurring from conception onward that produce some change in the organism. The nature-nurture dilemma is unreal. It is change in the environment of the cell that induces change in the genetically mediated metabolic systems of the cell. The functional state of the cell is a result of the interplay of these determinants. But realization that phenotypic traits depend on interaction between gene and environment imposes conditions on research aimed at assessing the environment contribution. Genes function within cells. They interact with chemical, thermal, or other physical events and not with the abstractions ("stress," for example) that too often have passed for environmental data. The ultimate questions implicit in the concept of gene-environment interaction are, for example: How does a noxious learning experience alter the environment of the cell? What response is elicited from the genetic program of the cell? How is the later operation of the cell modified? Of course, such questions cannot be approached directly today. But unless the environmental contribution is too variable from case to case to allow generalization, it should be possible to build up a series of associations between environment and behavior that would point toward the environmental events that enter into the gene-environment interaction. The critical requirement is that such associations be potentially

translatable into events that occur at the level of the gene. Despite all the research that has been done on the effects of environment on the development of schizophrenia, and despite the scope for environmental factors demonstrated by the differences between members of monozygotic twin pairs, practically no associations that meet this requirement have been established. Clinicians have learned to predict the effects of environmental features on their patients, but it is difficult to see any etiological clues in this body of experience. On general clinical grounds it makes sense to continue to study the effects of environmentally stimulated autonomic and endocrine responses. An association between lower birth weight and the development of schizophrenia in one member of a monozygotic twin pair has been reported (*21*), but it must be quite imperfect in view of the failure of other investigators to confirm it (*12, 23*). Perhaps differences in autonomic responses among children of schizophrenics that were described in a preliminary report from a wide-ranging prospective study (*33*) are the most promising associations so far defined. Almost everything remains to be done.

A second class of modifiers consists of complex traits that have been linked to schizophrenia by decades of empirical research. Somatotype has been found by several investigators to be associated with major modification of schizophrenia. Mesomorphs are underrepresented among schizophrenics, and especially underrepresented among schizophrenics younger than 25. Ectomorphs are corresponding overrepresented. Schizophrenic mesomorphs are predominantly paranoid and have a shorter mean period of hospitalization than other schizophrenics. Parnell (*34*), who has reviewed the subject and contributed his own data, found all these associations to be statistically significant. A relation between intelligence and the prognosis in schizophrenia is well known: the higher the intelligence the better the prognosis. But higher intelligence may also affect the expression of schizophrenia. Lane and Albee (*35*) found that the I.Q. of children who later became schizophrenic was seven points lower than that of their siblings who remained nonschizophrenic. There are a host of other established associations between complex traits and schizophrenia—for example, patterns of autonomic nervous system reactivity, immunological phenomena, resistance to certain chronic diseases, and tolerance of wound shock. Some such traits appear to be only oddities, given our present knowledge; others are known to be linked to favorable or unfavorable prognosis in schizophrenia, and still others are known only to be more frequent or infrequent among schizophrenics. Several reviews of these findings are available (*36*).

The large number of such complex traits and the magnitude of the modification of schizophrenia associated with some of them must mean that they have a significant role in the ecology of the disease. For one thing, they suggest a plausible solution to the puzzle posed by the persistence of high rates of schizophrenia. Sir Julian Huxley *et al.* (*37*) postulated that the gene responsible for schizophrenia conferred sufficient physiological or reproductive advantages to maintain a balanced polymorphism. They listed several physiological traits found in schizophrenics that could be due to pleiotropism. Although the number of traits listed seems large, widespread pleiotropism might result from a mutation at a regulatory locus (*38*). But many modifying traits are clearly not due to pleiotropism, and some of those—particularly differences in somatotype and intelligence—which demonstrably affect the outcome in schizophrenia must have conferred general biological advantages through much of man's history as well. In either event, schizophrenics possessing advantageous traits would

be expected to reproduce at relatively higher rates than those not possessing such traits. Over time, the evolutionary process would, theoretically, act to establish sets of favorable traits that, on the average, would tend to accompany schizophrenia. Theory aside, the popular association between genius and insanity, thought to be erroneous by Kallmann, was given some substance by Karlsson's finding that creative achievements and schizophrenia occurred in the same family lines (*39*). I reported a similar impression; however, the evidence was not gathered systematically (*40*). Although the problem posed by the persistence of schizophrenia remains theoretical and unsolved, further exploration of modifying traits provides as likely a path as any other now in view toward solution of the puzzle.

Modifying traits also suggest an approach to the problem of deviations from strict expectations under the dominance hypothesis. As pointed out above, polygenic theory can account for such deviations. But traits like somatotype and intelligence are themselves almost certainly polygenic. Polygenic modifiers of a single main gene explain the same facts, and indeed would yield the same mathematical results as simple additive polygenic theory per se. A multitude of genes summating to produce schizophrenia directly or a single main gene plus groups of genes summating to produce modifying traits account equally well for findings such as the tendency of monozygotic twins to be concordant with respect to severity of illness.

Conclusion

A main gene of large effect modified by multiple factors, including polygenic traits, suggests a number of testable hypotheses. Biochemical or other effects of a main gene should be present in schizoids as well as in schizophrenics. In family studies, the critical test of the place of the schizoid would be his reproductive performance in matings with normal individuals; 50 percent of the offspring of such matings should be schizoid or schizophrenic. However, polygenic modifiers should, on the average, maintain lesser degrees of disability in particular families. Thus, schizoid parents should have fewer schizophrenic but more schizoid children than schizophrenic parents. There is incomplete support for this contention in Kallmann's study (*11*) of the grandchildren of his schizophrenic subjects: the schizoid children of his schizophrenic probands had more schizoid and fewer schizophrenic children than their schizophrenic siblings, but members of the third generation, the grandchildren of the probands, were too young to yield decisive evidence. Along the same lines, it would be expected that nearly all schizophrenics should have at least one schizoid or schizophrenic parent. Although the work of Kallmann and the intensive family studies of Alanen (*10*) and Lidz (*22*) support this expectation, more rigorous evidence is needed. The traits that favorably modify schizophrenia should be more apparent among schizoid than among schizophrenic relatives of schizophrenics. One would hypothesize, for example, that the more mesomorphic or more intelligent among the children of schizophrenics would tend to have less severe illnesses and to have more children than the less mesomorphic or less intelligent. These hypotheses, and many more that are implicit in the preceding discussion, constitute a significant refinement of the genetic hypotheses so far explored in schizophrenia.

Summary

The importance of genetic factors in the development of schizophrenia has by now been established beyond reasonable dispute, although it is clear that environment too plays its etiologic role. The results of

recent research have refocused attention on schizoid disorders, a term applied to psychiatric disorders resembling schizophrenia which afflict relatives of schizophrenics. The many conceptual and research problems presented by the schizoid are considered.

Schizoids and schizophrenics occur with about the same frequency among monozygotic twins of schizophrenics. About 45 percent of the sibs, parents, and children of a schizophrenic are schizoid or schizophrenics, as are about 66 percent of the children of two schizophrenics. From the known risk of schizophrenia for the population as a whole, it is estimated that at least 4 percent of the general population will be afflicted with schizoid-schizophrenic disease.

Since monozygotic twins are identical genetically, it appears that the same genotype is compatible with either schizophrenic or schizoid disease. The proportions of affected first-degree relatives and segregation of affected individuals within families closely approximate theoretical expectations based on the hypothesis of a defect in a single autosomal dominant gene. However, modifying traits play a significant role; this is discussed and integrated into the main genetic hypothesis. Emphasis is placed on hypotheses testable by future research.

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Biochemical and Sleep Studies of Schizophrenia: A Review of the Literature 1960–1970

Part I. Biochemical Studies

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The etiology of schizophrenia remains undiscovered. Indeed, it is not yet clear whether the causative factors lie, as has often been assumed, in the biological realm or whether the widely accepted disease model of mental illness is, in fact, appropriate to the investigation of this complex disorder. All biochemical theories of schizophrenia are predicated on the belief that a qualitatively or quantitatively abnormal substance (such as a methylated amine or a protein) may play some role in producing schizophrenic episodes. Because existing biochemical "theories," at this preliminary stage of their development, might more accurately be termed research "leads" or "strategies," it is not necessarily an important scientific question whether these hypotheses are, in some absolute sense, true or false. A better question, it seems to us, is whether a given "lead" is worthy of further investigation or is an artifact.

The need to distinguish between artifact and reality has presented students of the biology of schizophrenia with a series of challenges perhaps unmatched in the history of science. That careful controls are essential in this research area was made abundantly clear by Kety (1959a and b) whose methodological criticisms of biochemical studies of schizophrenia are as relevant today as they were when his classic review was originally published. Since most investigators accept—at least in principle—the necessity for controls, we shall not repeat these criticisms for each individual study to be reviewed in these pages but, rather, emphasize here that results achieved in the absence of careful controls can be highly misleading. On a theoretical basis, the battle for controls has been won and need not be refought in this review. On a practical level, however, many studies fail to be well controlled.

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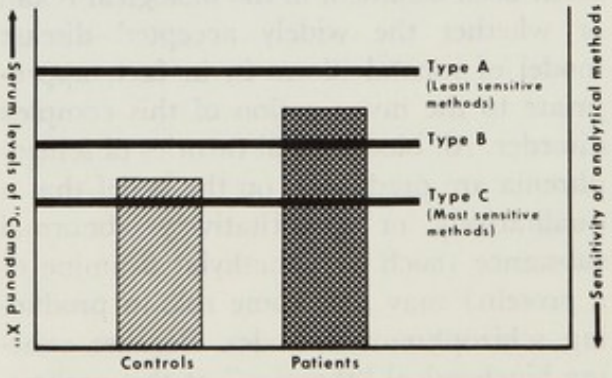
Special problems arise in the evaluation of research concerning biochemical abnormalities in schizophrenia, and an awareness of these difficulties is important for a proper understanding of the data to be reviewed here. For this reason, a number of these problems will be briefly summarized below:

In all probability, the term "schizophrenia" defines, not a *unitary disease,* but a *symptom complex* having multiple etiologies; if so, schizophrenia is similar to such familiar medical entities as anemia or jaundice. It is also possible that schizophrenia entails multiple biochemical abnormalities which may or may not be related. Because of the heterogeneity of patient populations, not all of these biochemical lesions could reasonably be expected to be identified in a single study. Clearly, a particular biochemical lesion which affected only a minority of the subjects in a given study would tend to be submerged in any overall evaluation and, thus, would not appear significant. This factor might help to explain an all too frequent phenomenon in schizophrenia research—the failure of different investigators, using the same research design, to obtain the same, or even similar, results.

Another significant problem in this research area is that of attempting to measure changes in *brain* biochemistry through the analysis of peripheral tissue or body fluids. Although the presumed site of origin of the schizophrenic process is in the brain, the biochemist usually can only measure secondary (plasma) or tertiary (urine) parameters as an index of what is occurring in brain tissue.

Because controlled biochemical studies of schizophrenia are notoriously difficult to carry out, many investigators have variously dispensed with controls entirely, used controls which are inadequate to account for reasonable sources of artifact, or utilized appropriate controls but failed to employ equally important double-blind methods. In conducting biochemical studies, it is important to insure that both schizophrenics and controls are subjected to as nearly similar environmental conditions as possible. Such factors as the effects of hospitalization on intestinal flora, stress, diet, and medication may be extremely important in a study measuring small biochemical differences between groups. Studies by Mann and LaBrosse (1959) and by Dastur, Mann, and Pollin (1963) found, for example, that certain significant urinary biochemical differences between schizophrenic and normal control subjects were due to the schizophrenics' greater daily consumption of coffee.

Biochemical studies are commonly marred by errors which derive from quantitative or qualitative flaws in research methods (see example in figure 1). A quantitative error is made when a substance in low concentrations or an insensitive methodology produces (or combine to



Results: Study A—Compound X not present
Study B—Compound X found only in patients
Study C—Compound X found in both patients and controls (sensitive but not adequately quantitative)

Figure 1. Effects of analytical methods with differing degrees of sensitivity on investigative results (hypothetical situation).

produce) errors of types A and B. Type A errors are ones in which the substance's presence is missed in both patients and controls, whereas type B errors occur when a substance, which may actually be present (in different concentrations) in both patients and controls, is seen in one group but not the other. A type C error is one in which a substance is found in both groups but differences in concentrations are missed. Finally, a substance can be easily misidentified qualitatively; this is especially true when it is present in physiologic concentrations that are generally low.

The importance of considering whether a biochemical abnormality shown to be associated with schizophrenia is a cause or an effect of this disorder can be seen if an analogy to obstructive jaundice is used. Although many biochemical abnormalities are associated with obstructive jaundice, only a *few* represent anything more than biochemical markers; *most* are in no way causally related to the basic disease process. Likewise, biochemical lesions demonstrated in schizophrenia may not be causally implicated in the basic disease process and may be of little value in the elucidation of its etiology. While bearing this cautionary note in mind, it is also important to recall that these lesions may, in fact, be manifestations of altered biochemical pathways in the brain which will yield clues important to the development of a "biochemical cure."

Since the literature in this area is vast, our focus will be on critical issues. Many of the data have been condensed into tabular form, enabling the reader to compare the results of many studies at a glance, and eliminating the need for vast quantities of textual material. Because space limitations force us to be selective in our choice of topics to be reviewed in detail, we will not consider some of the older material which has been amply covered in many previous reviews. For similar reasons we have not undertaken to discuss whether the "model psychoses" produced by amphetamines, LSD, and other hallucinogens represent processes analogous to schizophrenia.

The Transmethylation Hypothesis

In figure 2 the structures of some endogenous amines are compared to related compounds that are generally agreed to produce hallucinations in man. It can be seen that many of these compounds are methylated derivatives of catechol and indole nuclei. Mescaline, for example, is the 3,4,5-methoxy derivative of phenylalanine, while dopamine, a naturally occurring nonhallucinogenic catecholamine, is the 3,4-dihydroxy derivative of the same nucleus. Similarly, bufotenine is the N,N-dimethyl derivative of serotonin.

Osmond and Smythies (1952), noting the similarity between mescaline and norepinephrine, postulated that an alteration in the biochemical transmethylation of norepinephrine might, through the endogenous synthesis of methylated amines which would function as hallucinogens, be responsible for some forms of schizophrenia (see figure 3). If such a compound did, in fact, play a role in schizophrenia, it would have to fulfill the following descriptive requirements:

- It should be capable of producing or exacerbating physiological and/or psychological changes found in schizophrenic patients.
- If the compound is endogenous in origin, the schizophrenic patient should be capable of producing it from precursors; if normal persons can also produce this compound, its production and/or metabolism should be quantitatively different in schizophrenic and normal individuals.
- Likewise, if the compound is exoge-

nous in origin, its metabolism should be quantitatively different in schizophrenics and normals; this difference could be in its metabolism, in a narrow sense, or in distribution, binding, transport, or end organ effect.

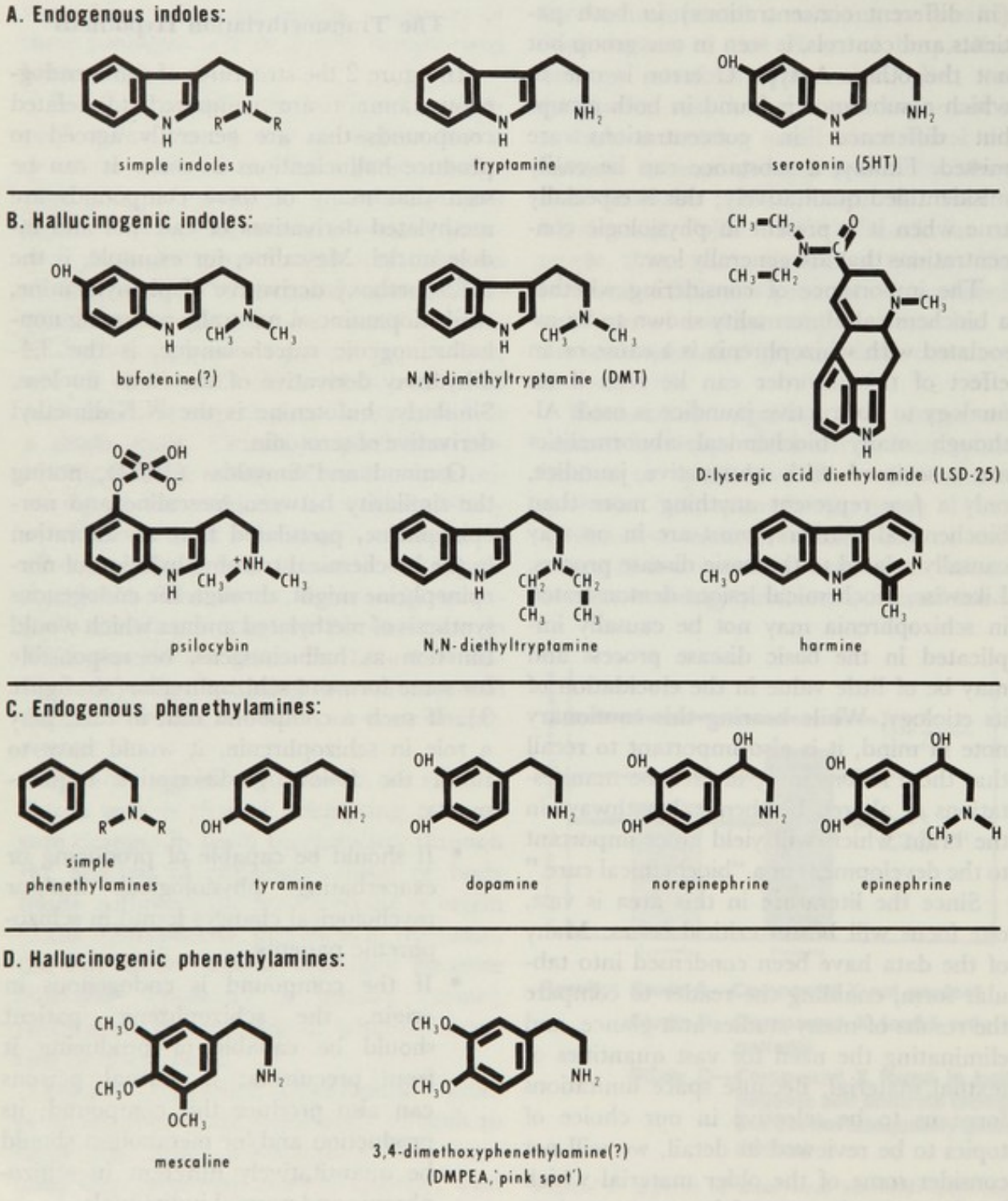
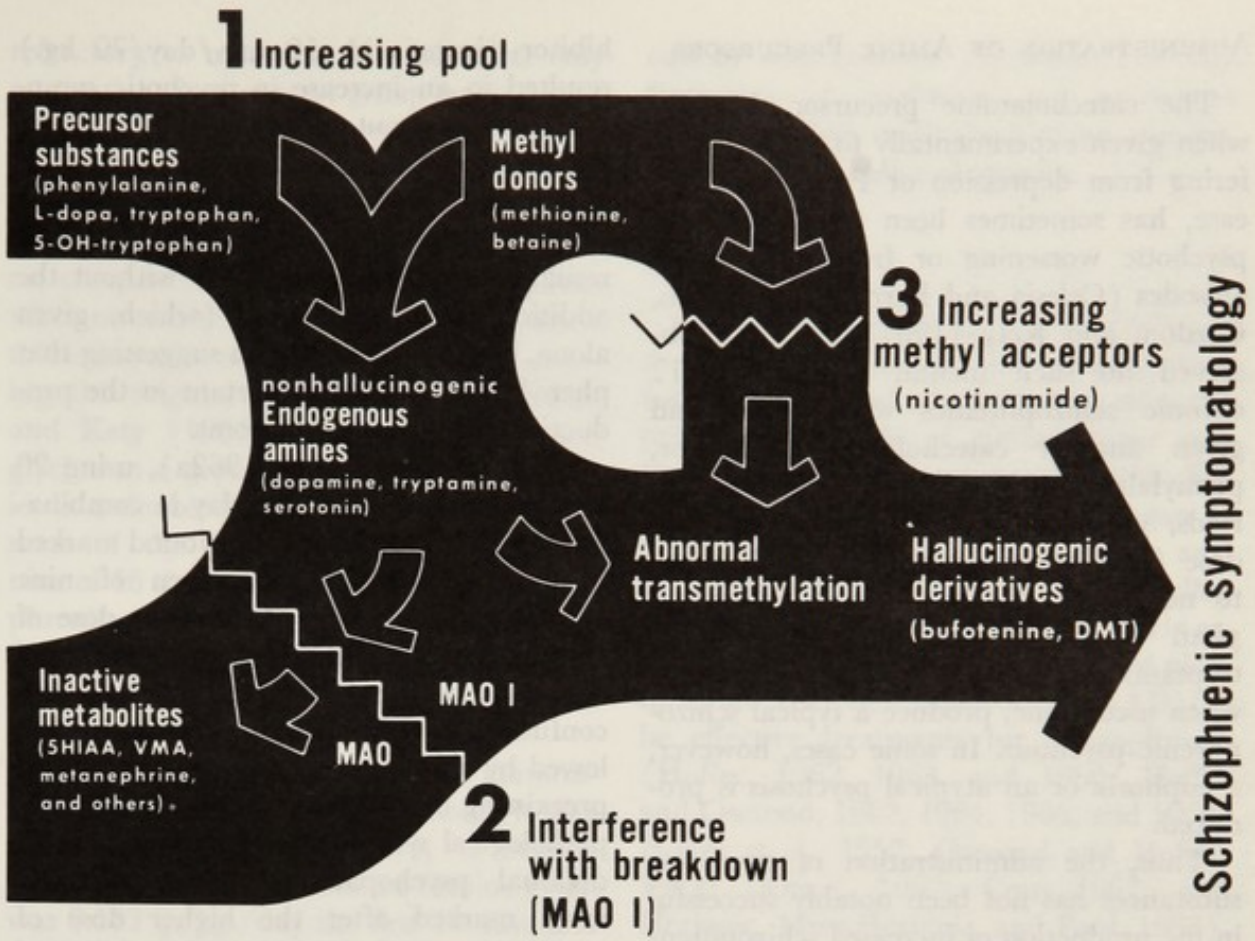


Figure 2. Structures of naturally occurring amines and some hallucinogens with similar structures. Question mark (?) indicates questionable hallucinogenic activity.



1. Increasing available pool of substances thought necessary to process: precursor substances and/or methyl *donors*. 2. Interfering with normal enzymatic breakdown by use of monoamine oxidase inhibitor. 3. Increasing available pool of methyl *acceptors*.

Figure 3. Strategies used to study the hypothesized *abnormal transmethylation in schizophrenia.*

The enzyme necessary for methylating hydroxyl groups (O-methylation) has been shown to be present in human brain. (O-methylation represents the major metabolic pathway for brain catecholamines.) With regard to indoles, the presence in rabbit lung of the enzyme for N-methylation was demonstrated by Axelrod in 1961. More recently, Mandell and Morgan (1970) reported the presence in human brain of an enzyme that N-methylates indole ethyl amines.

Compounds which increase the total amount of hallucinogenic derivatives should result in an exacerbation of the schizophrenic process. Similarly, a reduction in the amount of available hallucinogenic derivatives should result in an improvement in the schizophrenic state. On this basis, experiments have been performed which (1) administer precursor substances (L-dopa, phenylalanine, and tryptophan) or increase the amount of methyl donor substances available (administration of methionine and betaine), (2) decrease the normal metabolism of naturally occurring nonhallucinogenic amines (use of monoamine oxidase inhibitors), and (3) decrease the amount of methyl donor substances available by administering methyl acceptors (nicotinic acid or nicotinamide adenine dinucleotide).

Administration of Amine Precursors

The catecholamine precursor, L-dopa, when given experimentally to patients suffering from depression or Parkinson's disease, has sometimes been associated with psychotic worsening or frankly psychotic episodes (Celesia and Barr, 1970). Pollin, Cardon, and Kety (1961), however, observed no such mental changes in 12 chronic schizophrenics whom they had given another catecholamine precursor, phenylalanine (20 g./day), for 1-week periods, with and without monoamine oxidase (MAO) inhibitors. Frequently given to normals and schizophrenics, L-tryptophan (a precursor of the indoleamines, tryptamine and serotonin) also does not, when used alone, produce a typical schizophrenic psychosis. In some cases, however, a euphoria or an atypical psychosis is produced.

Thus, the administration of precursor substances has not been notably successful in the production of increased schizophrenic symptomatology. One possible explanation for this apparent failure is that the precursor substances given were metabolized too rapidly for any effect to have been shown. Or, alternatively, the oral or intravenous administration of these compounds may not result in any significant change in their levels in the brain.

Administration of Methyl Donors

Perhaps a more effective method of producing psychotic-like symptoms has been the administration of methyl donors—e.g., methionine. In all of the double-blind studies summarized in table 1, methionine was administered to chronic schizophrenic patients. Pollin, Cardon, and Kety (1961) found that, although methionine alone produced no symptoms in three chronic schizophrenics, methionine given in combination with a low dose of an MAO inhibitor (iproniazid, 50 mg./day/70 kg.) resulted in an increase in psychotic symptoms in three out of nine patients. With higher MAO inhibitor dosage (iproniazid, 150 mg./day/70 kg.), three out of three patients' symptoms were intensified. The results were the same with or without the addition of phenylalanine (which, given alone, had no effect), again suggesting that phenylalanine is not important in the production of psychotic symptoms.

Brune and Himwich (1962a), using 20 or 40 g. of methionine per day in combination with an MAO inhibitor, found marked behavioral alterations in seven of nine chronic schizophrenics with either dose of methionine. At first, the changes involved euphoria, disorientation, somnolence, and confusion, but this initial reaction was followed by a recurrence and accentuation of preexisting behavioral patterns and psychopathological symptoms. Aggravation of individual psychopathology was generally more marked after the higher dose of methionine, indicating that the ability of methionine to produce psychotic symptoms may be dose-related. Alexander et al. (1963) found no increase in psychotic symptoms in six chronic schizophrenic patients with methionine loading. With the addition of an MAO inhibitor (tranylcypromine), however, two of the patients showed hallucinations and delusions. No evidence of psychosis was found in two nonschizophrenic psychiatric patients when methionine was given, either with or without an MAO inhibitor. Park, Baldessarini, and Kety (1965) observed psychotic behavior in three of 17 chronic schizophrenics who had received methionine plus an MAO inhibitor; no such behavioral changes were noted when glycine was substituted for methionine. Haydu et al. (1965) noted that, following the administration of methionine, symptoms were exacerbated in seven of nine schizophrenics

refractory to treatment; by contrast, only one patient in a control group treated with hydroxychloroquine worsened. Berlet et al. (1965) found that chronic schizophrenic patients worsened while on methionine and an MAO inhibitor; these patients showed no comparable exacerbation of symptoms when on methionine plus tryptophan, however. Smythies and Antun (1970), repeating the original work of Pollin, Cardon, and Kety (1961), gave methionine and glycine to a group of chronic schizophrenics in a double-blind, crossover trial. While none of the patients reacted to glycine, nine of 16 showed an "unmistakably schizophreniform" reaction to methionine (10–20 g./day). These psychotic reactions subsided when methionine treatment was discontinued.

Brune and Himwich (1962b) administered betaine (another methyl donor), plus isocarboxazid (30 mg./day), to schizophrenic patients. The dose of betaine given was 0.113 g./kg./day the first 10 days and double that amount the second 10 days. Although betaine provoked behavioral changes similar to those seen with methionine—namely, accentuation of hallucinations and delusions and increase in thought disorganization—the betaine-induced behavioral changes appeared more slowly than did those produced by methionine.

Cysteine is another substance which has been reported to exacerbate schizophrenic symptomatology (Spaide et al., 1967); while cysteine is not a methyl donor, the presence of the thiol group is apparently important in the action of the enzyme O-methyl transferase (Smythies, 1968).

The frequent finding that a methyl donor (methionine), given in combination with an MAO inhibitor, intensifies psychotic symptoms would appear to support the transmethylation hypothesis; it is difficult, however, to differentiate conclusively between *drug toxicity* and a *true exacerbation of schizophrenic psychosis.* The high frequency of confusion and autonomic symptomatology with methionine administration are indicative of toxicity.

Nicotinic Acid

On a theoretical basis, it is interesting to note that nicotinic acid and its derivatives function as methyl acceptors and, thus, decrease the amount of methyl donor substances available for transmethylation. For this reason, Hoffer and Osmond began in 1952 to treat patients with nicotinic acid in large doses (5–10 g./day). In controlled and uncontrolled studies, they and their associates found both nicotinic acid and nicotinamide adenine dinucleotide (NAD) to be effective treatments for schizophrenia (Hoffer, 1962, 1963, and 1966; Hoffer and Osmond, 1962, 1964, 1966, and 1968; Hoffer et al., 1957; Osmond and Hoffer, 1962; Denson, 1962; Cott, 1967; and Herjanic, Moss-Herjanic, and Paul, 1967). More recently, Ananth et al. (1970) reported that nicotinic acid (3 g./day) produced improvement in chronic hospitalized schizophrenics. Ashby, Collins, and Bassett (1960) and Ban and Lehmann (1970), however, failed to confirm the effectiveness of either nicotinic acid or nicotinamide in chronic schizophrenics. Moreover, a substantial number of investigators have been unable to replicate the therapeutic effect of NAD; Gallant, Bishop, and Steele (1966), Kline et al. (1967), Nichols, Sugerman, and Murphree (1967), and Meltzer, Shader, and Grinspoon (1969) all have reported negative results.

Since the theoretical basis for the use of nicotinic acid in schizophrenia rests on its properties as a methyl acceptor, it would be of interest to determine if nicotinic acid is capable of reversing the exacerbations of schizophrenic psychosis which have been noted following the administration of a

Table 1. Methionine loading in human subjects. (Most studies were double blind.)

Author(s)	Patient sample	Time off drugs	Drugs given (daily doses)	Time	Description of reaction	Response A[1]	Response B[2]
Pollin, Cardon, and Kety (1961)	Chronic schizophrenics	18 mos.	Methionine (20g./70kg.) + phenylalanine (20g./70kg.) + MAOI–iproniazid (50mg./70kg.)	1 wk.	Increased flood of associations, word salad, increased anxiety, panic, increased hallucinations, increased tension, motor activity	3/9	3/9
			Methionine (20g./70kg.) + phenylalanine (20g./70kg.)	1 wk.	No reaction	0/3	0/3
			Methionine (20g./70kg.) + MAOI–iproniazid (50mg./70kg.)	1 wk.	Increased flood of associations, word salad, increased anxiety, panic, increased hallucinations, disorientation, agitation, increased tension, motor activity	3/9	3/9
			Methionine (20g./70kg.)	1 wk.	No reaction	0/3	0/3
			Methionine (20g./70kg.) + MAOI–iproniazid (150mg./70kg.)	1 wk.	Increased flood of associations, word salad, increased anxiety, panic, increased hallucinations	3/3	3/3
Brune & Himwich (1962a)	Chronic schizophrenics	2 wks.	D,L-methionine (20g./70kg.) + MAOI–isocarboxazid (30mg.)	5 days	Euphoria, volubility, increased activity, increased psychotic behavior	7/9	5/9
			D,L-methionine (40g./70kg.) + MAOI–isocarboxazid (30mg.)	2 days	Euphoria, volubility, increased activity, increased psychotic behavior	7/9	7/9
Alexander et al. (1963)	Chronic schizophrenics	2 wks.	L-methionine (20g.)	1 wk.	Nausea, increased alertness	2/6	0/6
			L-methionine (20g.) + MAOI–tranylcypromine (30mg.)	1 wk.	Hypnagogic hallucinations, delusions, fear, insomnia, drowsiness, lethargy, fatigue	5/6	2/6
	Nonpsychotic psychiatric patients	2 wks.	L-methionine (20g.)	1 wk.	Drowsiness, lethargy, fatigue, weakness	2/2	0/2
			L-methionine (20g.) + MAOI–tranylcypromine (30mg.)	1 wk.	Drowsiness, insomnia, fear, euphoria, fatigue, weakness, lethargy	2/2	0/2

Park, Baldessarini, & Kety (1965)	Chronic schizophrenics	3 wks.	Methionine (20g./70kg.) + MAOI–iproniazid (50mg./70kg.) or isocarboxazid (20mg./70kg.)	1 wk.	Grandiose delusions, disturbing nocturnal visions, increased paranoid behavior, increased visual hallucinations	3/17	3/17
			Glycine (20g./70kg.) + MAOI–iproniazid (50mg./70kg.) or isocarboxazid (20mg./70kg.)	1 wk.	No reaction	0/17	0/17
Beriet et al. (1965)	Chronic schizophrenics	10 mos.	Tryptophan (10g./70kg.) + methionine (20g./70kg.)	30 days	No reaction	0/4	0/4
	Chronic schizophrenics	2 mos.	Methionine (max. 40g./day) + MAOI–tranylcyromine (30mg.)	6–12 days	Exacerbations of characteristic symptoms of psychosis	8/8	7/8
Haydu et al. (1965)	Nonparanoid chronic schizophrenics	none	Methionine (5g.) + trifluoperazine (30mg.)	2 mos.	Worsening of clinical status, specific responses not given	7/9	7/9
			Methionine (5g.)	2 mos.	Worsening of clinical status, specific responses not given	7/9	7/9
Ananth et al. (1970)	Chronic schizophrenics	2 wks.	Methionine (20g.) + MAOI–tranylcypromine (30mg.)	4 wks.	Exacerbation of psychosis, increased sexual excitement, confusion, hyperactivity, ataxia, hallucinations	14/20	14/20
Spaide et al. (1969)	Chronic schizophrenics	18–24 wks.	Tranylcypromine (30mg.)	8 days	No reaction	0/4	0/4
			Tranylcypromine (30mg.) + tryptophan (10–40g.) + methionine (7–28g.)	20 days	Worsening of symptoms, hallucinations	3/4	3/4
Smythies & Antun (1970)	Chronic schizophrenics	Not given	Methionine (20g.–1st wk., 10g.–2nd wk.)	2 wks.	Delusions, hallucinations, paranoid ideation	9/16	9/16
			Glycine (20g.–1st wk., 10g.–2nd wk.)	2 wks.	No reaction	0/16	0/16
Narasimhachari et al. (1970)	2 Chronic schizophrenics & 6 normal controls	3 wks.	Tranylcypromine (30mg.)	7 days		1/2	2/2
			Cysteine (20g.max.)	20 days		0/6	0/6

[1] Number of patients with a positive response/total number in the group studied. [2] Number of patients with a psychotic response/total number in the group.

methyl donor and an MAO inhibitor. In a recent study Ananth et al. (1970) attempted to answer this question. Following combined administration of tranylcypromine and methionine, 14 of 20 hospitalized chronic schizophrenics showed an exacerbation of psychosis. Nicotinic acid was unable to prevent the occurrence of these exacerbations or to ameliorate them significantly. As a possible explanation for this failure the authors suggest that the dose of nicotinic acid may have been inadequate. They also recognize that either methionine or the methionine-tranylcypromine combination may have produced a toxic psychosis in the 14 patients whose behavior worsened. Interpreting data provided by Carlson, Levi, and Oro (1968), Ellerbrook and Purdy (1970) found no evidence that mega doses of nicotinic acid impair the methylation capacity of the body.

Although further research is currently in progress concerning the value and theoretical implications of the use of nicotinic acid in schizophrenia, only Drs. Hoffer, Osmond, and their collaborators have thus far brought forward strong support for their claims of its therapeutic efficacy. Furthermore, because little is known about the toxicity of nicotinic acid in high doses, it should be used with care. Particular caution is urged in its use in women during the child-bearing age and pregnancy, and in patients with a history of ulcer, gout, diabetes, or liver disease (Mosher, 1970).

The Pink Spot in Schizophrenia

Because methylated phenethylamines can produce catatonic-like behavior in laboratory animals (DeJong, 1945, and Ernst, 1962), Osmond and Smythies (1952) postulated that abnormal methylation of dopamine might play a role in producing clinical catatonia. The 1962 report of Friedhoff and Van Winkle that 3,4-dimethoxyphenethylamine (DMPEA) was found in the urine of 15 of 19 schizophrenics who had not received tranquilizing drugs for 2 weeks, but not in urine samples collected from any of 14 normal controls, started a flurry of investigative activity that has only recently begun to subside. Often referred to as the "pink spot," DMPEA, when dipped in ninhydrin-pyridine reagent and treated with a modified Ehrlich's reagent (p-dimethylaminobenzaldehyde dissolved in acetone and concentrated hydrochloric acid), immediately takes on a pink color which, upon standing, turns to orange. Friedhoff and Van Winkle's identification of the pink spot found in the urine of their schizophrenic subjects as DMPEA rested upon several lines of evidence including the fact that its chromatographic motility in butanol/acetic acid/water (4:1:1) and its staining properties with ninhydrinpyridine reagent and the modified Ehrlich's reagent were identical to those of authentic DMPEA. In addition, both the unknown and the authentic DMPEA could be converted into dinitrophenol derivatives and could be oxidized to 3,4-dimethoxyphenylacetic acid. Subsequently, Friedhoff and Van Winkle (1965) isolated the compound and reported that its melting point was identical with that of DMPEA.

Before considering whether DMPEA, in fact, occurs in the urine of schizophrenics and not in urine from normals, its chemical identification, and the influence of drugs, diet, and acuteness or chronicity of illness on its occurrence, two other problems should be discussed:

(1) Is there evidence that DMPEA causes schizophrenic-like symptoms in humans? In several studies, DMPEA has been given in doses of up to 1,000 mg. (with and without MAO inhibitors) to normal volunteers who, almost without exception, failed to exhibit schizophrenic-like symptoms (Hollister and Friedhoff, 1966;

Shulgin, Sargent, and Naranjo, 1966; Charalampous and Tansey, 1967; and Brown, McGeer, and Moser, 1968 [1]).

(2) Is there evidence for DMPEA's *in vivo* synthesis? Before excretion, DMPEA in man is almost completely converted to its corresponding acid, dimethoxyphenylacetic acid (DMPAA), although some is converted to N,acetyl DMPEA (Shulgin, Sargent, and Naranjo, 1966). It has been suggested that, if DMPEA is produced in the body, it might be formed from 3,4-dihydroxyphenethylamine (dopamine); this process would require enzymes that can produce 3,4-O-methylation. To test this possibility, Friedhoff and Van Winkle (1963) infused five schizophrenic subjects with tritium-labeled dopamine and then identified the dimethoxy acid derivative of DMPEA on paper chromatographs of the urine. A pooled sample of urine presumably contained purified DMPEA because it maintained a constant specific activity throughout four recrystallizations when added to authentic DMPEA. Friedhoff and Van Winkle sought to gain further evidence of the ability of schizophrenics to make DMPEA by incubating an homogenate from a DMPEA-positive patient's liver biopsy with tritium-labeled dopamine and carbon-14-labeled S-adenosyl-L-methionine. If DMPEA were formed from dopamine, they postulated, there should have been two carbon labels from each tritium label counted, indicating the addition of two methyl groups to dopamine's two hydroxyl groups. This was not found to be the case, however, as once again the dimethoxy acid derivative and not DMPEA was identified. Kuehl et al. (1964), using rat liver, catechol-O-methyl transferase (COMT), could find no evidence of conversion to di-O-methylated dopamine in an *in vitro* system. In studying liver and brain tissue preparations from normals and schizophrenics, Wagner et al. (1966) noted the inability of these preparations to convert labeled dopamine to DMPEA. It is possible that, since the tissues were obtained by autopsy, these results may have been due to a loss of enzyme activity; a relatively high degree of COMT activity was seen in these specimens, however, and Wagner et al. considered this an unlikely possibility. Urine samples from two patients given labeled 3,4-dihydroxyphenylalanine (DOPA) were also examined, and negligible amounts of labeled DMPEA or 3,4-dimethoxyphenylacetic acid (DMPAA) were seen. Thus, based on both *in vitro* and *in vivo* data, Wagner et al. concluded that DMPEA and DMPAA were not metabolic products of DOPA in chronic schizophrenics. Furthermore, Jones et al. (1969) found that, in schizophrenics, 90 percent of carbon-14-p-tyrosine could be identified as known non-p-methoxylated metabolites with no p-methoxy derivatives found.

As stated earlier, Friedhoff and Van Winkle's 1962 report that DMPEA was present in urine from schizophrenics but not from normals immediately stimulated a great many attempts to confirm or deny this finding (see table 2). While the subsequent research appeared initially to confirm these results, more recent studies have shown contradictory findings; some have found DMPEA in urine from both schizophrenic patients and controls, while others were unable to demonstrate it in either group.

Whether the pink spot exists at all as a differential indicator of schizophrenia is in itself the subject of controversy. The suggestion that it might merely represent metabolites of dietary substances (Faurbye and Pind, 1966 and 1967, and Takesada et al., 1963) is supported by the work of

[1] One subject in this study developed a mescaline-like response to DMPEA but it was briefer than the typical mescaline response.

Table 2. Studies of possible dimethoxyphenethylamine (DMPEA) or a DMPEA-like substance in human urine.

Reference	Time off drugs[1]	Controlled diet?	Blind urinalysis?	Schizophrenics: Description	Schizophrenics: No. positive diagnoses/ No. studied	Controls: Description	Controls: No. positive diagnoses/ No. studied	Comments
Friedhoff & Van Winkle (1962)	2 wks.	No	No	Hospitalized schizophrenics	15/19	Hospitalized surgical patients & staff	0/14	
Barbeau et al. (1963);	No drugs	No	No	None		Hospitalized patients with Parkinson's disease	14/16	
Barbeau (1966)						Hospitalized controls	7/26	
						Nonhospitalized controls	0/7	
Takesada et al. (1963)	3 wks.	No	No	Schizophrenics (no drugs for 3 wks.)	57/62	Psychoneurotics	14/21	Authors suggest origin of DMPEA as intestinal bacteria or diet
				Schizophrenics receiving drugs	13/16	Normal controls	21/46	
Perry (1963)	Not stated	Some on plant-free diet	No	Juvenile psychotics	0/18	None		Not all patients were schizophrenic
Sen & McGeer (1964)	Not stated	No	No	Acute schizophrenics	4/22	Normal	0/1	
Perry et al. (1964)	1 wk.	Plant-free diet 5 days	No	Acute schizophrenics	0/10	None		
Faurbye & Pind (1964)	Minimum 7 days	No	No	Chronic schizophrenics (hospitalized)	0/15	Nurses	0/10	
Kuehl et al. (1964)	Not stated	No	No	Acute and chronic schizophrenics	7/22	Normal subjects	0/10	

Nishimura & Gjessing (1965)	No drugs	Dairy products, sugar, vitamins, minerals, & water	No	Periodic catatonics	0/1	None		No DMPEA detected when MAOI (phenelzine) was given
Studnitz & Nyman (1965)	No drugs	Glucose, citric acid, & water	No	Chronic schizophrenics	0/6	Patients hospitalized for obesity	0/3	
		No dietary limits	No	Same patients as above	4/6	Same patients as above	2/3	Excretion of DMPEA increased slightly when MAOI was given
Faurbye & Pind (1967)	15–88 days	No	No	Chronic schizophrenics	0/14	Normal persons	0/5	
Faurbye & Pind (1966)	Not stated	No	No	Psychotic children	0/13	None		Most patients were autistic
Williams et al. (1966)	3 yrs. or no medications	No	No	Chronic schizophrenics	0/5	None		
				Acute schizophrenics	0/17			
Perry et al. (1966)	6 wks.	Plant- & cheese-free for 1–2 wks.	Yes	Chronic schizophrenics	0/12	Chronic hospitalized nonschizophrenic mental patients	0/7	
				Same patients after 1 wk. phenelzine	0/12	Same patients after 1 wk. phenelzine	0/7	
Nunn & Wheeler (1966)	Not stated	No	No	Chronic schizophrenics	1/10	None		Authors suggest correlations of pink spot with brain damage
Kuehl et al. (1966)	Not stated	No	No	Acute schizophrenics	6/7	Normals	7/9	
				Subacute schizophrenics	10/10			
				Chronic schizophrenics	3/3			

Table 2. Studies of possible dimethoxyphenethylamine (DMPEA) or a DMPEA-like substance in human urine. (Continued)

Reference	Time off drugs[1]	Controlled diet?	Blind urinalysis?	Schizophrenics		Controls		Comments
				Description	No. positive diagnoses/ No. studied	Description	No. positive diagnoses/ No. studied	
Boulton & Felton (1966)	Not stated	No	No	Nonparanoid schizophrenics	1/31	Normals	0/5	
Bell & Somerville (1966)	Patients on variety of drugs	No	No	Nonparanoid schizophrenics	3/27	None		
Bourdillon et al. (1965) Bourdillon & Ridges (1967)	On drugs	No	No	Paranoid schizophrenics	2/17	Nonhospitalized normals	1/250	No relationship between time off drugs and occurrence of pink spot was noted
				Nonparanoid schizophrenics	44/67	Mentally healthy hospitalized inpatients	0/120	
						Nonschizophrenic hospitalized mental patients	0/17	
	On drugs	No	Yes	Nonparanoid schizophrenics	20/69	Nonschizophrenics	1/77	
				Paranoid schizophrenics	2/62	Relatives of positive schizophrenics	0/19	
				Schizophreniform syndrome	5/88			
Friedhoff & Furiya (1967)	2 wks.	No	No	Schizophrenics	DMPAA 8/9	None		
Closs, Wad, & Ose (1967)	Patients received chlorpromazine	No	Yes	Schizophrenics	13/13	Nonschizophrenic mental patients on chlorpromazine	14/14	
	Patients received variety of other drugs	No	Yes	Schizophrenics	19/24	Same type patients received variety of other drugs	24/30	
	No drugs	No	Yes	Schizophrenics	1/9	Same type patients but with no drugs	1/6	

Vogel et al. (1967)	2 years	Same diet during collection period	No	Chronic schizophrenics	DMPEA 7/9 DMPAA 7/9	Staff	DMPEA 8/8 DMPAA 7/7	
Predescu et al. (1968)	Not stated	No	No	Schizophrenics	23/51	Nonschizophrenic mental patients	0/55	
						Parkinson's disease	1/9	
						Physically ill	0/79	
						Normals	0/27	
Boulton et al. (1967)	Not stated	No	No	Schizophrenics	0/73	None		A spot similar to the pink spot was seen in 7 patients but authors conclude this was paratyramine
Rinne & Sonninen (1967)	None	No	No	None		Parkinson's disease	17/20	
						Other neurological diseases	7/9	
Creveling & Daly (1967)	Not stated	No	No	Pooled sample from 2 female schizophrenics	1/1	None		Substance was identified as DMPEA by mass spectrometry
Stabenau et al. (1969)	Minimum 4 days	No	Yes	Acute & chronic schizophrenic members of twin pairs	4/11	Nonschizophrenic members of same twin pairs	4/6	Samples were not obtained from all nonschizophrenic twins
Widelitz & Feldman (1969)	2 wks.	No	No	Childhood schizophrenics	8/12	Normal children	5/6	
Welch et al. (1969)	Some on drugs	No	No	Hospitalized schizophrenics (most chronic)	1/18			
				Homocystinuric with schizophrenia	0/1			

Table 2. Studies of possible dimethoxyphenethylamine (DMPEA) or a DMPEA-like substance in human urine. (Continued)

Reference	Time off drugs[1]	Controlled diet?	Blind urinalysis?	Schizophrenics		Controls		Comments
				Description	No. positive diagnoses/ No. studied	Description	No. positive diagnoses/ No. studied	
Stam et al. (1969)	Some on drugs	No	No	Schizophrenics (many types)	18/22	Nonschizophrenic mental patients	2/19	
						Parkinson's disease	3/3	
						Normals	0/4	
Pue et al. (1969)	Some on drugs	No	Yes	Acute & chronic schizophrenics	34/154	Nonschizophrenic mental patients	14/79	No significant difference seen between schizophrenics & nonschizophrenics
						Staff controls	8/130	
Stabenau et al. (1970)	No drugs	Normal diet + tea	No	None		Normal subjects	2/3	Appearance of DMPEA in urine was positively correlated with ingestion of tea
		Glucose, citric acid + water	No	None		Same subjects	0/3	
		Glucose, citric acid, water + tea	No	None		Same subjects	3/3	

[1] This column refers to tranquilizing medications only. Patients may have been receiving other drugs concurrently.

Studnitz and Nyman (1965), Nishimura and Gjessing (1965), and Perry (1963) and his collaborators (1964 and 1966), all of whom studied subjects on restricted or plant-free diets and failed to demonstrate DMPEA (or any pink spot corresponding to that observed by Friedhoff and Van Winkle) in urine from either patients or normal controls. When Studnitz and Nyman (1965) limited the diet of four DMPEA-positive chronic schizophrenic and three obese patients to 150 g. glucose, citric acid, and water per 24 hours for 3 days, all became DMPEA negative, only to become DMPEA positive when again placed on a regular diet. A similar experiment by Stabenau, Creveling, and Daly (1970) demonstrated (using mass spectrometry) that a common brand of tea provided a source of urinary DMPEA in normals who, when placed on a restricted diet, failed to become DMPEA positive. A limited study with sporadic sampling indicated that restricted diet apparently did not affect excretion of other catecholamine metabolites. Thus, a significant possibility exists that the pink spot is of endogenous dietary origin (though the evidence in support of this contention is by no means conclusive).

Other investigators have suggested that the pink spot is actually a p-tyramine (Boulton, Pollitt, and Majer, 1967, and Heslinga, Van Tilburg, and Stam, 1970), that it contains monoacetyl cadaverine (Watt et al., 1969, and Perry, Hansen, and MacDougall, 1967), that it is the product of the activity of intestinal bacteria (Perry et al., 1966, and Takesada et al., 1963) and that it represents metabolic products of drugs used in the treatment of schizophrenia (Closs, Wad, and Ose, 1967, and Steinberg and Robinson, 1968). Mitigating against this final explanation is the fact that Ridges and Harper (1970), using gas chromatography in combination with mass spectrometry, concluded that the material they identified as the pink spot was not derived from phenothiazines or their metabolites; they failed, however, to specify either the details of their procedure or the number of urine samples subjected to this analysis.

Ridges and Harper (1970) also pointed out a chromatographic abnormality with an R_f value close to that of DMPEA, which they referred to as "faster running pink spot" and which is associated with anti-Parkinsonian therapy. This observation is interesting in view of the close association which has been reported between Parkinson's disease and the pink spot (Barbeau et al., 1963; Barbeau, 1966; Rinne and Sonninen, 1967; Predescu, Florescu, and Radulescu, 1968; and Stam, Heslinga, and Van Tilburg, 1969).

Much of the controversy over the occurrence of the pink spot in schizophrenic urine may stem from the fact that different investigators have used different methods to identify it. In an attempt to clarify some of the analytical procedures used, Pind and Faurbye (1966) compared their own method with the methods of Friedhoff and Van Winkle (1962) and Takesada et al. (1963). They concluded that Friedhoff and Van Winkle and Takesada et al. were measuring the same compound, which was not identical with DMPEA, while they themselves were measuring genuine DMPEA. Although Pind and Faurbye made no attempt to identify the compound measured by the method of Friedhoff and Van Winkle and by that of Takesada et al., they indicated that the former method was less sensitive than the latter. Therefore, some of the divergent results obtained by different authors may perhaps be explained on the basis of (1) different methods used to measure different compounds and (2) differential sensitivity of different methods. (Type A, B, or C errors, figure 1.)

In summary, DMPEA has not yet been shown to be responsible for any schizophren-

ic-like symptoms when given to humans, either in the presence or absence of MAO inhibitors. Small quantities of DMPEA's acid metabolite have been shown to be produced in the body. Although DMPEA has been identified by the best methods available (e.g., mass spectrometry), well controlled studies present no unequivocal evidence for the hypothesis that it is more common in the urine of schizophrenics than in that of normals. Moreover, diet (e.g., tea consumption) may be a very important source of DMPEA in the urine.

Mauve Factor

Having noted the appearance of a mauve-colored spot on many chromatographs of schizophrenic urine, Hoffer and his collaborators (Hoffer and Mahon, 1961, Irvine, 1961, and Hoffer and Osmond, 1963) used this spot as the defining characteristic of a new disease entity, which they termed "malvaria." Although not all schizophrenics are "malvarians," these authors report that from one-half to two-thirds of acute schizophrenics and unrecovered treated schizophrenics are mauve positive. The presence of the mauve spot is by no means limited to schizophrenics alone, however; about one-third of patients with anxiety neurosis, alcoholism, mental retardation, depression, and personality problems are also mauve positive. In addition, a few surgical patients, patients with toxic psychoses, and recovered schizophrenics (less than 5 percent of each group) are malvarians. In an independent study of malvaria's incidence, O'Reilly, Ernest, and Hughes (1965) found that 10.5 percent of normals, 11.9 percent of normals under stress, 11.9 percent of normal children under stress, 25.5 percent of all disturbed children, 41.8 percent of all psychiatric cases, and 52.3 percent of schizophrenics were mauve positive.

The mauve factor's occurrence has been confirmed by at least four groups of investigators (O'Reilly et al., 1965; Yuwiler and Good, 1962; Sohler et al., 1967; and Ellman, Jones, and Rychert, 1968). In 1967, Sohler et al., attempting to identify the composition of the mauve factor, suggested that it was a mixture of pyrroles and/or furan derivatives. Ellman, Jones, and Rychert (1968), however, believe that the mauve factor represents phenothiazine metabolites, since it tends to disappear after discontinuance of phenothiazine treatment and to appear in normals given phenothiazines. Irvine et al. (1969), using a two-dimensional chromatographic system and mass spectrometry, were able to identify 2,4-dimethyl-3-ethylpyrrole, a finding that has recently been confirmed by Sohler, Beck, and Novel (1970). In their tests of rabbits, Sohler's group found this compound produced sedation rather than the stimulation thought to be present in schizophrenics.

Bufotenine

Bufotenine is a naturally occurring compound found in certain mushrooms (*Amanitae* species), in sea anemone nematocysts, in the seeds of *Piptadenia peregrina,* and in the glandular secretions of some toad species. Interest in this compound dates from 1956 when Fish and Horning discovered that snuff used by a South American Indian tribe was capable of producing hallucinations. Because this snuff was thought to be made from the seeds of *Piptadenia peregrina,* these seeds were examined and were found to contain dimethyltryptamine (DMT) and bufotenine. Subsequently, however, Holmstedt (1967) reported that *Piptadenia peregrina* was *not* in fact the main constituent of the Indians' snuff (which was found to contain DMT and methoxy-bufotenine, but not bufotenine itself). Thus, an initial misidentification was responsible for 15 years of experimental

work on bufotenine's relationship to schizophrenia.

Interest in the rule of bufotenine or a bufotenine-like substance in the etiology or pathogenesis of schizophrenia is based on the following observations:

- Bufotenine (N,N-dimethylserotonin) is the dimethylated derivative of serotonin.
- Axelrod (1961) demonstrated the presence in rabbit lung tissue of an enzyme which could N-methylate serotonin *in vitro* to bufotenine; subsequently, Mandell and Morgan (1970) reported the occurrence of this enzyme in the brain.
- Several authors have found bufotenine or a bufotenine-like substance in urine from schizophrenics but have not found this substance, or have found it in lower concentrations, in normal urine.
- Bufotenine has been shown to be capable of producing a schizophrenic-like syndrome when administered to humans.

It has been postulated that normally occurring indolic compounds (e.g., serotonin) may, through some abnormal biochemical mechanism, be converted by methylation into hallucinogenic indoles (e.g., bufotenine) in schizophrenic patients. Several authors have found that the addition of compounds that donate methyl groups (e.g., methionine and betaine) can produce an exacerbation of schizophrenic symptomatology. Cysteine has also been reported to produce this effect; while cysteine is not a methyl donor, the presence of the thiol group apparently enhances the action of the enzyme O-methyl transferase. The fact that the behavioral worsening is intensified by the addition of an MAO inhibitor (e.g., tranylcypromine) suggests that the effects may be mediated through some biogenic amine. Furthermore, Brune and Himwich (1962b) and Spaide et al. (1968) have noted a correlation between the amounts of indolic compounds excreted and degree of psychotic behavior.

Bufotenine in Urine

Many authors have attempted to determine whether bufotenine or a bufotenine-like substance is, in fact, present in urine from either normal or schizophrenic subjects (see table 3). A bufotenine-like substance was found in each of three studies in which only urine from normal subjects was examined (Bumpus and Page, 1955; Perry et al., 1962; and Gross and Franzen, 1964) and also in each of these studies in which only urine from schizophrenics was examined (Perry, 1963; Tanimukai et al., 1967a; and Spaide et al., 1968). Of the 16 investigations in which urine from both schizophrenic and nonschizophrenic subjects was studied, three found and six failed to find a bufotenine-like substance in the subjects' urine; the seven remaining studies found evidence of a bufotenine-like substance in urine from the schizophrenic subjects only (Fischer et al., 1961; Brune, Hohl, and Himwich, 1963; Heller, 1966; Fischer and Spatz, 1967; Acebal and Spatz, 1967; Narasimhachari et al., 1970; and Rosengarten et al., 1970).[2] Two of the studies which found a bufotenine-like substance in both schizophrenic and normal control urine reported that schizophrenics excrete higher amounts of this compound than normals (Sireix and Marini, 1969, and Fischer and Spatz, 1970). Thus, although it is probable that bufotenine occurs in human urine, there are at present only suggestive data to sustantiate a differential production of bufotenine or a bufotenine-like substance in schizophrenics and nonschizophrenics. It is possible that

[2] None of these seven studies used blind urinalysis methods or dietary controls.

Table 3. Summary of studies investigating the possibility of bufotenine or a bufotenine-like substance in urine.

Reference	Schizophrenics		Controls		Time off drugs	Controlled diet	Blind urinalysis	Sensitivity of method (estimate)	Comments
	Description	No. positive/ No. studied	Description	No. positive/No. studied					
Bumpus & Page (1955)	None		Pooled sample from 4 healthy adult normal subjects	1/1	—	No	No	Crude	Compound was not definitely identified as bufotenine
Rodnight (1961)	Schizophrenic	0/6	Mentally ill nonschizophrenics	0/2	?	No	No	5ug./day	
Feldstein et al. (1961)	Chronic schizophrenics given 130ug. labeled serotonin	0/15	Normals given 130ug. labeled serotonin	0/10	3 wks.	No	No	?	
Fischer et al. (1961)	Hallucinating or catatonic schizophrenics	24/26	Nonschizophrenics	0/15	15 days	No	No	?	
Perry et al. (1962)	None		Normal children	1/20	No drugs	No	No	?	
			Normal children given MAOI	4/6	No other drugs	No	No	?	MAOI increased excretion of bufotenine
Perry (1963)	Juvenile psychotics, some given MAOI	2/18	None	—	No other drugs	Some patients on plant-free diet	No	?	Same concentration bufotenine was excreted as in normal children in previous paper
Sprince et al. (1963)	Chronic schizophrenics given (1 wk. each): placebo tranylcypromine, L-tryptophan, L-methionine, tranylcypromine + L-tryptophan, & tranylcypromine + L-methionine	0/4	Psychoneurotics given same drug regimen as schizophrenics	0/2	?	No	No	?	6x6 Latin square design was utilized, only 200-300 ml. of each 24 hr. urine were analyzed

Brune et al. (1963)	Schizophrenics with active psychoses given placebo and later isocarboxazid + betaine	3/3 (placebo) 3/5 (isocarboxazid + betaine)	Nonpsychotic mental defectives	0/3	?	Constant protein diet	No	20 ug./l.	Spots were larger and more intensive in color during combined drug therapy
Gross & Franzen (1964)	None		Healthy controls	50/50 (urine) 9/50 (blood)	No drugs	No	No	1 ug./l.	
Siegel (1965)	Newly-admitted schizophrenics (4 with hallucinations)	0/21	Normal donors	0/5	?	No	No	0.1ug./ 100 ml.	
Heller (1966)	Schizophrenics (4 catatonic, 3 hallucinating, 1 hebephrenic, 3 paranoid)	10/11	Nonschizophrenic psychiatric patients	0/3	15 days	All patients received regular hospital diet	No	?	MAOI caused appearance of bufotenine-like spot but also caused clinical worsening in 9/10 chronic schizophrenics
	Nonproductive chronic schizophrenics	3/10	3 alcoholics 1 presbyophrenic	0/4					
	Nonproductive chronic schizophrenics given MAOI (phenelzine)	10/10	3 alcoholics 1 presbyophrenic given MAOI (phenelzine)	0/4					
Perry et al. (1966)	Chronic male schizophrenics	0/12	Chronic non-schizophrenic patients	0/7	6 wks.	plant- & cheese-free diet	Yes	2 ug./ 24 hrs.	
	Same with MAOI (phenelzine)	0/12	Same with MAOI (phenelzine)	0/7					
Runge et al. (1966)	Chronic schizophrenics (most hallucinatory) (no drugs)	1/22	Nonpatient controls (15) + patient controls (2)	0/17	60 days	No	No	?	Spots which were seen in urine of patients receiving phenothiazines were thought to be drug metabolites
	Chronic schizophrenics with phenothiazines	13/14 (spot was shown not to be bufotenine)							

Table 3. Summary of studies investigating the possibility of bufotenine or a bufotenine-like substance in urine. (Continued)

Reference	Schizophrenics: Description	Schizophrenics: No. positive/No. studied	Controls: Description	Controls: No. positive/No. studied	Time off drugs	Controlled diet	Blind urinalysis	Sensitivity of method (estimate)	Comments
Acebal & Spatz (1967)	Schizophrenics	7/10	Epileptics	0/7		No	No		
Tanimukai et al. (1967a)	Chronic schizophrenics given L-cysteine	1/4 (free) 3/4 (conjugated)	None		4–6 wks.	Yes	No	1 ug./day	Diet controlled as above
	Chronic schizophrenics given L-cysteine + MAOI (tranylcypromine)	4/4 (free) 3/4 (conjugated)							
Tanimukai et al. (1967b)	Chronic schizophrenics	6/6 (free) 6/6 (conjugated)	Mental defectives	1/4 (free) 4/4 (conjugated)	7 days	Yes	No	1 ug./l.	Preformed catecholamines and indoles were excluded from diet
Fischer & Spatz (1967)	Schizophrenics	6/7	Control	4/6	8 days	No	No		
Spaide et al. (1968)	Chronic schizophrenics with methionine load	2/4 (free) 1/4 (conjugated)	None		4–6 wks.	Yes	No	1 ug./l.	Diet controlled as above, bufotenine levels were higher when patients' behavior was worse
	Same patients with cysteine load	1/4 (free) 3/4 (conjugated)							
	Same patients with MAOI load (tranylcypromine)	4/4 (free) 3/4 (conjugated)							
	Same patients with MAOI + cysteine load	4/4 (free) 3/4 (conjugated)							

Faurbye & Pind (1968)	Chronic schizophrenics	6/7	Control	4/6	8 days	No	No	0.7 ug./l.
Sireix & Marini (1969)	Untreated, acute schizophrenics	19/20 mean excretion 15.5 ± 8.8ug./ 100ml.	Normals	18/20 mean excretion 2.1 ± 0.97 ug./ 100ml.	No drugs	No	No	Not given
Sireix & Marini (1969) (contd.)			Nonschizophrenic mental patients	19/20 mean excretion 2.9 ± 1.4- ug./ 100ml.				
Fischer & Spatz (1970)	Untreated, acute schizophrenics	All positive—86/86 (mean excretion = 16.6ug.%)	Nonschizophrenic (67 normals, 11 epileptics, 9 depressives, 8 psychopaths, 18 others)	113/133 (mean excretion = 3.5 ug.%)	10 days or no drugs	No	No	1 ug.
	Previously treated chronic schizophrenics	All positive—45/45 (mean excretion 6.9ug.%						
Narasimhachari et al. (1970)	2 chronic schizophrenics	2/2	6 normals	0	3 wks.	Yes	No	—

the failure of some studies to find bufotenine in either the urine of schizophrenic or normal control subjects may reflect the use of analytical methods too insensitive to pick up minute quantities of this compound (often less than 1 μg. per 24 hours). On the other hand, Tanimukai et al. (1967b) demonstrated that the use of acetone in some of the earlier analytical methods could have created bufotenine-like condensation products—a suggestion which casts doubt on some of the positive findings which have been reported.

Dietary controls and the exclusion of other psychoactive medications from patients being studied are important variables to be considered in any attempt to evaluate studies like those discussed above. Runge et al. (1966) found a bufotenine-like spot after chromatography in 13 of 14 chronic schizophrenics who were being treated with phenothiazines, but found a similar spot in only one of 22 nonphenothiazine-treated chronic schizophrenics and in none of 17 control subjects. Subsequently, this spot was shown to be, not bufotenine, but, in all probability, a phenothiazine metabolite. Some authors have dismissed the bufotenine-like substances reported in these studies as dietary artifacts or the result of bacterial metabolism in the gut.

Only a few of the 23 studies reported in table 3 utilized a blind urinalysis method. Perry et al. (1966), who used blind analyses and a plant- and cheese-free diet, found no evidence for a bufotenine-like substance in urine from either schizophrenics or nonschizophrenics, with or without MAO inhibitors. Significantly, most studies which have reported a differential incidence of bufotenine or a bufotenine-like substance in schizophrenics and normals did not use a blind method of analysis.

Psychosis-Producing Properties of Bufotenine

When administered to humans, bufotenine has been reported to cause a psychotomimetic state similar to that caused by LSD. Fabing and Hawkins (1956), for example, administered from 1 to 16 mg. of bufotenine to four prison inmates, via a 3-minute intravenous drip; no attempt was made to "blind" either the subjects or the observers. All subjects reported mild to moderate somatic complaints, such as feeling needles in the face, a tightness in the throat, a racing pulse, and a sensation of increased body weight. While there was no change in the subjects' cardiac status, their faces became blue, with dilated pupils and nystagmus. At the highest doses, nausea and vomiting occurred, and the subjects reported illusions of colored spots, lines, and poor concentration—effects which lasted from 2 to 12 minutes. The physiological changes appeared to take somewhat longer than the psychological changes to return to normal. Based on these observations, Fabing and Hawkins concluded that bufotenine is hallucinogenic and that there is a progression in symptoms as the dose is increased. Although there is general agreement on the physiological properties of bufotenine, it should be noted that its reported hallucinogenic effects have not gone unchallenged. Turner and Merlis (1959), for example, gave subjects up to 20 mg. of bufotenine intravenously, and were unable to produce hallucinations despite profound EEG changes, loss of consciousness, and intense peripheral action of a serotonin character.

In a recent attempt to explain the hallucinogenic action of substituted tryptamines, Smythies, Benington, and Morin (1970) have suggested that serotonin binds to nucleic acids by intercalation between base pairs in the helical double-stranded nucleic acids or ordered purine bases in single-stranded nucleic acids. The primary receptor in the neuronal membrane, they postulate, may consist of helical double-stranded RNA, specifically a prostaglandin-RNA complex. These authors go on to suggest that this complex controls the ionic

conducting channels of the membrane and that the transmitter binds to the RNA, disrupting hydrogen bindings and further joining the hydrogen bonds by a charge transfer process, which initiates channel openings. They note that this mechanism, in acting first as an agonist of serotonin and, in larger doses, as an antagonist, is consistent with the action of LSD and with the psychological action of tetrahydrocannabinol (thought to be the active drug in cannabis).

Histamine

Although its physiological role is uncertain, histamine, a substance which is present in the brain and partially metabolized there (Brown, Tomchick, and Axelrod, 1959; White, 1961; Marshall, 1961; Gustafsson and Forshell, 1963; and Bjuro, Westling, and Wetterqvist, 1963), has interested psychiatric researchers because of reports that:

- schizophrenic patients have a relatively low incidence of allergies (Cassell and Fisher, 1963, and Simpson and Kline, 1961);
- the onset of schizophrenia often coincides with a remission of asthmatic symptoms (Mandell and Younger, 1962, and Weblin, 1963);
- schizophrenics are insensitive to histamine (Simpson and Kline, 1961; Leblanc and Lemieux, 1961; and Cassell and Fisher, 1963);
- and histamine blood levels are elevated in schizophrenics (Stengers and Gooszen, 1946–1947; Lovett Doust, Husdan, and Salna, 1956; and Stern et al., 1957).

As can be seen in table 4, abnormalities in histamine metabolism have frequently been linked to schizophrenia. Early investigators tried to alter this postulated histamine abnormality by administering, and then observing the schizophrenic patient's ability to tolerate, large quantities of histamine. Another approach has been to measure histamine in blood from schizophrenic and normal subjects. Four such studies have found higher histamine levels in schizophrenic than in normal serum (Den Hartog Jager[3]; Lovett Doust, Husdan, and Salna, 1956; Stern et al., 1957; and Cassell, Newton, and Cho, 1967); a fifth study found that normals and schizophrenics have equal cerebrospinal fluid histamine levels (Ermala and Autio, 1951). In a more recent report, Pfeiffer et al. (1970) pointed out that these previously published studies may have been measuring spermidine in addition to histamine. Using a more sophisticated technique, Pfeiffer et al. found low blood histamine levels in many of their chronic schizophrenic subjects but they also found that a few patients had more histamine in whole blood than normals. The authors, unfortunately, don't document the drug status of their patients, but suggest that they will in future reports.

In another study of blood histamine, Bernstein, Mazur, and Walaszek (1960) measured the histaminolytic activity in blood from 68 chronic schizophrenic patients and 37 normals (hospital personnel). Because phenothiazines have known antihistaminic properties, all patients were taken off drugs 2 weeks prior to blood collection. Although the schizophrenics' blood samples appeared to have significantly greater histaminolytic activity than blood from normal subjects, it is not clear whether the 2-week period off drugs was sufficiently lengthy to insure the validity of these findings.

A number of investigators have reported that the subcutaneous injection of histamine produces a smaller wheal in schizophrenics than in normals. Indeed, the only study which has thus far failed to find such

[3] Data presented on p. 137 of Ermala and Autio, 1951 (see references).

Table 4. Histamine abnormalities in schizophrenia.

Author(s)	Patient Sample	Control Sample	Other Drugs Given	Diet Controlled Yes/No	Method	Results	Comments
Ermala & Autio (1951)	113 schizophrenics from 2 hospitals (inpatients)	53 neurology patients, 15 medical students 57 other psychiatric patients, 14 manic depressives	Not stated	No	Measured histamine reflex erythema 5 min. post-injection	Schizophrenics showed less erythema than any other group	Catatonic schizoprhenics were lowest of schizophrenic group
Den Hartog Jager (as reported in Ermala & Autio)	Schizophrenics	Normal persons	Not stated	Not stated	Blood histamine levels	Histamine in schizophrenic blood averaged 65% higher than in normals' blood	
Ermala & Autio (1951) Report of previous study	3 schizophrenics	25 normal subjects	Not stated	Not stated	CSF histamine levels	No difference in CSF histamine was found between schizophrenics and normals	
Lucy (1954)	50 schizophrenics (grouped by length of illness)	10 long-term nonschizophrenic patients	Not stated	No	Histamine tolerance (fall in blood pressure sure after subcutaneous injection)	Longstanding schizophrenics tolerated large doses of histamine better than acute schizophrenic patients; nonschizophrenic patients tolerate better than acute schizophrenic patients but not as well as contemporary schizophrenics	
Lovett Doust et al. (1956)	29 schizophrenics	12 mentally healthy, 5 epileptics, 66 other psychiatric diseases	Not stated	No	Measurement of blood histamine levels	Schizophrenics had significantly higher blood histamine levels than normals; other psychiatric diseases were higher than schizophrenics & epileptics were highest	

Freedman et al. (1956)	22 chronic schizophrenics (12 hebephrenic, 7 catatonic, 3 paranoid) (average age 41)	22 medical students (all below age 30)	Not stated	No	30-min. wheal response to intradermal histamine	Schizophrenics had consistently smaller wheal response to histamine	Patients were as responsive to allergens as controls
Stern et al. (1957)	40 schizophrenics	7 oligophrenics, 10 patients with progressive paralysis	Not stated	No	Measurement of blood histamine levels	Schizophrenics had higher levels of histamine than oligophrenics, who were higher than patients with paralysis	
Weckowicz & Hall (1958)	145 schizophrenics	30 nonschizophrenic mental patients and normals	Not stated	No	Measurement of histamine wheal formation (up to 10 min. after injection)	Schizophrenics had significantly smaller wheal formation	Blind method used
Jodrey & Smith (1959)	176 schizophrenics, mostly chronic	66 manic depressive patients, 51 normals (staff)	Many tranquilizers, reserpine was only one which affected assay & patients were omitted	No	Measurement of histamine wheal after 10 min.	No difference was seen between groups, except for patients on reserpine, who showed significantly increased wheal area	Reserpine significantly lowered skin histamine levels
Bernstein et al. (1960)	68 chronic schizophrenics	37 hospital personnel	No drugs given for 2 wks.	No	Histaminolytic activity of blood (histaminase levels)	Schizophrenic serum showed significantly greater histaminolytic activity than normals' serum	
Leblanc & Lemieux (1961)	53 psychotics (65% schizophrenic)	15 normals	All patients were on drug therapy after admission	No	Intradermal histamine flare measured at 10 min.	Mental patients showed less flare than normal controls (at admission) before drug treatment	Higher reactivity to histamine seen after drug therapy and improvement

Table 4. Histamine abnormalities in schizophrenia. (Continued)

Author(s)	Patient Sample	Control Sample	Other Drugs Given	Diet Controlled Yes/No	Method	Results	Comments
Kobayashi & Freeman (1961)	12 chronic schizophrenics (S)	7 normal controls (C)	Not stated	No	Excretion of intradermally injected, labeled histamine	Total radioactivity excretion S = C; urine excretion of histamine & methylhistamine and free imidazole-4-acetic acid S = C; 1-methylimidazole-4-acetic acid, C greater than S; conjugated imidazole-4-acetic acid, S greater than C	
Simpson & Kline (1961)	58 chronic schizophrenics, 53 acute schizophrenics	33 normal controls 26 acute nonschizophrenics	None given for initial study	No	Measurement of histamine wheal after 1 hr.	Chronic schizophrenics showed significantly smaller wheals than other groups	Age no factor, imipramine & prochlorperazine reduced size of wheal
Brown et al. (1962)	12 chronic schizophrenics	11 volunteer controls	No medicines for 3 wks. before study	Yes	Measured excretion of labeled histidine and its metabolites	No significant difference was found between schizophrenics and normals in total radioactivity, excretion of hydantoin propionic acid, histidine, 1-methylhistidine, or free and conjugated imidazoleacetic acid	
Cassell et al. (1967)	28 schizophrenics (new admissions)	33 nonschizophrenic psychiatric patients (new admissions)	Not stated	Both groups received hospital diet	Measurement of serum histamine levels	Schizophrenics had significantly higher serum histamine levels than nonschizophrenic patients	

Pfeiffer et al. (1970)	20 chronic schizophrenics	14 normals	Not stated	No	Whole blood histamine	Schizophrenics lower than normals	
	72 schizophrenic outpatients	14 normals	Not stated	No	Whole blood histamine	Schizophrenics slightly less than normal	Several depressed schizophrenics had high levels
Cowen (1969)	21 schizophrenics (6 catatonic, 11 paranoid, 4 simple)	21 normals 26 senile psychiatric inpatients	No medicines	No	Measurement of maximum wheal after histamine injection	Catatonic schizophrenics showed less response than other types of schizophrenics and other groups	In all groups males had larger wheal response than females

a difference (Jodrey and Smith, 1959) used such large doses of histamine that a maximal response may have been produced in all subjects, thus precluding the demonstration of a differential effect.

In an excellent review of histamine in the nervous system, Green (1964) has offered the following mechanisms as possible explanations for the relative insensitivity of schizophrenics to histamine:

- an adaptation to the vascular effects of histamine;
- an abnormal degradative route for histamine which causes the production of a large amount of relatively inactivated compounds (e.g., conjugated histamine);
- rapid inactivation of histamine in schizophrenics;
- and either excessive amounts of antihistaminic substances in the tissues of schizophrenics or a lack of substances which potentiate the effects of histamine.

Kobayashi and Freeman (1961) studied histamine metabolism by normal and schizophrenic subjects after intradermal injection of minute quantities of histamine. Although no differences were found between the two groups with regard to total urinary excretion of radioactivity, unchanged histamine, methylhistamine, or free imidazole-4-acetic acid, the schizophrenic subjects did excrete significantly less 1-methylimidazole-4-acetic acid and significantly more conjugated imidazole-4-acetic acid than their normal counterparts. The differences between the two groups were not of sufficient magnitude, however, to serve as diagnostic tests for schizophrenia.

To summarize, there is considerable evidence that some abnormality of histamine metabolism exists in schizophrenics; the significance of this abnormality, however, has yet to be determined and, indeed, the anomaly itself is not clearly defined. Despite the fact that histamine abnormalities have been consistently found, the histamine hypothesis is not now undergoing investigation by a great many research groups. In view of the recent finding that some of the older studies in this area were probably measuring spermidine as well as histamine, the literature on histamine abnormalities in schizophrenia must be interpreted with caution. The finding of Pfeiffer et al. (1970) that there are two populations of schizophrenics, those with high blood histamines and those with low blood histamines, suggests that schizophrenia may not be a homogeneous disease but, rather, at least two, in some sense, opposite diseases. This approach to the study of schizophrenia appears to be a promising one.

Taraxein

Heath and his coworkers (Heath et al., 1954, and Heath and Leach, 1962) have reported that schizophrenic patients are characterized by abnormal spiking in the septal region of the brain, an area important in the production of emotions, particularly pleasure. Schizophrenic patients have also been found to produce an abnormal blood protein called taraxein (Heath et al., 1954; Heath et al., 1959; Heath, 1966; Heath and Krupp, 1968; and Heath, Guschwan, and Coffey, 1970) which, when injected into healthy humans, produced schizophrenic-like symptoms (Heath et al., 1957, and Heath et al., 1959. When injected intravenously or intraventricularly into monkeys, taraxein also produced septal spiking similar to that seen in schizophrenic patients (Heath, 1966; Heath et al., 1959; and Heath, Guschwan, and Coffey, 1970).

A study which attempted to replicate taraxein's reported ability to produce psychotic symptomatology in humans was carried out by Robins in 1957. Prisoner volunteers who served as subjects in this experi-

ment received injections (given in random order) of normal saline or serum from either schizophrenic patients or normal controls. The serum preparation was done completely blind, and because the serum had a characteristic color and consistency, the syringes were taped over to prevent observation of the material injected. Thus, no one in the room in which the experiment was conducted knew whether the subject was receiving patient serum, normal serum, or normal saline. Of eight normal saline injections, one produced equivocal results and seven, no reaction; of four normal serum injections, one produced an equivocal reaction and three, no reaction; and of five injections of schizophrenic serum (which had been prepared in Heath's laboratory), two produced equivocal reactions and three, no reaction. There were *no positive reactions* (see, also, Siegel et al., 1959). The major criticism of Robins' work made by Heath was that, although the activity of taraxein deteriorates within several hours, Robins' group waited 10 days before beginning their human testing.

As mentioned above, Heath and his coworkers (Heath, 1966; Heath et al., 1959; and Heath, Guschwan, and Coffey, 1970) have reported that intravenous or intraventricular injections of taraxein produce septal spiking in monkeys. Other workers have likewise obtained positive results using this assay (Melander and Martens, 1958). By employing protein fractionation techniques, Heath determined that taraxein is present in a specific subfraction of schizophrenic gamma G immunoglobulin (IgG). He further reports that most—but not all—serum preparations from schizophrenic subjects have positive monkey assays, while relatively few preparations from normal sera produce septal spiking in monkeys. In an NIMH special report on schizophenia, however, Mosher and Feinsilver (1970) noted that, in a pilot study, sera from control subjects produced spiking about as frequently as did sera from schizophrenics. More work is needed to determine this assay's specificity for schizophrenia.

Heath has proposed an autoimmune theory of schizophrenia (Heath and Krupp, 1967a and b; and Heath et al., 1967a and b), which is based on the notion that schizophrenics produce antibodies against their own brain tissue or, more specifically, against antigens contained in portions of the limbic system (septal area and caudate nucleus). The reaction between these antibodies and antigens, Heath postulates, might interfere with certain aspects of the brain's functions, ultimately resulting in the manifestation of overt schizophrenic behavior. Empirically, he finds that fluorescein-tagged antiglobulin binds to cell nuclei of post-mortem schizophrenic patients' brain slices, causing them to fluoresce under ultraviolet light, a phenomenon not noted in brain slices from nonschizophrenics. Whittingham et al. (1968) used immunofluorescence techniques to examine post-mortem brain tissue from three chronic schizophrenics and serum from 53 schizophrenics (13 acute, 40 chronic) and 53 age- and sex-matched controls. These authors could not show that globulin became bound *in vivo* to nuclei of brain cells of schizophrenics; nor could they show that the incidence of serum antibodies against brain cell nuclei was any higher in schizophrenic patients than in controls. Using an immunofluorescent technique similar to that of Heath and Krupp with schizophrenic brain tissue and serum from acutely schizophrenic patients, Logan and Deodhar (1970) could find no evidence of fixed or circulating antibodies. Similarly, Rubin (1965) failed to find any precipitate formed between sera of floridly psychotic patients and brain homogenate of normal or schizophrenic brains.

In a study of antirabbit heterophile hemolysin levels in schizophrenics and non-

schizophrenics, Turner and Chipps (1966) found that the incidence of high titers was significantly greater in the schizophrenic group than in nonschizophrenic psychotics, general hospital patients, or healthy subjects. Neither Turner and Turano (1968) nor Gershom et al. (1968) were able to confirm these results, however. When Lang and Corvin (1969) assayed serum from schizophrenics, nonpsychotic psychiatric patients, medical and surgical patients, and normal blood-bank donors, they could not distinguish between the schizophrenics and the other hospitalized groups on the basis of rabbit hemagglutinin titers; their hospitalized group as a whole, however, was significantly different from their nonhospitalized groups, which suggests that the incidence of high levels of rabbit hemagglutinins is not characteristic of schizophrenics in particular but, rather, is associated with hospitalization. In 1967, Friedman, Cohen, and Iker found that, after cholera vaccine, schizophrenics had higher agglutination antibody levels than either depressed or normal subjects. More recently, Solomon et al. (1969) reported that both schizophrenic and nonschizophrenic psychiatric patients had elevated IgA and IgM concentrations. Strahilevitz and Davis (1970), on the other hand, found that, although schizophrenics had elevated IgA concentrations, as compared with those observed in nonschizophrenic psychiatric patients or in blood donor controls, there were no differences among these groups of subjects in IgG and IgM concentrations.

Seal and his collaborators (Seal and Eist, 1966; Seal, Swaim, and Eist, 1967; and Seal and Swaim, 1968) observed elevated levels of serum protein-bound carbohydrates, haptoglobin, fibrinogen, and plasminogen concentrations in schizophrenic patients. Lovegrove and Nicholls (1965), however, did not find any difference between the haptoglobin subtypes of schizophrenics and normals. Fessel's group (Fessel, 1961; 1962a,b, and c; 1963; Fessel and Grunbaum, 1961; and Fessel, Hirata-Hibi, and Shapiro, 1965) has reported an elevated S19 macroglobulin in schizophrenics, a finding which was not confirmed by Bishop et al. (1966).

Clearly, much of the work reviewed above awaits independent replication; but even if we disregard contradictory results and accept the reliability of this research, the etiological significance of these findings to schizophrenia is nonetheless problematical.

Serum Factors

A frequently used strategy in schizophrenia research has been to define a bioassay system (e.g., some aspect of animal behavior) which is altered by material obtained from schizophrenics and not by material obtained from controls. Once this "schizophrenic" substance has been found, further research is then directed to chemically identifying or otherwise characterizing it. All of the investigators whose research is reviewed below have utilized this approach.

Gardner (1968) found that the injection of plasma from chronic schizophrenics (who had been drug-free for 2 weeks) was associated with an impairment in food-motivated bar pressing in rats, an effect which was not produced by plasma from normal subjects. Likewise, Bishop (1960) observed a highly significant difference in avoidance learning between rats injected with plasma from chronic schizophrenics and control animals injected with plasma from normal subjects. In comparable studies, however, Stewart and Irvine (1962), Gowdey and Lovegrove (1966), and Throne, Gowdey, and Lovegrove (1966) failed to demonstrate such performance differences.

In 1963, German reported that the application of schizophrenic sera to the cortex of rats produced a significantly greater en-

hancement of the cortical evoked response than that produced by normal sera. But when Stenhouse et al. (1965) failed to duplicate these results, German et al. (1965) redid German's original study using a more rigidly defined, double-blind method; with the addition of these experimental controls, they no longer found any significant differences in the evoked responses of rats who had received schizophrenic or normal sera, thus invalidating German's earlier reported finding.

Ferguson and Fisher (1963) found that the intraperitoneal injection of schizophrenic serum or plasma into monkeys trained to perform precision time tasks resulted in a significant prolongation of the time needed for task completion. Although this effect was not seen following injections of serum or plasma from normals, serum and plasma from *stressed* normals also prolonged the task completion time. Similarly, Domino et al. (1966) reported that schizophrenic serum produced behavioral impairment in rats.

Winter and Flataker (1958) observed that intraperitoneal injections of plasma from psychotic patients into rats could produce a syndrome similar to—but not identical with—that produced by injections of LSD. In rats trained to climb rope, injection of plasma from schizophrenics produced significantly greater performance deficiencies than normal plasma. In an attempt to duplicate these results, Ghent and Freedman (1958), however, were unable to find comparable performance differences. Plasma fractions isolated by Sanders et al. (1965) also failed to differentiate schizophrenics from normals. In other studies of schizophrenic plasma's effect on rope climbing, Bergen et al. (1965) found that, when an extract from schizophrenics (Bergen's fraction) was injected into trained rats, their rope-climbing performance was 81 percent slower than that seen following injection of plasma samples from control subjects. Bergen's fraction also produced an alteration in photically evoked potentials in the rabbit, a change not seen when normal serum was used (Bergen, Czicman, and Koella, 1963). Indirect evidence from dialysis studies and the use of MAO inhibitors suggest that the schizophrenic properties of Bergen's fraction, which has been characterized as an alpha-2-globulin (Pennell et al., 1967), may reside in a small molecule associated with the protein, possibly a phenylethylamine (Bergen, Czicman, and Koella, 1963; Bergen, 1966; and Bergen, 1970). Both DMPEA and its metabolic product, N acetyl DMPEA, produce impairment on this test system (Bergen, 1966; Bergen et al., 1968; and Vogel, 1968), bind to this type of plasma protein (Bergen, 1970, and Sanders, 1967), and increase the impairment produced by Bergen's fraction on the rope-climbing assay (see section on DMPEA). Proctor et al. (1968) proposed a test for the toxic factor in schizophrenic plasma by its potentiations of the lethal effect of DMPEA on aggregated mice pretreated with an MAO inhibitor; Proctor's test was not supported by Meltzer and Boyer (1969) or Masur et al. (1969). The postulated existence of a blood-borne schizophrenia factor remains an unproven lead at this time.

Frohman Factor

Studies by Frohman and his collaborators (Frohman et al., 1960a and b, 1961, 1963, and 1966; Beckett et al., 1963; Brown, 1964; Sullivan et al., 1966 and 1967; and Bergen et al., 1968) have indicated that serum from schizophrenic patients may contain a protein factor which alters the anaerobic metabolism of chicken red blood cells. Chicken erythrocytes differ from those of human origin in that they are nucleated and apparently contain all of the enzymes necessary for intact operation

of the tricarboxylic acid cycle. When chicken erythrocytes were incubated with plasma from schizophrenics, a lower production of pyruvate and a higher lactate/pyruvate (L/P) ratio were seen than when chicken erythrocytes were incubated with plasma from normal controls.

A subsequent study, carried out on a blind basis at both the Lafayette Clinic in Detroit and the National Institute of Mental Health in Bethesda, demonstrated that, using L/P ratios as predictors, schizophrenics could be biochemically differentiated from nonschizophrenics (Frohman et al., 1961, and Stabenau et al., 1969). Several other groups (Mangoni, Balazs, and Coppen, 1963; Brown, 1964; and Buhler and Ihler, 1963), however, have been unable to confirm these alterations.

In studies of motor activity, Frohman et al. (1963) found that significant amounts of the "Frohman factor," as evidenced by elevated L/P ratios, were not present in schizophrenic patients at all times. Only insignificant (or less impressive) differences in L/P ratios were seen between normals and schizophrenics when plasma samples were taken in the sleeping state or after 10 minutes' rest. Following normal ward activity and moderate exercise (stair climbing), significant differences in L/P ratios could once again be demonstrated between the control and schizophrenic groups. Since the significance of the difference between the schizophrenic and control subjects increased with increasing physical activity, it appears that the plasma factor is markedly influenced by the degree of motor activity of the subject.

Sullivan et al. (1966 and 1967) have reported that the family members of schizophrenic patients who had high L/P ratios were themselves more likely to have elevated L/P ratios than were close relatives of patients with low L/P ratios. Schizophrenic symptomatology, however, did not correlate with elevation of the L/P ratio in these family members.

Since elevated L/P ratios have been found in schizophrenic patients who have been free of drugs for as long as 5 years, drug ingestion does not seem to be responsible for the Frohman factor's occurrence. Moreover, prisoner volunteers who lived and ate on the same ward with schizophrenic patients did not evidence this factor. Thus, diet does not appear to play a part in the Frohman factor's etiology.

A recent study (Bergen et al., 1968) has shown that the plasma factor studied by Frohman's group at the Lafayette Clinic is probably identical to that studied by Bergen's group at the Worcester Foundation (see above). Using a double-blind experimental design, the two groups exchanged and subjected to their respective analytical procedures samples which had previously been assayed for the presence of the other group's plasma factor (i.e., the Frohman factor or Bergen's fraction). Thus, the Worcester group submitted 16 samples to the Lafayette group for interpretation. On the basis of their standard procedure (i.e., the production of rope-climbing delay in rats), the Worcester group had identified half of the samples as active (schizophrenic) and half as inactive (control). The Lafayette group concurred on the identification of 13 of the 16 samples. The Lafayette workers, in turn, submitted eight samples which they had previously analyzed for elevated lactate/pyruvate ratios to the Worcester group for study. In this instance, the two groups were in agreement on the identification of all eight of these samples. While this study does not unequivocally prove that the two groups have been studying the same plasma factor, it does provide convincing evidence that this is probably the case.

Gottlieb, Frohman, and Beckett (1969) have suggested that the Frohman factor, present in about 60 percent of chronic

schizophrenics, is identical not only to Bergen's fraction but also to a plasma factor isolated by Russian workers (Krasnova, 1967, and Lozovsky et al. 1967). The Russians' factor, a labile alpha-2-globulin with a molecular weight of about 400,000 and a blood concentration of 1/150,000 (w/w), is a lipoprotein which may selectively alter many cell membranes (Kolyaskina, Kushner, and Gaskin, 1967; Uzunov, Iordanov, and Doseva, 1967; and Tikhonov, Lozovsky, and Glezer, 1967) and which may be associated with certain immunological abnormalities said to be present in schizophrenics (Semenov, Glevov, and Chuprikov, 1967; Kuznetsova, 1967; and Kolyaskina, Kushner, and Gaskin, 1967). Gottlieb, Frohman, and Beckett (1969) have also found that plasma from schizophrenics increases the rate of accumulation of glutamic acid, tryptophan, 5-hydroxytryptophan, and alanine into chicken red cells. Recently, Gottlieb and his coworkers (1970) hypothesized that present in this serum fraction is a protein having an alpha helix (a protein having a beta helix being present in controls). This alpha helix may be associated with an increase in intracellular concentration of tryptophan which, they speculate, could result in higher brain serotonin or methylated metabolites. This group has also suggested that a protein said to be associated with hemolysis (Turner and Chipps, 1966; Lideman and Bokova, 1967; and Lozovsky et al., 1967) is different from the protein associated with increases in the L/P ratio (Gottlieb, Frohman, and Beckett, 1969).

Using a sample which comprised 25 chronic schizophrenics, 27 chronically hospitalized nonschizophrenic psychiatric patients, and 30 nonhospitalized normal volunteers, Ryan et al. (1968) measured the effects of their plasma on the production of lactate by chicken erythrocytes. No differences were noted in the effects of schizophrenic and nonschizophrenic patients' plasma. The nonhospitalized subjects' plasma, however, had less effect on this system than plasma from either patient group. In light of these results, Ryan et al. believe that previously described differences in the effects of schizophrenic and normal serum on chicken erythrocytes may be traced to the fact that earlier studies compared *hospitalized* schizophrenics with *nonhospitalized* volunteers. Why chronic hospitalization should produce this result, however, is as yet unknown.

Serum Enzymes

Creatine phosphokinase (CPK) is an enzyme found in highest concentrations in skeletal muscle, heart, and brain, although it is present in other tissues as well. This enzyme catalyzes the reversible transfer of high energy phosphate groups from ATP to creatine, yielding phosphocreatine and ADP. Since CPK elevations are reportedly associated with head injury, meningitis, strokes (Dubo et al., 1967, and Eisen and Sherwin, 1968), and epilepsy (Belton, Backus, and Millichap, 1967), it is possible that a nonspecific correlation might exist between CPK elevations and brain damage. (The type of CPK which has been identified as elevated, however, is muscle rather than brain CPK.) Moreover, several authors have noted increased concentrations of CPK and aldolase (fructose 1,6-di-phosphate aldolase) in serum from schizophrenics.

Schiavone and Kaldor (1965) found an increase in blood creatine kinase (CPK) in nine of 24 schizophrenics. In a study of 30 schizophrenics being treated with phenothiazines, Bengzon, Hippius, and Kanig (1966) measured serum levels of sorbitol-dehydrogenase (SDH), serum glutamic pyruvic transaminase (SGPT), aldolase, and CPK. Although SDH and SGPT showed

no abnormalities, either before or during phenothiazine therapy, aldolase and CPK levels were markedly elevated before phenothiazine treatment was begun, returning to normal several weeks after initiation of therapy. Baseline CPK levels were four times as high in male as in female schizophrenics. In an attempt to confirm these findings, Bengzon and his coworkers found that 50 percent of a group of 60 acute psychotics showed elevated CPK levels. Unable to attribute the observed enzyme increases solely to muscular activity, these investigators postulated that a possible disturbance in energy supply at the cellular level might have led to membrane permeability changes which, in turn, allowed release of these enzymes from the cell.

In a recent series of studies, Meltzer and his collaborators (Meltzer, 1968, 1969a, and 1970; Meltzer, Elkun, and Moline, 1969; Meltzer and Moline, 1970a and b; Meltzer et al., 1970a and b; Engel and Meltzer, 1970; Fischman, Meltzer, and Poppei, 1970; and Meltzer and Engel, 1970) replicated these findings and have attempted to determine the source of this enzyme and the cause of its elevation. Their studies indicate that elevations of both CPK and aldolase are not generally seen in chronic schizophrenic patients, nonpsychotic anxious patients, or nonpsychotic depressed patients but are characteristic of patients with acute schizophrenia, periodic catatonia, or depressive psychoses. These elevations were found using several different assay systems and substantiated by substrate specificity, temperature-dependence, heat inactivation, and isoenzyme characterization. The serum CPK is of the muscle-type isoenzyme, and the serum aldolase has been shown to be of the muscle rather than the liver type. No change was noted in CPK or aldolase activity in the cerebrospinal fluid when plasma activity was elevated.

About 50 percent of acutely psychotic patients had histochemical abnormalities or muscle biopsies of the myopathic variety, often associated with alkaline phosphatase reaction. These muscle changes were generally correlated with the elevated levels of muscle isoenzyme CPK and occurred in several patients who had not received phenothiazines prior to biopsy.

Other enzymes—e.g., serum glutamic oxalic transminase (SGOT), serum glutamic pyruvic transminase (SGPT), lactate dehydrogenase (LDH), alkaline, and acid phosphatase—were not often elevated in these patients. Elevations in CPK and aldolase can occur in Duchenne's muscular dystrophy, hypothyroidism, alcoholism, myocardial infarction, and acute brain syndrome, drug psychosis, barbiturate overdose, injection of chlorpromazine, or muscle trauma (Eisen and Sherwin, 1968).

Extensive attempts have been made to eliminate nonspecific factors which might produce this enzyme abnormality. In an effort to determine if the enzyme changes were caused by corticosteroids, Meltzer (1968) gave two patients 40 units of corticotropin gel subcutaneously; no changes in CPK or aldolase resulted. In other patients, CPK concentrations and 24-hour urine corticosteroid excretions were negatively correlated. Weight loss and gross muscle disintegration, established by urinary myoglobin determinations, did not seem to be causal factors either. Activity, as measured by a standardized bicycle exercise test to the point of exhaustion, produced only slight increases in CPK activity.

Recently, Meltzer et al. (1970a) demonstrated that CPK elevation lagged behind sleep losses seen in acute psychotic patients. Kupfer et al. (1970) further noted the occurrence of a small rise in CPK activity and a delayed rise in aldolase with 30–36 hours of sleep deprivation in normals.

Warnock and Ellman (1969) have reported that serum levels of CPK are correlated with intramuscular (I.M.) injec-

tions of phenothiazine drugs, rather than with acute psychosis. Five out of a group of 25 acute psychotics showed elevated CPK levels; three of these patients had been given I.M. injections of chlorpromazine within the preceding 72 hours. Two of 33 nonacute psychotics also showed elevated CPK levels, although none had previously received I.M. chlorpromazine. A group of rabbits given I.M. chlorpromazine showed significantly greater elevations of CPK than control animals given either I.M. injections of normal saline or of the vehicle of a commercially available chlorpromazine preparation (without chlorpromazine). The authors have suggested that the I.M. injection of chlorpromazine causes local irritation which results in elevated levels of CPK. Their study, however, failed to explain the CPK elevations seen in patients who had received no drugs or who had been given phenothiazines only.

Commenting on the findings of Warnock and Ellman, Meltzer (1969b) agreed that, after I.M. injections of chlorpromazine, some patients do show elevations in CPK as a result of the locally induced irritation. He added the proviso, however, that such elevations generally last from 2 to 4 days, while the increases which presumably occur as part of the acute psychotic process last from 10 to 14 days. Meltzer also offered the following points as possible explanations for the apparent disparities between his results and those of Warnock and Ellman: (1) Warnock and Ellman utilized a patient group which mainly consisted of chronic psychotics who were experiencing an exacerbation of their illness, while he had used a more acutely ill population. (2) In Warnock and Ellman's study, there was a long delay between the time of the acute psychosis' onset and the time blood samples were drawn. (3) There may be a particular subtype of psychotic patients which shows elevated CPK levels not found in other subtypes; thus, an unequal distribution of patients in the two studies might have been responsible for the contradictory results.

While it does appear that some acute schizophrenics, early in their illness, have a rise in plasma enzyme activity, this is also seen in other acute psychotic diseases and in a host of seemingly unrelated processes. It will be of considerable interest to follow developments in uncovering the source and cause of this abnormality.

Summary (Part 1)

The biochemical investigation of schizophrenia has largely been based on the belief that a qualitatively or quantitatively abnormal substance may be causally related to schizophrenia's occurrence. Among those substances which have elicited substantial investigative interest are the following: methionine, nicotinic acid, DMPEA, mauve factor, bufotenine, histamine, and such serum factors as taraxein, Bergen's fraction, and the Frohman factor. To date, no biochemical abnormalities have been consistently and exclusively associated with schizophrenia, although a failure to respond to histamine has frequently been found in schizophrenic patients. There is also a growing body of evidence that methyl donors, such as methionine, increase psychosis in some schizophrenics; but whether this psychotic worsening represents a toxic psychosis or a true schizophrenic-like disorder is not known. Insuring that a given finding is not an artifact due to such factors as diet, drugs, and chronic hospitalization remains a major (and all too seldom surmounted) difficulty in conducting biochemical research.

. . . A Review of the Literature—1960-1970

Part II. Sleep Studies

Richard Wyatt, MD; Benedict A. Termini, MD; and John Davis, MD

Similarities among dreams, hallucinations, and primary process thinking are often compared. Based on earlier ideas of William James and Hughlings Jackson, Feinberg and Evarts (1969) recently formulated three hypotheses associating dreams and hallucinations:

- Neurophysiological processes associated with dreams in the sleeping state are also associated with hallucinations in the waking state.
- Those mechanisms involved in the perception of visual hallucinations and dreams are the same mechanisms which underly normal vision.
- Dreams and hallucinations result from the elimination of an inhibitory process.

Since hallucinations are one of the most striking characteristics of some forms of schizophrenia, it is not surprising that considerable effort has gone into studying the physiology of sleep in schizophrenic patients. The most important stimulus for these efforts was the observation that there are periodic episodes of rapid eye movements (REM) during sleep (Aserinsky and Kleitman, 1953) and that these REM periods are highly correlated with dream reports (Aserinsky and Kleitman, 1955, and Dement and Kleitman, 1957). Normally, REM sleep alternates with the rest of sleep (nonREM sleep) in 90-minute cycles and occupies 20–25 percent of total sleep.

In an important series of experiments aimed at delineating a function for REM sleep, subjects were intentionally deprived of REM sleep for periods lasting from several days to over 1 year. This deprival was accomplished by either awakening a subject every time a REM period began (as evidenced by EEG tracings) or by giving him one of the many psychoactive drugs which suppress REM sleep. When the subject was once again permitted to have REM sleep (regardless of which method of REM deprivation had been used), REM sleep periods took up a higher proportion of the night than they had during baseline (pre-REM-deprivation) observations. This finding suggested a hydraulic model of REM sleep—i.e., that during REM deprivation the brain was capable of storing some "neurohormone" which discharged during the period of REM rebound (Dement and Fisher, 1963)—which, in turn, suggested that this increased REM pressure might tend to dissipate itself in a pathological manner (e.g., hallucinations) during waking hours.

While initial reports indicated that REM

deprivation in normal subjects (Dement, 1960; Dement and Fisher, 1963; and Sampson, 1966) produced heightened anxiety, irritability, and difficulty in concentrating, subsequent better controlled experiments (Dement, 1964; Kales et al., 1964; and Dement, 1966) failed to produce gross psychological changes, although relatively subtle deviations were sometimes noted. Furthermore, no significant adverse effects were noted in a series of patients with depression (Wyatt et al., 1971) or narcolepsy (Wyatt, Fram, and Snyder, 1970) who had received phenelzine (a monoamine oxidase inhibitor which induces REM deprivation) for as long as a year. Because it seems unlikely that the brain could retain a constantly built-up "neurohormone" for a year, these findings tend to discredit the hydraulic model of REM sleep; nonetheless, this model has been an important impetus for many studies of schizophrenic sleep.

Some investigators have hypothesized that, if schizophrenic patients were found to have an abnormally high amount of REM sleep (Fisher and Dement, 1963), a corresponding tendency might exist for REM to manifest itself in some manner during waking hours (Rechtschaffen, Schulsinger, and Mednick, 1964). Most studies of chronic schizophrenic patients have not, however, demonstrated marked deviations from normal in amount of REM sleep (Dement, 1955; Koresko, Snyder, and Feinberg, 1963; Feinberg et al., 1964; Feinberg, Koresko, and Gottlieb 1965; and Traub, 1970). While a number of investigators have noted markedly lower than normal amounts of slow-wave sleep in schizophrenic subjects (Caldwell and Domino, 1967; Caldwell, 1969; Feinberg, 1967 and 1969; Feinberg et al., 1969; and Kunugi, 1970) this finding's significance is unclear since depressed patients (Mendels and Hawkins, in press), some mental retardates (Feinberg, Braun, and Shulman, 1969), chronic brain syndrome patients (Feinberg, 1967), the normal elderly (Feinberg, Koresko, and Heller, 1967), and students under stress (Lester, Burch, and Dossett, 1967) also have decreased slow-wave sleep.

Two studies of chronic schizophrenic patients have shown contrasting abnormalities in amounts of REM sleep. Gulevich, Dement, and Zarcone (1967) found an *increased* amount of REM sleep in 13 chronic, nonmedicated, remitted schizophrenic patients, as compared to seven nonpsychotic controls, while Azumi (1966) demonstrated that REM time was *lower* in a group of 35 chronic, nonmedicated schizophrenics than in 33 normals. It seems probable that Azumi's chronic patients were more actively ill than those in the Gulevich group's study and possible that acutely ill schizophrenic patients might have even lower amounts of REM sleep. This possibility is supported by a study which revealed that short-term schizophrenic patients had significantly lower values for emergent stage 1 EEG ("REM time") and REM than did long-term patients (Feinberg et al., 1964). Abnormally low amounts of REM sleep were also seen in a study in which the sleep of six acute schizophrenic patients was monitored nightly during 10 psychotic episodes occurring over many months (Kupfer et al., 1970). The patients' behavior was monitored during this period, and each psychotic episode was divided into a waxing and waning phase. In the waxing phase of the illness, there was a decrease in both REM and non-REM sleep; the REM decrease, however, was proportionately greater than the non-REM decrease and lagged behind non-REM in returning to normal during the waning phase of the illness. The absence of a subsequent REM rebound in these patients was a surprising finding, particularly since psychotically depressed patients with

similar REM deficits evidence very large REM rebounds upon recovery (Snyder, 1969). Marked decreases in the amount of REM sleep have also been noted in smaller, less comprehensive studies of acute schizophrenics (Lairy, 1966; Lairy et al., 1965; and Stern et al., 1969); Vincent et al. (1968) did not observe any REM deficits in schizophrenics monitored with telemetry.

Studies by Zarcone et al. (1968), Zarcone and Dement (1969), and Azumi et al. (1967) support previous naturalistic observations that active chronic schizophrenic patients do not evidence compensatory REM increases following experimental periods of REM deprivation (although Zarcone et al. did observe greater than normal REM rebound in *remitted* schizophrenic patients). In the one study in which chronic patients *did* show compensatory REM increases (Vogel and Traub, 1968), REM deprivation had been accomplished by the use of amphetamine, a drug which suppresses REM sleep but is also associated with large REM rebounds when its use is discontinued. Moreover, the chronic schizophrenics in this study lacked florid symptomatology and may have been more similar to Zarcone et al.'s remitted patients than to their active patients. In none of these studies was there an increase in patient symptomatology during REM deprivation.

A recent study by Wyatt et al. (1970) suggests that schizophrenia may be characterized by a breakdown in the normal boundaries between the REM-sleep and waking states. These investigators report that spontaneous palmar skin potential fluctuations in seven of eight nonmedicated acute schizophrenics were more frequent in REM sleep than in other stages of sleep and equal in frequency to waking values. By contrast, normal controls showed a marked decrease in skin potential fluctuations during REM sleep. Since studies of cats have demonstrated that the skin potential is actively inhibited during REM sleep, the frequent fluctuations noted during the REM sleep of these acute schizophrenic subjects may represent a failure of normal inhibitory processes. The recent finding that autistic children's evoked potential amplitudes are *increased* (rather than decreased as is normally the case) during REM sleep has been similarly interpreted (Ornitz et al., 1968).

A series of animal and human pharmacological studies have suggested a model which may ultimately prove more useful for explaining REM abnormalities in schizophrenia than the previously discussed hydraulic model. This alternative model stems from recent investigations of parachlorophenylalanine (PCPA), an inhibitor of tryptophan hydroxylase (the rate-limiting enzyme in serotonin synthesis). When Dement et al. (1969) administered PCPA to cats, monophasic sharp waves (which normally occur almost exclusively in REM sleep) were produced in both nonREM-sleep and waking states. Because of their spike-like appearance and location in the pons, geniculate, and occipital regions, these sharp waves are referred to as PGO spikes. Along with PGO spiking, daily PCPA administration was associated with a marked diminution of both REM and nonREM sleep and with aberrant behavior in the waking state—rage, hypersexuality, hyperphagia, and activity reminiscent of humans undergoing hallucinations. Attempting to explain these responses to PCPA, Dement et al. postulated that the PGO spikes acted as internal stimuli which were too disturbing to allow the cats to sleep. These investigators also considered the PGO spiking responsible for the production of "hallucinatory" behavior in the cats. The diminution of REM and nonREM sleep associated with PCPA administration tended to be a relatively transitory phenomenon, for REM and nonREM sleep time generally returned to normal levels after approximately 1 week of dim-

inution.[1] PCPA-induced abnormalities in behavior and PGO spiking, however, continued unabated. After administration of either 5-hydroxytryptophan (which bypasses the PCPA enzymatic block) or chlorpromazine all PCPA-induced changes were reversed.

Data also exist on the effects of PCPA in man. Recently, Wyatt (1970) and his associates (1969) reported on the sleep of 11 patients who had been given PCPA for its possible therapeutic effects. While the decrease in nonREM sleep seen in cats did not occur, all 11 patients showed diminished REM sleep over a 2–3-week period. When the drug was discontinued, REM required over 3 weeks to return to normal levels. Again, compensatory increases in REM sleep time did not occur in the period following PCPA-induced REM deprivation. For this reason, it was concluded that PCPA irreversibly blocks tryptophan hydroxylase in human brain, resulting in a decrease in the synthesis of serotonin (believed to play a fundamental role in REM production). Supporting this interpretation was the finding that, when the enzymatic block was bypassed by oral administration of 5-hydroxytryptophan, REM sleep returned to normal levels. Because possible methods for measuring the presence of PGO spikes in man have only recently been proposed (Wilson and Nashold, 1969; Pivik and Dement, 1970; and Rechtschaffen et al., 1970), they have not yet been used with patients receiving PCPA; hopefully, data on this subject will become available in the near future.

The psychological effects of PCPA administration in man are unclear. In an early study, PCPA (in a dose up to 3 g./24 hr.) was given to prisoner volunteers without significant psychological effects (Cremata and Koe, 1966). When PCPA was later administered to patients with carcinoid tumor (4 g./24 hr.), however, such psychological symptoms as depression, confusion, hallucinations, and anxiety were present in four out of five subjects (Engelman, Lovenberg, and Sjoerdsma, 1967). Subsequently, in a more careful, double-blind study of seven patients with carcinoid tumor, behavioral changes (as measured by a psychiatric interview and rating scale) were significantly correlated with the period of highest PCPA dosage (Carpenter, 1970). The behavioral changes noted in this study included depression, anxiety, restlessness, irritability, crying, agitation, withdrawal, and lack of interest. The fact that maximum PCPA dosage was generally smaller than in the earlier study of carcinoid patients and that particularly labile patients were not given the drug may explain the absence of hallucinations or clear delusions in these patients. It is possible that higher amounts of PCPA might have produced effects similar to those seen in cats who received PCPA in amounts greater than 50 mg./kg./day (the highest dosage of PCPA that has yet been administered to man).

If schizophrenics are characterized by a deficiency in serotonin metabolism, as predicted by the sleep studies, it does not necessarily follow that these patients must have low brain serotonin concentrations. An hypothesis concerning the mechanism of action of LSD, for example, suggests that this hallucinogen blocks serotonin receptor sites, thereby increasing brain serotonin concentrations (through a feedback mechanism) and decreasing concentrations of serotonin's metabolite, 5-hydroxyindoleacetic acid (5HIAA) (Aghajanian, Foote, and Sheard, 1968). Smythies, Benington, and Morin (1969) have also speculated about the blocking of serotonin receptors by hal-

[1] It is interesting to note that the cats, like the REM-deprived schizophrenics discussed above, did *not* evidence REM rebound in the period following PCPA-induced REM deprivation.

lucinogenic drugs. Thus, depending on its cause, a functional deficiency in serotonin metabolism could be associated with either an absolute increase or decrease in brain concentrations of serotonin or its metabolites. Symptomatic of the uncertainty surrounding this subject is the fact that Woolley, who initially postulated a serotonin deficit in schizophrenia (Woolley and Shaw, 1954), later reversed himself and predicted a serotonin excess in this disorder (Woolley, 1962).

The results of studies of serotonin concentrations in schizophrenia are not uniform, and, of course, these levels can only be measured peripherally. Feldstein, Hoagland, and Freeman (1959) found no differences between chronic schizophrenic and normal blood serotonin concentrations, although low concentrations were noted in acute psychotic patients. By contrast, Jus, Laskowska, and Zimmy (1958) reported low blood serotonin concentrations in chronic schizophrenics. Ljungberg (1963) observed higher urinary 5HIAA concentrations in patients with "fatal catatonia" than in other psychotics, and Banerjee and Agarwal (1958) found high urinary 5HIAA concentrations in schizophrenics. These findings must be contrasted with those of Buscaino and Stefanachi (1957) who noted low urinary 5HIAA concentrations in schizophrenics, of Leyton (1958) who reported urinary 5HIAA excretion to be low in 20 percent of the schizophrenic patients he examined, and of Fragoso Mendes and Lopes do Rosario (1959) who found no difference in urinary 5HIAA between normals and schizophrenics.

To test the possibility that schizophrenics are unable to synthesize adequate amounts of serotonin, Lauer et al. (1958) administered tryptophan to both schizophrenic patients and normal control subjects. While they found no increase in 5HIAA excretion in the schizophrenic urine, there was a 100 percent increase of 5HIAA in the urine of normals. Neither Kopin (1959) nor Shaw, Lucas, and Rabinovitch (1959) were able to confirm this finding in their respective studies of adult and childhood schizophrenics. More recently, Christodoulou and Papaevangelou (1966) found no difference in the urinary 5HIAA excretion of schizophrenic and normal subjects to whom they had administered diets high in protein and carbohydrate.

In studies more closely related to brain function, Bowers, Heninger, and Gerbode (1969), Ashcroft et al. (1966), and Chase, Schnur, and Gordon (1970) found lower 5HIAA cerebrospinal fluid concentrations in schizophrenic patients than in either neurological patients or normal controls. Persson and Roos (1969), however, found no difference between schizophrenic and normal 5HIAA concentrations. In each of these studies, psychoactive drugs were administered within a few days of the 5HIAA determination, and the effect of these drugs is not clear (Chase, Schnur, and Gordon, 1970).

Attempts to treat schizophrenia with serotonin or its precursor, 5-hydroxytryptophan, have been generally unsuccessful (Woolley, 1962; Klee et al., 1961; Hoagland, 1958; and Pollin, Cardon, and Kety, 1961). However, both Sherwood (1955), who injected 15–75 ug. (2–3/wk.) of serotonin intraventricularly to four chronic schizophrenics, and Ljungberg (1963), who gave unspecified dosages of 5-hydroxytryptophan to nine "fatal catatonics," reported "great improvement" in the patients they had studied.

Studies of serotonin deficits in schizophrenia are subject to the same general criticisms that have been directed to investigations of other possible biochemical defects in schizophrenia—i.e., failure to adequately control for experimental biases related to such factors as diet, drugs, and hospitalization. Thus far, the serotonin hypothesis—like so many others—has not

been consistently supported by experimental evidence.

Summary (Part 2)

Because of obvious parallels between dreams and hallucinations, the physiology of sleep in schizophrenic patients has evoked substantial investigative interest. Particular attention has been directed to possible abnormalities of rapid-eye-movement (REM) sleep—periodic episodes which are highly correlated with dreaming and which usually occupy 20–25 percent of total sleep time. Although most studies of chronic schizophrenics have not found marked abnormalities in amount of REM sleep, both *acute* and *actively symptomatic chronic* patients reportedly evidence lower than normal amounts of REM sleep. Thus, decreased REM sleep appears to be associated with the waxing phase of the schizophrenic disorder. But since experimentally induced REM deprivation has generally failed to produce gross adverse psychological effects in normal subjects, the significance of this finding is unclear. Another unusual characteristic of actively ill schizophrenics is their failure to evidence compensatory increases in REM sleep time (REM rebound) following periods of REM deprivation. Various theories have been offered as explanations for these and other abnormalities in the sleep of schizophrenics—the two most important being the hydraulic model of REM sleep and the REM-sleep / serotonin-deficit hypothesis. Thus far, however, none of these theories has been consistently supported by experimental evidence.

Conclusion

This review has focused on several major areas of the biochemical investigation of schizophrenia. How many of these areas focus on postulated aberrations of biogenic amines is immediately apparent. The Frohman factor, for example, is thought to alter red-cell uptake of amines, and the physiological sleep abnormalities which characterize acute schizophrenia have been induced in both animals and man by manipulating brain serotonin concentrations. This focus of interest is not surprising since, when we look at our academic psychiatric centers, a very large percentage of biological researchers are studying one or another aspect of biogenic amines. Whether this convergence of interest will prove to be of practical importance in the prevention and treatment of schizophrenia remains to be seen.

The transmethylation hypothesis of schizophrenia has excited considerable investigative interest and has generally been studied using the "precursor-load" strategy. Both methionine and betaine seem to make schizophrenic patients more psychotic, but because toxic and schizophrenic psychoses have not been clearly differentiated, the significance of this psychotic worsening is difficult to assess. Furthermore, although methionine loading has increased brain concentrations of S-adenosylmethionine (the putative methyl donor) in rats (Baldessarini, 1967), no such increases have yet been found following methionine loading in man. Given the schizophrenic's postulated "abnormal" ability to form, or inability to metabolize, methylated substances, methionine loading should theoretically cause differential reactions in schizophrenic and nonschizophrenic subjects; but since the methionine precursor-load strategy has only twice been carried out in nonschizophrenic subjects (Alexander et al., 1963), this important aspect of the transmethylation hypothesis cannot be meaningfully evaluated.

On the grounds that they are methyl acceptors which theoretically should lower brain concentrations of aberrant methylated substances, nicotinic acid and NAD have

been used to treat schizophrenics for almost 20 years. Nevertheless, no evidence exists that nicotinic acid or NAD, in fact, perform this function in man, and current evidence of their therapeutic efficacy in schizophrenia is, at best, equivocal.

During the last 8 years, DMPEA (or "pink spot") has attracted as much worldwide attention as most of the other biochemical substances in the study of schizophrenia combined. This interest probably stems from Osmond and Smythies' (1952) identification of DMPEA as a possibly provocative compound with regard to the transmethylation hypothesis. Over the years, the study of DMPEA has been plagued by repeated failures of one investigator to replicate another's experiments—failures which, for the most part, appear to result from inadequate biochemical methodology leading to type A, B, and C errors (see figure 1 and the discussion on pp. 32–33). DMPEA's presence in urine has been demonstrated through mass spectrometry (Stabenau, Creveling, and Daly, 1970), but whether it is formed in the body or is obtained from preformed plant foods (e.g., tea) is not yet clear. The fact that DMPEA's presence in or absence from the urine correlates with the addition or removal, respectively, of tea from the diet of normal subjects is suggestive but not conclusive evidence that tea is the source of DMPEA in schizophrenics. It is also possible that DMPEA occurs in one particular subgroup of schizophrenics (e.g., acute schizophrenics) but is generally absent from other types of schizophrenics.

First described 10 years ago, the "mauve factor" now appears to be a group of substances (including a pyrrole derivative). Neither its significance to schizophrenia's etiology nor its differential occurrence in schizophrenics, as opposed to normals, has been established.

Studies of bufotenine, like those of DMPEA, have suffered from inadequate biochemical methodology and either poor or nonexistent controls. While the recent finding in human brain of an enzyme capable of N-methylating serotonin to bufotenine (Mandell and Morgan, 1970) is presumptive evidence of bufotenine's existence in man, and while it may be present in greater concentrations in schizophrenics than normals (Sireix and Marini, 1969, and Fischer and Spatz, 1970), conclusive evidence of bufotenine's hallucinogenic properties in man has yet to be brought forward. Since bufotenine probably does not cross the blood brain barrier, its role in schizophrenia will be hard to demonstrate.

One of the most consistent findings in the biochemical investigation of schizophrenia has been that there is some abnormality in the schizophrenic's ability to handle histamine. It is therefore surprising that only four studies of the histamine-schizophrenia relationship have been carried out in the last 10 years. A possible explanation for this neglect is the fact that, although histamine is in part metabolized by methylation, none of its metabolites are considered hallucinogenic, which, of course, does not jibe with the widely accepted transmethylation hypothesis. Only recently, in fact, has *any* theoretical hypothesis about histamine's relationship to schizophrenia been formulated (Cowen, 1969, and Pfeiffer et al., 1970).

Studies of taraxein, serum factors, and other substances thought to be involved in immune systems have presented a confusing array of results, most of which have not been replicated in experiments carried out by researchers other than the original investigator. This failure to replicate may stem from the complexity of immunological systems and protein chemistry and from psychiatric researchers' general unfamiliarity with them. Until independent investigators are able to consistently replicate

each other's findings, the importance of taraxein and comparable substances will remain in doubt.

Although there is considerable evidence of the Frohman factor's presence in schizophrenic patients, its chemical structure and function remain an open question. Recently, Ryan et al. (1968) found a substance in the plasma of nonschizophrenic, chronically hospitalized patients which was quite comparable to that found in schizophrenic patients (i.e., the Frohman factor) but different from that found in normal controls. From their study, it appears that some correlate of hospitalization—rather than schizophrenia, per se—may produce the Frohman factor.

Most of the better known and established biochemical views of schizophrenia are discussed above, but new areas of interest are constantly developing and old ones reopening. Three suggestive new findings, for example, are that the sex of the fetus may determine the presence of puerperal psychosis (Taylor and Levine, 1969), that hexenoic acid is present in the sweat of schizophrenics (Smith, Thompson, and Koster, 1969) and that 6-hydroxydopamine may be formed by schizophrenics (Stein and Wise, 1971). The generalized theory that excessive or deficient concentrations of substances normally present in the human body (i.e., the "orthomolecular theory") are involved in the schizophrenic process (Pauling, 1968) is an organizational research strategy frequently applied to schizophrenia.

While it is relatively new and untested, the REM-sleep/functional serotonin-deficit theory is promising in that it combines data from physiology and biochemistry, provides an animal model, proposes a functional relationship between dreams and hallucinations, and can be used in conjunction with other hypotheses involving a disturbance of serotonin metabolism. Despite this theory's attractiveness, no adequately controlled studies have demonstrated differences between schizophrenic and normal serotonin metabolism and no properly controlled study has shown clinical improvement in schizophrenic patients in whom serotonin concentrations have been elevated.

The biochemical investigation of schizophrenia has been hampered by the complex, inaccessible nature of the brain. To date, peripheral tissue examination has not unlocked secrets of practical importance to schizophrenia, and attempts at direct examination of the brain have not yet been successful. The discovery of enzyme defects in diseases of glycogen storage, amino aciduria, and lipid storage affecting the brain points toward more rewarding findings to come. Moreover, research methodology is constantly improving, and this, too, will aid in our further investigative efforts.

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Amphetamine Psychosis: A Multi-dimensional Process

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Studies of amphetamine psychosis have recently entered the limelight, not only because of their interesting research aspects, but also because of an absolute increase in the incidence of amphetamine psychosis itself. It must now be considered in the differential diagnosis of any patient presenting with a paranoid schizophrenic picture. In her review of the amphetamines, Kalant [33] noted a substantial recent increase in the number of reported cases of amphetamine psychosis. Askevold [3] reported an incidence of 0.2 per cent in the years 1947 to 1957; in 1964, Johnson and Milner[30] reported that 3.5 per cent of the admissions to a psychiatric hospital were for a psychiatric state directly related to amphetamine consumption. Even more recently, in 1968, Rockwell and Ostwald [47] reported up to 15 per cent of the patients admitted to a metropolitan psychiatric unit had amphetamines in their urine. Kalant [33] pointed out that amphetamine psychosis had been five times more common in men than in women, but that recently the trend became reversed and that women now made up 53 per cent of the cases. The incidence of amphetamine psychosis is greatest in the 20 to 40 age group and is rarely seen in older patients.[11,33] There is, of course, growing concern about the number of adolescents who abuse amphetamines and in whom the psychosis[12] develops. The problem associated with the increasing incidence of amphetamine psychosis is seriously compounded by its, at times, fearful aggressive and violent nature. Even hippies have noted the dangerous violent aspects of amphetamine abuse in their slogan "Speed kills."

Amphetamine psychosis develops over time and is secondary to the user increasing his intake of amphetamine, usually more than 150 mg. and at times up to 600 to 1000 mg. per day.[11,33] The psychosis, however, may also be produced by a single large doses, [1,2,11] and, indeed, Connell reported 13 such cases in his 1958 series. There are at least two types of chronic abuse. In one variation, as tolerance develops, the individual increases his dose of amphetamines, often gradually, over a period of weeks and months; barbiturates are often used as a sedative at night. The second variation is one in which the individual injects I.V. doses (usually methedrine) continuously and in immense quantities (up to 1500 mg. q.d.) over a period of four to six days, during which time he does not sleep. The individual then either stops or passes out from exhaustion, sleeps for 24 to 48 hours, awakens and starts the cycle over again, often reaching successively larger doses with each cycle.[35] Although the amphetamine psychosis develops over time, the patient is usually seen by the

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examining physician toward the end of this process, when he presents a paranoid schizophrenic-like psychosis and has, in fact, very often been misdiagnosed as suffering from such. Although there is great individual variability in amphetamine psychosis, there is a fairly distinct syndrome with delusions of persecution, ideas of reference, visual and auditory hallucinations, changes in body image and hyperactivity and excitation, but without disorientation or clouding of memory. In fact, one of the remarkable features of this psychosis is the hyperamnesis for the psychotic episode which allows the physician to explore, in some detail, the features of the psychosis. The absence of disorientation has been emphasized especially by Connell [11] who pointed out that usually disorientation is considered a cardinal feature of toxic psychosis. Other features that distinguished this psychosis from other toxic psychoses are the much more developed and fixed delusions, certain patterns of repetitious "compulsive behaviors" and the above-mentioned hyperamnesis. Amphetamine psychosis can usually be distinguished from schizophrenia by the increased incidence of visual hallucinations and because the individual often retains a relatively appropriate affect. However, the urine test for amphetamines remains the final arbiter.

The incidence of symptoms corresponds closely in all the reported series. Reporting on 30 cases of amphetamine psychosis secondary to chronic abuse, Connell [11] found paranoid delusions in 81 per cent of the patients; ideas of reference in 59 per cent; auditory hallucinations in 69 per cent; visual hallucinations in 50 per cent; tactile hallucinations in 12 per cent; and olfactory hallucinations in 9 per cent. Disorientation was noted in only 7 per cent. In 1966, Kalant [33] summarized the data from 94 cases excluding those of Connell. These included cases from the original reports by Young and Scoville (1938),[58] Greving (1941),[25] Staehelin (1941),[53] and, from the more recent literature, Bell and Trethowan (1961),[7] Marley (1960),[39] and Beamish and Kiloh (1960).[5] From this summary, Kalant reported delusions of persecution in 83 per cent, ideas of reference in 19 per cent, visual hallucinations in 54 per cent, auditory hallucinations in 40 per cent, tactile hallucinations in 12 per cent, olfactory hallucinations in 6 per cent, disorientation in 7 per cent and hyperactivity and excitation in 41 per cent of the cases. Hostility and aggressiveness were found in 22 per cent. Thus, when observed at the latter stages, amphetamine psychosis usually turns out to be a fairly well-delineated, characteristic syndrome.

In both research and in discussions of amphetamine psychosis, it has been useful for this author to think of amphetamine psychosis as an interaction between several variables and as a process over time. The variables which stand out most often in this psychosis are presented in Fig. 1. In this diagram, it is graphically demonstrated that certain predisposing personality types appear to seek out the stimulating properties of amphetamines and conversely the chronic abuse of amphetamines interacts with the given personality. Mutual interactions between the environment, personality and stimulation of specific central nervous systems will be the major orientation throughout the rest of the discussion.

An illustration of this interaction of variables over time is noted in the development of the paranoid delusions themselves. Generally, almost all patients (80%)[14] who take heavy doses of amphetamines become suspicious; in the earlier stage of amphetamine abuse, they are suspicious of their family, friends, strangers and lovers. The environment directly influences this process, especially if it provides the individual with reasons to be suspicious. In the intermediate

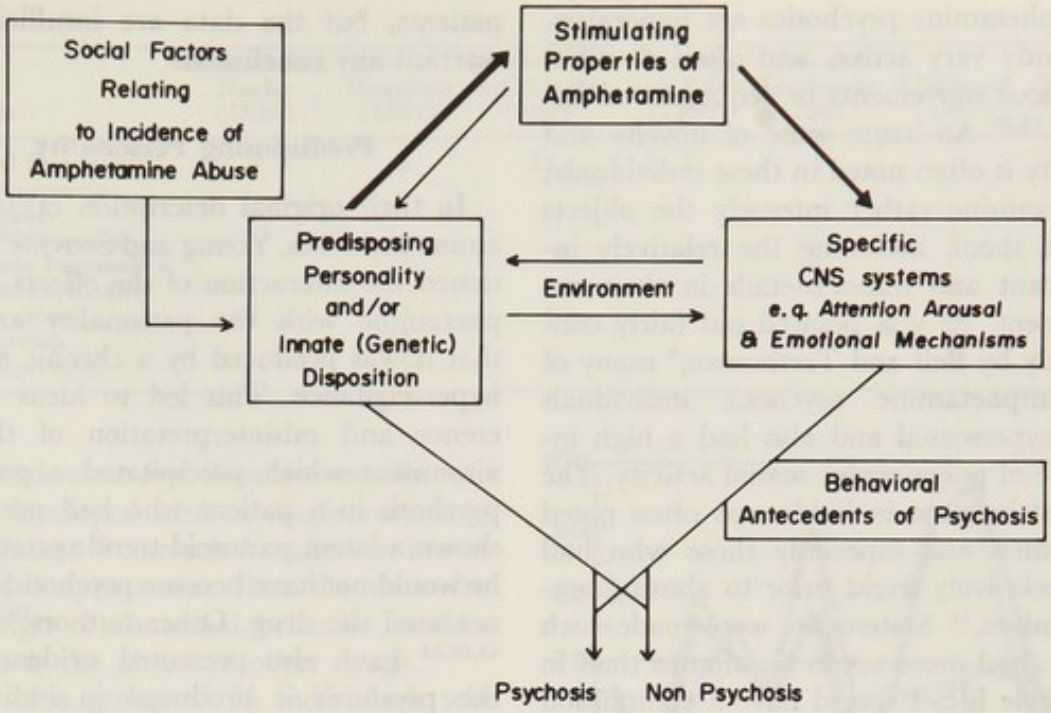

Figure 1

stage of amphetamine abuse in this country, amphetamine addicts are especially attuned to the real possibility of being followed and solicited by federal agents. Quite commonly, this later became the vehicle for persecution.[14,35] "The Feds were everywhere—under the bed, in the next car, in the trees, following on the street and even one watching from a light bulb." When Connell [11] reported his cases of amphetamine psychosis from England where there is less emphasis on federal control of drugs, his examples demonstrated that delusions of persecution were concerned with being followed by gangs or that the individuals were often persecuted by international spy rings. In the intermediate stage of abuse, Kramer et al. have pointed out that amphetamine addicts often play a half-serious, half-humorous game of cops and robbers, often turning the tables on their "persecutors." [35] At a later stage of development and/or in more psychosis-prone individuals, this manipulation-countermanipulation takes more bizarre forms, ". . . you're a power generator. We can transmit through you." Patients feel that they are not only being monitored, but are also being manipulated by hypnosis, radio, television, transmitters and unknown power sources, with which they, in turn, manipulate others.

Descriptions of other aspects of this psychosis also depict this developing process. Both visual and auditory hallucinations often originated in stimulus-induced illusions. Visual hallucinations started with fleeting glimpses of just recognizable images in the peripheral vision. Later they became fully formed and stable. Auditory hallucinations began with the perception of simple noises. In more psychotic stages, the patient would carry on long conversations with his persecutors. Gross distortions of the body are common. Frequently the patient thinks his body is transparent or invisible. This makes him feel particularly vulnerable because others can "see his feelings and read his mind."

Amphetamine psychotics are hyperalert, frequently very active, and often manifest repetitious movements or sequences of behavior.[14,35] An acute sense of novelty and curiosity is often noted in these individuals; they examine rather intensely the objects around them, including the relatively insignificant and minor details in their environment. As was pointed out fairly conclusively by Bell and Trethowan,[6] many of the amphetamine psychotic individuals were hypersexual and also had a high incidence of polymorphic sexual activity. The greatest increase in libido was often noted in women and especially those who had been relatively frigid prior to abusing amphetamines.[14] Statements were made such as ". . . had more sex in six months than in my whole life. I would have a compulsion at times and would have sex even if there were other people in the room" and "It makes you more freakish and you experiment more." Sexual intensity is often sustained and orgasm retarded. Some of the details of these patterns of behavior will be described later. The acute hallucinatory hyperactive state usually stops within two to three days after withdrawal of amphetamines, although the delusions and other thinking disorders may persist for long periods afterward.[11,14]

Often, after withdrawal, the patients are lethargic and sleep and dream for several days. During this period, they may become confused, but this is not a frequent occurrence. Varying degrees of depression are often reported, at times persisting beyond the withdrawal phase.[6,11,14] Suicide is a danger during this period of depression,[6,11] but suicide attempts are also reported during periods of fear and terror at the height of the psychosis.[14] Several authors,[5,14,33,43,58] however, have reported individuals who have become psychotic not during chronic amphetamine ingestion but after the withdrawal of amphetamine, sometimes months later. This is a rare, interesting group of patients, but the data are insufficient to warrant any conclusions.

Predisposing Personality

In their original description of amphetamine psychosis, Young and Scoville[58] questioned the interaction of the effects of amphetamine with the personality and felt that it was produced by a chronic state of hyper-vigilance. This led to ideas of reference and misinterpretation of the environment which precipitated a paranoid psychosis in a patient who had previously shown a latent paranoid trend; presumably he would not have become psychotic had he not used the drug. Other authors[10,14,21,41,44,50,51] have also presented evidence that the psychosis is produced in individuals with a prepsychotic disorder or a predilection for paranoid adaption. To give some estimate of the incidence of personality types, data from several reports are summarized in Table 1. Since the literature contains a variety of reports that use different systems of diagnostic classification, this summary was limited to the clinical material of those authors that described their cases in general conformity to the *Diagnostic and Statistical Manual of the American Psychiatric Association.*

Psychopathic personality and schizophrenia are noted to represent a disproportionate 70 per cent of the total. There is considerable diagnostic variability across reports, especially between antisocial personality and schizophrenia. This variability may represent the fact that many of these patients are borderline individuals. Ellinwood[14] has pointed out that many resemble Dunaif and Hock's[13] description of pseudopsychopathic schizophrenia. Most authors also describe many predisposing traits including difficulties with work, marriage, and sexual adjustment. Except for Connell,[11] relatively few authors describe any patients with normal personalities prior

Table 1

Diagnosis	Herman and Nagler (1954)	Hampton (1961)	Bartholomew and Marley (1959)	Beamish and Kiloh (1960)	Bell and Trethowan (1961)	Ellinwood (1967)	Total % (N = 82)
Antisocial Personality	7	9	11	7	2		45%
Passive Aggressive Personality					3	2	6%
Schizoid Personality					2	2	5%
Inadequate Personality					4		5%
Hysterical Personality					3	1	5%
Psychoneurosis	1	1	1				4%
Schizophrenia		16				4	25%
Manic-depressive		5		7		1	8%

to the toxic state and these are usually cases which developed after a single very large dose. Kalant [33] reminded readers in her review of amphetamine that the most frequent sign of abnormal behavior in these patients is the abuse of other drugs.

Out of a group of 25 individuals who had taken large doses of amphetamines over at least a three-month period, Ellinwood [14] compared the diagnosis of those who developed psychosis with those who did not. There was a much higher incidence (50%) of antisocial personality in the non-psychotic group, whereas the psychotic group more often retained a psychotic diagnosis (50%) even after their withdrawal from amphetamines. In contrast to this diagnostic finding, there was little or no differences in the MMPI profiles of those who developed the psychosis versus those who did not. The profiles of both groups peaked on the schizophrenic, psychasthenic, psychopathic deviant and hysterical scales. When this particular composite profile was compared to the general Lexington Addiction Hospital MMPI profile, fairly distinctive differences were found (Fig. 2). Using two tail "T" tests, the differences between the peak scores and general addict profile for each sex separately was noted to be significant at $P<0.05$ for the hypochondriasis scale, whereas all other peak score differences were significant at $P<0.005$. Thus, even when compared with an addict population, patients who had a proclivity to use amphetamines appeared to be more sociopathic and to exhibit more eccentric and bizarre behavior.

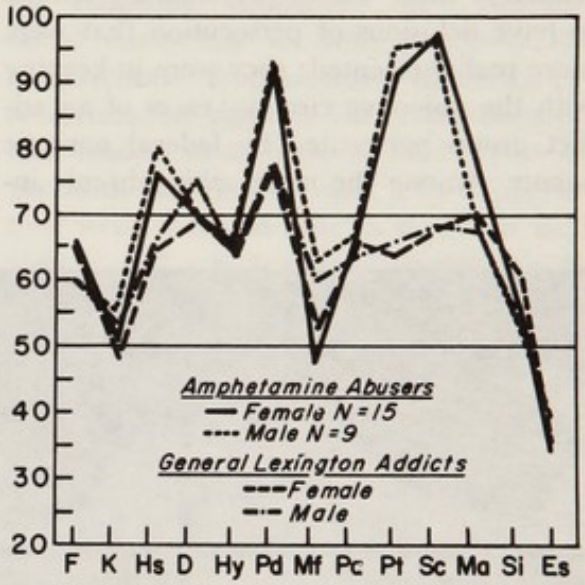

Figure 2. MMPI composites of amphetamine abusers contrasted with general Lexington addicts.

The premorbid personality affects the form of the amphetamine psychosis.[14] Thus, schizoid and schizophrenic individuals were rarely noted to be aggressive in their psychotic state but appeared fearful and passive. Individuals with fairly aggressive personality traits more often acted out aggressively the feelings associated with their delusions. In a similar manner, when given chronic doses of amphetamines, experimental cats react differently depending on whether they are wild farm cats or

whether they have come from the city pound.[17] The wild farm cats become extremely aggressive, fearful, hissing and striking with all attendant postures quite frequently, whereas the tamer city pound cats more often develop patterns of sniffing and curiosity (Fig. 3). Ellinwood[14] found that predisposing personality and the environment at the time of the amphetamine psychosis significantly influenced the content of delusions. Those patients who had relatively more stable personalities tended to have delusions of persecution that were more reality oriented; they were in keeping with the objective circumstances of an addict group persecuted by federal narcotic agents. Among the more schizophrenic individuals, delusions were more bizarre (e.g., they were persecuted by Martians, evil spirits, and devils).

Drug Effect

Separating drug effect from its interaction with a premorbid personality is difficult. The primary difficulty centers around the facts that sociopathic personalities and schizophrenics have a predilection to the use of amphetamines and that schizophrenics and schizoid individuals are more prone to develop psychosis. Thus, we have a rather great selection factor even before attempting to assess the role of amphetamines

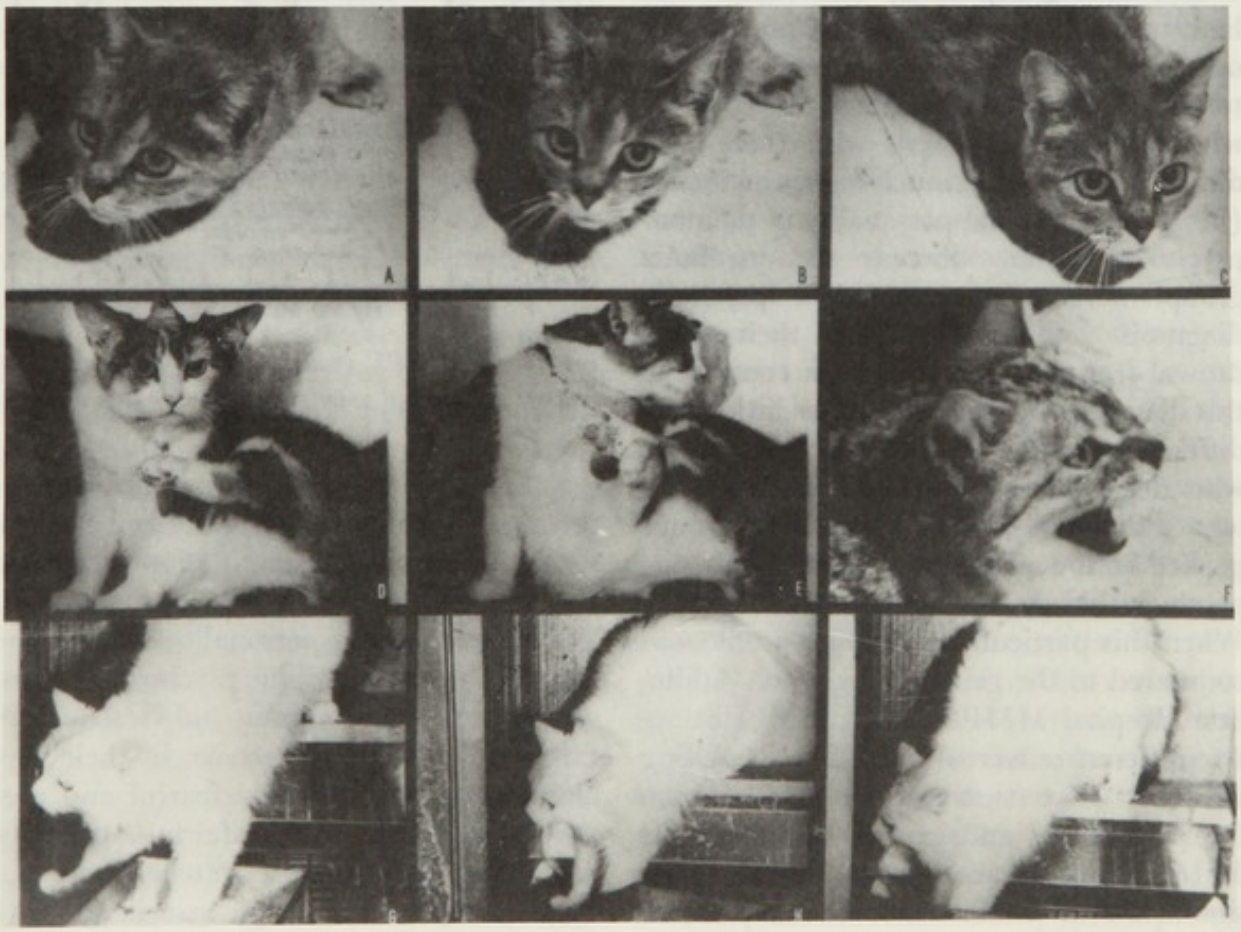

Figure 3. Repetitive stereotyped patterns of behavior induced by chronic methedrine administration: (A-C) side-to-side head turning and looking; (D-E) abortive grooming reaction; (F) hissing on any approach; (G-I) sniffing small area in cage.

in the psychosis. As others have said, the amphetamines may only be stimulating the underlying behavioral patterns of a given group of individuals.[10,21,41,44,50,51]

Previous authors have addressed themselves to this question by comparing the psychotic manifestations of amphetamines with those induced by other drugs. Their underlying assumption is that if a group of drugs all produce a similar, fairly specific psychosis in a variety of individuals, then this would indicate the drugs' role in producing the psychosis. Greving thought that although the prepsychotic personality was contributory, the mental symptoms during intoxication with high doses of methamphetamine were suggestive of mescaline action.[25] Staehelin[53] discussed the similarity between amphetamine psychosis and those produced by such drugs as cocaine and khat. All produce a remarkably similar paranoid, schizophrenic-like psychosis. Staehelin felt that hallucinations in amphetamine psychosis were, to a great extent, secondary to sensory hyperacuity and that illusions were based partly on a direct drug effect which impaired reality and orientation by nonspecific stimulation of sensory sensitivity and associations. Beamish and Kiloh[5] drew the conclusion that these paranoid states are not specific effects of amphetamines because other agents may give rise to a similar picture. However, they found little support for the view that in these cases, incipient or latent schizophrenia had been precipitated by amphetamines, since there were marked differences in the natural history of the psychosis as well as differences in background factors from those found in schizophrenia. Connell[11] presents the view that amphetamines have a strong psychotomimetic effect like LSD and mescaline, because they produce psychosis in normal individuals both during chronic use and from large, single toxic doses.

Behavioral Antecedents of Amphetamine Psychosis

An alternative method for examining the intrinsic psychotogenic effects of prolonged large doses of amphetamine is to compare the similarity and differences of symptoms in those individuals who develop the amphetamine psychosis and those who do not. The writer[14] examined the behavioral manifestations of amphetamine abuse and made the following appraisals: (1) behaviors noted commonly in both psychotic and nonpsychotic amphetamine abusers; (2) behaviors that appeared in both groups but that tended to increase in intensity as the psychosis developed; and (3) behaviors that were observed only in psychotic individuals and which tended to precede the psychosis.

Some behaviors were common to both those who developed psychosis and those who did not. Most amphetamine abusers initially noted an increased loquaciousness, decreased ambivalence, a sense of cleverness and crystal-clear thinking and an invigorating aggressiveness. Both psychotics and nonpsychotics appeared to have had a hyperacute memory during the period of abuse both for relevant and extraneous material. Other symptoms noted to be common both in psychotics and nonpsychotics were bruxism, touching and picking of the face and extremities, an acute sense of novelty, distortion of time, sense, and suspiciousness. Practically all patients at some time became mildly suspicious; it was a prevailing symptom in all the psychotic patients and in 50 per cent of the nonpsychotic patients.

Certain feelings, perceptual changes and behavior were present in both psychotics and nonpsychotics but become progressively more severe in those who developed the psychosis. Fear, suspiciousness, a feeling or awareness of being watched, and visual il-

lusions in the peripheral fields were quite definitely progressive. At first, patients (including nonpsychotics) were suspicious of the usual motives of people around them and constantly sought out hidden motives in others. Associated with increasing suspiciousness was a heightened awareness and overreaction, especially to slight movements in the peripheral vision which in turn became, at a later stage, the stimulus for initial illusions. Later, when the patient was in crowds, alone, or in the dark, suspiciousness was omnipresent. Frequently it was a ubiquitous feeling that someone was watching from behind or from the side. Not unlike "a presence," a symptom noted in parietal lobe lesions, this symptom became organized in a delusional manner with the development of the psychosis. The well-formed delusions of persecution in amphetamine psychosis appeared to be a clear extension of the earlier suspiciousness and awareness of being watched. Amphetamine abusers state that they can often recognize others taking amphetamines by their constant suspicious sideward glancing.

Another symptom which became much more intense as the patients became progressively psychotic was that of increased thinking and especially the feelings associated with thinking. There was a sense of portentousness and significance associated with one's thinking even in some of the nonpsychotic patients. This was primarily manifested in usually unsophisticated philosophical concerns dealing with "beginnings, meanings and essences." [14] Revelations of significant insights were frequently experienced. These profoundly emotional "Eureka!" experiences often ushered in prolonged periods of thinking about "the meaning of life." One patient's description was "everything became relative to some truth; a light ray would prove unity; a light ray breaking up would prove why men break up . . . I suddenly discovered how the world began." Another patient said, "I began to put details together from the past and present. Now I think I know what is going to happen to this world." Intense religiosity and involvement with the zodiac systems were also noted. Later, philosophical involvements degenerated into delusional systems. Two processes that were common to both philosophical and delusional concerns were the sudden emotional insights and the compulsion to analyze a variety of details to find meaning and explanation. It would appear that at least the emotional drive behind certain forms of thinking was stimulated by the amphetamines and that these forms were later involved in the elaboration of delusional systems.

Other symptoms appeared to be relatively more frequently associated with psychosis-prone individuals who developed the psychosis. Certain patterns of behavior seemed harbingers of psychosis. Those that developed the psychosis reported a rather marked increase in sexual interest and drive and there was a rather dramatic increase in polymorphous sexual activity.[14] Psychotic individuals demonstrated a rather overwhelming concern with eyes, faces and their later distortion. They also described frequently misrecognizing people around them. They were more likely to have felt either estranged from their environment or conversely to have experienced déjà vu. They more often described a fairly acute sense of curiosity and described in elaborate detail how they would examine and dismantle many objects in their environment. It was noted that even common, ordinary objects took on new emotional significance; they became "overcathected." Often neutral objects such as windows, chairs and pencils took on an evil cast. Psychotic patients (90 per cent) described a compulsion to take objects apart, to analyze, to sort and, on rare occasions, to put these objects back together.[14] These patients analyzed details in a very concrete

and repetitive fashion. The more paranoid patients tended to search intensely for signs and meanings. One patient said "I looked everywhere for clues—under rugs, behind pictures—I took things apart. I read magazines, looking at periods with a jeweler's glass for codes . . . they were to help me solve the mystery." This obsession of analyzing a variety of details, hoping to see everything at once or the "big picture," was a recurrent theme noted not only in the more florid paranoid systems but also often in the philosophical concerns of the less psychotic individuals. Watches, doorknobs, television sets, radios and phonographs, tape recorders, typewriters, and children's toys were among the common items of curiosity and analysis. Some were valueless, such as old television sets from the junk yard. Many were quite expensive, one man dismantled a $1200 hi-fi set. Another sorted, filed and put on display repainted electronic parts, both new and worthless ones. This same man polished and painted everything around. He tiled his apartment, including the walls, in Armstrong vinyl pebble tiling, then painted the individual pebbles red, yellow, gold and black. Besides this concrete expression of curiosity, analysis, and obsession with detail, more abstract visual constructive trends were noted. One patient loved to read blueprints; others analyzed materials for their weave, make-up, pattern, color and space. Two patients analyzed "in 3-D." Rylander [48] has reported this repetitious type of analysis, sorting, polishing and taking objects apart in 70 per cent of his patients who had abused Preludin. Kramer et al.[35] described similar stereotyped repetitious behavior in their cases of amphetamine abuse.

A consistently reported hallucination (100%) in the amphetamine psychotics was the fairly marked distortions of facial percepts.[14] Faces melted, faded, appeared with stockings or masks on them; blood and bones appeared; eyes changed their slant or shone; faces became hairy, developed deep crevices and lines; they glowed and were transformed into those of witches or monsters. These changes originated with an increased awareness of eyes and faces; patients would search the faces of others for expression and meaning. In the later stages, patients were still overconcerned with faces, but the physiognomy would suddenly become distorted.

Although a moderate degree of anxiety and fear was mentioned by most amphetamine abusers, intense fear and terror were major symptoms described by the psychotics. Frequently the fear was associated with delusions or hallucinations, but others described a diffuse anxiety especially over losing control. It was not uncommon for the patients to hide alone for weeks from their tormentors or in their state of terror to attempt suicide. Another symptom that was noted only in those who developed a psychosis was that of olfactory hallucinations. In some, these were rather marked and interacted with the paranoid delusions. Sense of smell was used by one patient to analyze who had been in his room while he was absent. This man believed that he could ferret out the smell of women, their sex and powder; he identified men by their body odor and could also "sniff out evil like a blood hound." Tactile hallucinations were found only in the psychotic group and were primarily hallucinations of small microanimals. Olfactory and tactile hallucinations are mentioned because they are rather more uncommon in functional psychoses.

Thus, there appear to be three classes of behavioral characteristics associated with chronic amphetamine abuse: (1) behavioral patterns that are developed by amphetamine abusers who do not develop psychosis as well as those who do; (2) changes in behavior and perception that, although found in both the psychotics and nonpsychotics, increase progressively and

appear to interact with the developing psychosis; and (3) behavior patterns and emotions that are noted primarily in the psychosis-prone amphetamine abusers. The findings indicate to this writer that there are several forms of behavior that are enhanced by amphetamines and that certain of these behavioral patterns interact in a potentiating manner. The most clear example of this potentiation is emotional enhancement of certain forms of *thinking, examining, attention to detail and significance, interacting with certain forms of hyperactive peripheral attention, suspiciousness and fear* within the context of a given individual and his environment to produce paranoid delusional systems.

Comparison with Other Organic Psychoses

It is well known that toxic, infectious, metabolic, epileptic conditions, cardiac decompensation, and sedative withdrawal are associated with a paranoid-like psychosis with many of the features noted in the amphetamine psychosis.[38,40,56,57] These symptoms include paranoid ideation, delusions of persecution and parasitosis, visual, auditory, tactile and olfactory hallucinations, sexual changes, fear and misidentification of others. As Connell [11] pointed out, the main distinguishing feature of amphetamine psychosis is the relative absence of disorientation and confusion. Another fairly important feature is that most toxic conditions last only a few days, thus not allowing time for distorted perceptions to be elaborated in thought nor time for delusional thought processes to become relatively more fixed. For example, microanimals are seen or felt and picked at in many toxic conditions but are not evolved into ideas or delusions of infestation.

The two psychoses that most resemble the amphetamine psychosis are those associated with cocaine abuse and temporal lobe epilepsy. Like the amphetamine psychosis, both conditions are noted to proceed over an extended period of time allowing cognitive and belief processes to develop and are associated with a relative absence of disorientation and confusion. The psychosis associated with temporal lobe epilepsy has a striking correspondence, including the paranoid delusions, ideas of influence, thought disorders, paranoid ideas often colored with religiosity or philosophical concerns, complex visual hallucinations, olfactory hallucinations, distorted facial percepts, depersonalization, estrangement, déjà vu, "ideas of a presence" and bruxism.[13,52] There is the same portentousness and heightened significance to thought, insight, and the meaning of signs. Patient statements quoted in Slater and Beard's report [52] on epileptic psychoses illustrate the similarity of thought: "I had two thoughts side by side, then realized the untruth of Christianity"; "It all falls into a pattern"; "Things have some kind of connection"; "People's Christian names have a significance." As was pointed out by Slater and Beard, depersonalization and estrangement experiences were basic symptoms both in temporal lobe epilepsy and the associated psychosis.

The amphetamine psychosis is in many ways indistinguishable from the psychosis associated with the chronic heavy use of cocaine, noted mainly at the turn of the century. The hyperalertness, fear, terror and persecutory delusions are almost identical, as are the overconcern with minute objects and details, delusions of parasitosis, hypersexuality and sexual perversions.[8,33,40] With withdrawal of cocaine, like amphetamine, hallucinations disappear but delusions may continue.

Comparison of Amphetamine and Cocaine Delusions of Parasitosis

To illustrate further the nature of some of the drug-induced behaviors, it would be illuminating to compare one symptom

complex that is found with an uncommonly high frequency in amphetamine psychosis, that of delusions of parasitosis. A similar increased incidence is found in other toxic psychosis, but especially in the other stimulant psychosis, cocaine insanity. In both psychoses, the associated symptoms that appear to lead to this delusion are quite alike. Description in the literature on both types of psychosis are numerous.[8,24,29,40,41,55] McCormick [41] described two of his six amphetamine abusers as developing excoriative dermatitis. Knapp [34] reported that three of his seven cases of amphetamine habituation had acne vulgaris due to picking and scratching.

In our own studies on this phenomenon,[18] we have noted in 17 patients similar descriptions to those reported. Most described an intense sensation of either tingling, creeping or itching leading to tactile examination, rubbing and scratching. Incessant rubbing and picking resulted in raw blemishes, acne, and scars in many. Often there was a compulsive pattern of unconsciously rubbing the face, locating a follicular plug (or reparative crust of a previous injury) and digging with the fingernails until an excoriation was effected. The above patterns are noted in approximately 50 per cent of all amphetamine abusers, both psychotic and nonpsychotic. The intensity tends to increase as the psychosis progresses. With the amphetamine psychosis, individuals develop very stereotyped delusions of parasitosis. Most of these believe they have vermiform parasites incysted under the skin or that small mites or lice are dug into the surface of the skin. Often the patient presents himself initially only for treatment of these parasites. Descriptions by these patients also demonstrate the intimate association between skin sensations and fairly automatic grooming behavior.

In the delusional patients, punctuate scars that were often noted demonstrate the intensity of the urge to dig out these parasites. Many instruments including knives, fingernails and surgical instruments were used to gouge out small bits of skin which the patient often presents to the physician. In the more florid forms of delusions of parasitosis, the patients not only feel these small parasites but see them everywhere including in the food, water, on the furniture and in their clothes. This grooming behavior demonstrates again the several stages in development toward more psychotic behavior.

There is remarkable similarity of the amphetamine tactile hallucinations and delusions to those noted in the cocaine-induced paranoid psychosis. Indeed, cocaine insanity is often characterized by the "cocaine bugs." [8] Mayer Gross, Slater and Roth [40] described this psychosis: ". . . tactile hallucinations are rather specific for cocaine psychosis, although not always present. These, the 'signe de Magnan', are possibly related to the effect of cocaine on the peripheral nerves. The patient feels small animals, worms, ants, lice in the skin of his hands and all over the body, or he complains of electricity or cocaine crystals entering his skin. He may not only feel, but also see these; and the reality of the hallucinations may be so great that he pierces his skin with needles to try to pick out these foreign bodies." The itching and crawling sensations are most often felt about the face, neck, shoulders, forearms and hands. This is true both for the cocaine and amphetamine-induced sensations. Maier [38] pointed out that in the cocaine-induced delusions of parasitosis, the tactile hallucinations are soon connected with visual hallucinations of these same parasites. The patients also hear the insects buzzing about, and one of Maier's patients was more plagued by the disagreeable smell of the tactically hallucinated bedbugs than by the other sensory disturbances.

Similar delusions of parasitosis are found (although with a lower incidence) in postencephalitic parkinsonism,[38] chronic toxic

psychosis, cardiac decompensation, paranoid schizophrenia, involutional reactions and paranoia.[38,56] The stereotype nature of this "grooming behavior" (including psychotic behavior) argues for an *underlying intrinsic behavior pattern* as is found in lower animals. Recent observations from our laboratory[18] demonstrate that approximately 15 per cent cats and approximately 30 per cent monkeys developed repetitive but abortive grooming responses on chronic administration of methedrine (Fig. 3). Fitz-Gerald [20] described the same self-picking to the point of producing sores in chimpanzees who have been given amphetamines. Because of these striking similarities in several syndromes, but with a marked increase in incidence in the stimulant-induced psychotic syndromes, it would appear that rather intrinsic patterns of behavior are being stimulated and then integrated into the often stereotyped delusional material.

Discussion

Because of the stereotyped nature of many of the amphetamine-induced behavior patterns in humans, e.g., the grooming behavior described above, it would be important to know if similar stereotype patterns of behavior are observed in lower animals when chronically stimulated with amphetamines. Most of the previous work with chronic daily administration has been accomplished by giving a single dose level over a period of days. Utena et al.[54] administered 6 mg. of methamphetamine/Kg. per day for several days. They comment that guinea pigs with this dose schedule became more docile and passive and less responsive to external stimuli. Other Japanese studies as reviewed by Utena [54] have reported sluggishness in mice and decreased excitability, decreased hostility and increased antisocial behavior in cats. It can be questioned whether animals given one dose level of amphetamine do not soon develop a tolerance to the drug. With single, acute doses of 5 mg./Kg., Randrup and Munkvad [45,46] noted chronic sniffing patterns in mice. The mice also demonstrated licking and biting, as well as grooming responses. The behavior of cats under the influence of an acute dose of amphetamine has been noted by Randrup and Munkvard [45,46] to consist of continuous movements of the head and eyes from side to side, with looking and searching often associated with fear responses. Lapin[36] reported that forms of stereotypy are different in three strains of mice, manifested in one strain as grooming and sniffing, in another as vertical movements and, in a third, as gnawing.

Using much larger single doses (10 to 30 mg. methedrine/Kg.), Ellinwood and Escalante[16] noted two basic reaction types in cats. In one, cats were noted to become gradually more attentive to objects or sounds in the periphery. Even though these cats would compulsively attend to objects in the area of peripheral vision, they would disregard any new object put in front of them. Often this developed into a continuous pattern of looking from side to side as described by Randrup and Munkvad.[45,46] Apparent fear responses were most noticeable in these animals, which often react aggressively with hissing and piloerection to any approach (Fig. 3).

The second pattern of behavior was that of compulsive sniffing movements usually consisting of repetitively sniffing the same 2–5 square-inch area continuously for three to four hours after the injection of amphetamine. Often, a second pattern of behavior, a repetitive but abortive grooming response, was interspersed with the chronic sniffing. For instance, one cat had a repetitive sniffing sequence along the floor of his cage, back to his feet, then suddenly looking to his right which then was followed by an abortive grooming response of his right

hind leg. This sequence was observed to occur over 600 times during a 2½-hour period. These sequences were repeated day after day with chronic doses of methedrine which, as tolerance developed, were subsequently increased up to 50 mg./Kg. per day.

Chronic methedrine cats appeared to elaborate the patterns of behavior initially activated by the first dose of amphetamine; for example, sniffing cats became chronic sniffers. This sniffing pattern would be noted to proceed for hours. The cat would repetitively sniff the same spot and he would return to sniff this spot even if he were taken out of his cage and placed in another part of the room. The repetitive nature of these behavioral sequences is a constant feature of chronic intoxication. Cats that have been off all amphetamine for six months or more will return to the original stereotyped behavior pattern within minutes of a subsequent single dose. Cats that had originally reacted with side-to-side looking and fear responses continued to do so, usually becoming more aggressive and fearful as time progressed. At times, these cats would suddenly turn to one side or the other as if they had heard or seen a stimulus in that direction. An interesting feature was that, when under the influence of amphetamine, cats with aggressive and fearful dispositions usually developed an exaggerated aggressive and fearful pattern of behavior. However, the experimental environment was also important: cats that, to facilitate photography, were observed in the open, tended to develop the stereotyped looking or searching and fear responses, whereas cats left alone in their cages tended to develop the sniffing or grooming patterns of behavior. Almost all cats were noted to salivate profusely within approximately 15 minutes after the amphetamine injection and subsequently regurgitated approximately 3 to 5 cc. of stomach contents.

The most consistent feature of amphetamine intoxication in cats is the general alerting and arousal which may either lead to the stereotyped mechanisms involving the side-to-side movements of the head and eyes and the lateral search patterns or may lead to stereotyped investigative sniffing. As already noted, similar patterns of peripheral attention, hyperalertness and associated fear have been described in man.[14] It remains moot whether the chronic sniffing patterns noted in cats can be related at all to the observed patterns of mechanical and intellectual curiosity in man.

Several lines of evidence indicate that amphetamine intoxication is activating systems (at several levels in the central nervous system) subserving attention and arousal. Observable behavioral components are noted; in general, arousal, stereotyped patterns of attention, emotional arousal, postural and cardiovascular changes and changes in various stages of sleep, especially the R.E.M. stage.

Amphetamine intoxication appears to be stimulating systems that, when stimulated electrically, produce contralateral attending responses,[15,16] with subsequent emotional arousal. Kaada et al.[32] and Fangel and Kaada[19] produced these unilateral attention responses by stimulation in areas such as the frontal eye fields, the cingulate cortex, certain areas of the temporal-parietal junction and limbic areas, especially the amygdala. Electrical stimulation in many locations in these areas first produces attention or orienting response, but with successively higher voltage or frequency, a behavioral or emotional response is noted (especially cringing fear-like withdrawal or aggression).[32] Arousal centers in the brain stem are also involved. From their studies of brain stem preparations in cats, Bradley and Key[9] concluded that the mesencephalic reticular activating system was the area necessary for amphetamine-induced activation of the cortical EEG.

Both acute[49] and chronic[26] amphetamine

administration decreases endogenous content of brain norepinephrine. Chronic administration, however, is associated with much more marked depletion and usually with an increase in serotonin.[16,26,54] Studies of catecholamine distribution by fluorescent techniques[23] have noted high concentrations of catecholamine neurons and nerve terminals in the posterior hypothalamus, midbrain, lower brain stem, striatum, anterior limbic system and olfactory bulbs. Using this fluorescent technique, Ellinwood and Escalante[16] demonstrated depletion of catecholamines after chronic amphetamine intoxication, which is most marked in and about the mesencephalic reticular activating system and in brain stem areas coordinating eye movements with postural tone and vestibular balance. There also appear to be areas of primary depletion in the hypothalamus, amygdala, parts of the hippocampus and the olfactory bulb.

Many observations, including clinical ones previously cited, indicate that the temporal cortex, amygdala and anterior limbic system are intimately involved in the behavior induced with chronic amphetamine intoxication. Neurophysiological studies have noted that spike activity was induced in the amygdala of the cat by repeated administration of amphetamine.[22,54] Stimulation of the amygdala in normal animals produces many of the same behavioral responses that are noted in amphetamine intoxication, e.g., contralateral orienting, fear-like and aggressive-responses, salivation, piloerection, sniffing and searching behavior. From these stimulation experiments, it appears that emotional responses are closely allied with attending mechanisms, which would be important to an animal in the wild where it must be alert and fearfully responsive to predators. The manner in which these attending systems have evolved in man is a matter of speculation, but it would seem reasonable, from observation in amphetamine abusers, that fear-like and aggressive responses can be stimulated along with hyperalertness in ways analogous to those noted in lower animals.

The writer believes that amphetamine stimulation of the limbic system and the associated temporal lobe may heighten as well as distort the emotional interpretation of experience and memory. It is not unlike the emotionally charged memories elicited following stimulation of the temporal and parietal cortex.[42] Stimulation of these systems may also be related to the intense sense of reality often associated not only with normal and distorted percepts but with thought contents during the amphetamine psychosis as noted in temporal lobe epilepsy. This heightened sense of reality may be the intervening step in fixation of delusional thinking. It was previously reported [14] that 80 per cent of a group of amphetamine psychotics, after withdrawal, still felt that many of their bizarre experiences were real. The question can be raised as to the long-term effects of delusional thought that became relatively fixed during the period of the amphetamine psychosis. Certainly this is a difficult question to answer because of the interaction with different predisposing personalities; however, the writer has examined at least three individuals that still have firm beliefs in their delusional systems and still believe that their bizarre experiences were real, over two years after the last amphetamine intake. This also further raises the question as to whether the schizophrenic patterns noted after withdrawal of amphetamines are strictly a matter of predisposing personality or may, in part, represent residue from the amphetamine psychosis.

Summary and Conclusions

Psychopathic and schizophrenic individuals are much more prone to abuse amphetamines than any other diagnostic groups.

Schizophrenic and borderline schizophrenics tend to be more susceptible to developing the psychosis. The predilection of these individuals to use amphetamines and to develop the amphetamine psychosis does not, however, explain the fairly constant form of the psychosis, a paranoid schizophrenic-like psychosis with certain stereotypical symptom clusters. From observations of certain of these stereotyped behavior patterns in humans as well as lower animals chronically medicated with amphetamine, it appears that central nervous system arousal and attention mechanisms are being stimulated and are, in part, responsible for the form of the psychosis. The amphetamine psychosis can best be understood as an interaction of predisposing personality, environment and stimulation of central nervous system arousal systems.

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Drugs, Neurotransmitters, and Schizophrenia

Phenothiazines, amphetamines, and enzymes synthesizing psychotomimetic drugs aid schizophrenia research.

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In searching for biochemical correlates of schizophrenia, the first thing to be determined is whether schizophrenia is a distinct entity or simply a conglomeration of more or less distinctive illnesses. When there are no defined organic pathologic disturbances, the psychiatrist is forced to make diagnoses on the basis of fairly arbitrarily selected symptoms. Accordingly, it is not surprising that from country to country and culture to culture there are great disparities in the criteria for a diagnosis of schizophrenia. Since at least some forms of schizophrenia have powerful genetic determinants (*1*), investigators have been able to discern particular symptoms or histories that correlate with apparent genetic loading. In certain of these studies, it has been found that patients with an acute onset and good premorbid history and prognosis seem to lack a genetic "taint," while genetic factors play a prominent role for those whose disturbance begins more insidiously and progresses to profound deterioration. Whether one or several different forms of the disease are genetically determined is unclear.

For patients with "classic" schizophrenia, about whose diagnosis most psychiatrists would concur, certain psychological characteristics, defined by Bleuler (*2*) as the "fundamental" symptoms of schizophrenia, are fairly constant. These include a peculiar thought disorder; a disturbance of emotional, or affective, responses to the environment; and autism, a withdrawal from interactions with other people. Bleuler felt that hallucinations and delusions, which are certainly among the most dramatic manifestations of schizophrenia, are only secondary symptoms, since they are not constant or essential to the disease. The schizophrenic thought disorder, abnormal affect, and autism are difficult to define and even more difficult to identify reliably and reproducibly in patients. By contrast, secondary symptoms are relatively straightforward and have provided more reliable diagnostic techniques for schizophrenia (*3*). Accord-

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ingly, many authors have questioned whether Bleuler's primary symptoms are indeed primary. Still, the notion of focusing upon particular behaviors as reflecting either primary or secondary symptoms of schizophrenia might be helpful in seeking biochemical correlates. For instance, if a particular drug regularly evokes hallucinations but no other symptoms of schizophrenia, we would question its value in explaining the pathophysiology of the disease.

While confusion about diagnosis has been a major stumbling block, one must invoke other explanations for the many false hopes and subsequent disappointments in biochemical studies of schizophrenia. Innumerable "discoveries" of the biochemical abnormality in one or another body fluid of schizophrenics have relentlessly been followed by failures of confirmation in other laboratories. Reported abnormalities in parameters as diverse as carbohydrate, protein, amino acid, and lipid metabolism have been advanced, only to be shown by more careful studies to derive from factors such as drug ingestion, diet, muscular activity, and the effects of chronic hospitalization. Besides these difficulties, the discouraging experiences may also stem from a strategy that is sometimes tantamount to searching for a needle in a haystack. Of the literally millions of chemical systems in the human body, why should nature have chosen to inflict the "schizophrenic abnormality" upon whatever specific chemical the experimentalist happens to be best equipped to measure?

A less direct, but perhaps more heuristic, approach might be to follow up leads suggested by known "biochemical" features of schizophrenia. One aspect of schizophrenia with definite biochemical ramifications is the response of patients to drugs. Drugs can be useful in two ways. Phenothiazine drugs are generally acknowledged to be highly efficacious in alleviating symptoms of schizophrenia. If the actions of these drugs derive from effects on whatever is fundamentally deranged in schizophrenic brains, then understanding the mechanism of action might help elucidate purported abnormal brain functioning in schizophrenia. Another way in which drugs can be useful is in eliciting model psychoses, or intensifying schizophrenic symptoms. Certain drug-induced psychoses may be relatively accurate models of schizophrenic disturbance. In some cases, drugs exacerbate symptoms by increasing the schizophrenic pathology itself, rather than merely superimposing nonschizophrenic symptoms. Knowing the neurochemical bases of such drug action should also help in elucidating the pathophysiology of schizophrenia.

If certain drugs appear to be related to schizophrenic disturbance, then one would be justified in seeking out biochemical systems capable of synthesizing the chemicals predicted by drug action to be relevant to the disease. The most promising leads have involved neurotransmitters, especially the catecholamines and indoleamines, and those drugs with which they interact prominently.

Phenothiazines

More than anything else in the history of psychiatry, the phenothiazines and related drugs have influenced positively the fate of schizophrenic patients. They have enabled many patients, relegated in earlier days to a lifetime in mental institutions, to function normally or almost normally in society. In determining the relevance of phenothiazines to brain mechanisms in schizophrenia, we must assess whether their therapeutic action involves something fundamental to the disease or whether these drugs are merely some sort of supersedative. One way would be to compare the clinical efficacy of phenothiazines with that of standard sedatives. In large-scale, well-controlled, multihospital collaborative

studies sponsored by the National Institute of Mental Health (NIMH) and the Veterans' Administration (VA), a variety of phenothiazines have been compared to sedatives, especially phenobarbital (*4*). Phenobarbital was no more efficacious than the placebo in any of these studies of schizophrenia, whereas most phenothiazines were significantly more effective than either phenobarbital or placebo. One could conceivably argue that other sedatives, such as diazepam (Valium) or chlordiazepoxide (Librium), which are more powerful antianxiety agents than phenobarbital, might compete better with the phenothiazines in the treatment of schizophrenia. However, most trials of these agents have shown them to be ineffective in the treatment of schizophrenia, despite their accepted efficacy in relieving anxiety. Indeed, since drugs such as diazepam and chlordiazepoxide are more effective than phenothiazines in relieving anxiety, one can conclude that anxiety per se is not a unique and primary feature of schizophrenia. Some authorities have argued that phenothiazines can be used to "quiet down" patients. However, numerous studies have demonstrated that, while phenothiazines do calm hyperactive patients, they also "activate" withdrawn patients (*4*).

The NIMH-VA studies provided another means of judging the extent to which phenothiazines exert a selectively antischizophrenic action. Since a large number of patients was rated for a variety of symptoms, one can analyze the extent to which particular clinical features were affected by the drugs. What Bleuler (*2*) referred to as the fundamental symptoms of schizophrenia tend to show the greatest response to drug treatment. Secondary symptoms, such as delusions and hallucinations, respond somewhat less, and nonschizophrenic symptoms, such as anxiety and depression, fail to show any specific improvement with phenothiazines. By contrast, sedatives relieve agitation with much less influence upon thought disorder or the abnormality of affective response to the environment. From data such as these, one can argue fairly convincingly that phenothiazines exert a unique therapeutic effect on schizophrenic patients. One must be cautious before concluding that the drugs directly reverse whatever is biochemically abnormal in the brains of schizophrenics. Phenothiazines might affect by way of an independent pathway emotional functions that are separately influenced by the site of disturbed activity in the brains of schizophrenics. The fact that phenothiazines, although facilitating remission, do not "cure" schizophrenic patients indicates such relatively indirect action. Indeed, failure to maintain schizophrenic patients on phenothiazines while they are in remission results in a much greater incidence of relapse (*5*).

Stimulants

Amphetamines and related stimulants have two effects on brain mechanisms in schizophrenics. In large doses, amphetamines elicit a psychosis that can be clinically indistinguishable from acute paranoid schizophrenia. In very small doses, the stimulant can selectively exacerbate the symptoms of schizophrenic patients (see box on page 109).

Many cases of amphetamine psychosis have been misdiagnosed as acute paranoid schizophrenia until the history of drug use was obtained (*6, 7*). Accordingly, Kety (*8*) suggested that amphetamine psychosis might be a heuristic model of schizophrenia. Amphetamine psychosis is most frequently observed in addicts who have consumed enormous amounts of the drug over prolonged periods—for example, 500 to 1000 milligrams of *d*-amphetamine every day for a week or more. Patients develop a paranoid psychosis that usually resolves within a few days after they stop taking

the drug. They frequently experience auditory hallucinations much like those typical of schizophrenia, including vague noises and voices and occasionally having conversations with the voices. The visual hallucinations in amphetamine psychotics tend to resemble those observed in very acute schizophrenics (*7*).

One factor that has caused some confusion in relating the symptoms of amphetamine psychosis to those of schizophrenia is the fact that amphetamines can evoke more than one type of psychosis. Amphetamines can give rise to an acute "toxic" psychosis, with delirium, confusion, and disorientation that does not resemble the schizophrenia-like amphetamine psychosis. Toxic amphetamine psychosis usually occurs after only one or two extremely large doses, rather than after prolonged use of the drug. Of the 42 cases of amphetamine psychosis studied by Connell (*7*), visual hallucinations occured primarily among patients who became acutely psychotic after one or a few large doses, and, hence, were presumably suffering from a toxic psychosis. By contrast, hallucinations were usually auditory in patients whose illness developed gradually, after frequent doses. The toxic amphetamine psychoses probably account for the fact that more visual hallucinations occur in amphetamine intoxication than in schizophrenia. In making comparisons with schizophrenia, one should focus primarily on the "nontoxic" amphetamine psychosis, in which patients retain their orientation to person, place, and time and which often closely resembles clinical schizophrenia.

Some authors have criticized amphetamine psychosis as a model schizophrenia, arguing that it might be related to lack of sleep, overexcitement, or precipitation of psychosis in borderline schizophrenics. However, in controlled studies in which large doses of amphetamine were administered to subjects who had no evidence of preexisting schizophrenia or schizoid tendency, psychosis was uniformly produced within 1 to 4 days (*9, 10*). Thus, amphetamine psychosis is not likely to be simply a precipitation of latent schizophrenia. Since some patients became psychotic in about 24 hours, there could not have been sufficient deprivation of sleep to account for the psychosis. As for the question of overexcitement, after some initial moderate euphoria, most subjects were sullen rather than excited, although it is conceivable that there was "internal" hyperexcitement, which might not be evident to observers.

Although amphetamine addicts who have become psychotic after ingesting large amounts of the drug are often clinically indistinguishable from paranoid schizophrenics, subjects in some experimental studies of amphetamine psychosis apparently lack typically schizophrenic thought disorders or affective disturbances (*9*). However, in other studies, with dosage schedules more closely mimicking the pattern of ingestion of amphetamine addicts, thought disorder, affective disturbance, and auditory hallucinations are consistently observed (*10*).

One important reservation about treating amphetamine psychosis as a model schizophrenia is that it rarely resembles nonparanoid schizophrenia. It is conceivable that amphetamines possess a "pure" schizophrenia-mimicking action, but that some other effect of the drug transforms the clinical picture into a predominantly paranoid one. Perhaps such paranoid action results from the well-known alerting effects of amphetamines on the central nervous system. One might speculate that the major feature differentiating paranoid schizophrenics from other schizophrenics is a hyperalert striving to turn their bewildering array of psychotic transformations into a coherent and meaningful process.

Amphetamines and related stimulants of the central nervous system can, in small doses, exacerbate symptoms of schizophrenia (*11*) rather than superimpose a dis-

tinctive psychosis upon the illness. Patients themselves perceive that their illness is worsening under the influence of the drug. By contrast, when schizophrenics are treated with other psychotomimetic drugs, such as LSD (D-lysergic acid diethylamide), they recognize that the superimposed psychosis differs from their own mental disturbance (*12*). The amphetamine analog methylphenidate (Ritalin) produces a florid exacerbation of schizophrenic symptoms when given in extremely low doses—often as rapidly as 2 minutes after an intravenous injection (*11*). To control for the possibility that amphetamines exacerbate schizophrenic symptoms by a nonspecific stimulation of the central nervous system, Angrist *et al.* (*13*) administered large doses of caffeine to schizophrenic and nonschizophrenic subjects. Although all showed tremor, anxiety, and increased heart rate, none showed an increase of psychotic symptoms.

Yet another item favoring an association between amphetamine-induced mental disturbance and schizophrenia is the fact that phenothiazines and butyrophenones seem to be the best antidotes for amphetamine psychosis and can rapidly reverse amphetamine-induced intensification of schizophrenic symptoms (*10, 14*). By contrast, barbiturate sedatives fail to alleviate amphetamine psychosis and in some cases accentuate the symptoms (*14*).

Psychedelic Drugs

Psychiatric researchers first became interested in LSD primarily as a drug that could elicit model schizophrenia. They were impressed by the fact that LSD reproducibly evoked a psychotic state which differed from toxic drug psychoses in that subjects were aways alert and reasonably well oriented to time, place, and person. However, detailed comparisons of the mental states produced by LSD and related psychedelic drugs such as mescaline, dimethyltryptamine (DMT), and psilocybin with the typical functioning of most schizophrenics in mental hospitals revealed many differences (*12*). Psychedelic drugs tend to alter visual perception, with few changes in auditory perception. By contrast, although schizophrenics can experience visual hallucinations, these are much less frequent than auditory hallucinations. The psychedelic drug experience is frequently pleasurable, while for most schizophrenics their psychosis presumably is an unpleasant experience. Whether or not a typically schizophrenic disturbance of thinking and feeling takes place in psychedelic drug-induced psychosis is a matter of controversy. Moreover, unlike the case with amphetamine psychosis, individuals under the influence of drugs such as LSD can be readily distinguished from schizophrenics in mental institutions. Schizophrenics receiving psychedelic drugs report that the drug experience is unlike their endogenous psychosis; it seems like something "different" superimposed upon their fundamental disease (*12*).

However, one should be cautious before rejecting out of hand any possibility of a relationship between psychedelic drug psychosis and schizophrenia. Even if a drug acted by disturbing the same site in the brain that is affected in schizophrenia, one would still not expect the effects of the drug to be identical to those displayed by schizophrenic patients. Patients with schizophrenia have been suffering from their disturbance for many years, probably long before overt symptoms were manifested, whereas the drug experience is acute and short-lived. Moreover, an individual receiving a psychedelic drug knows exactly what is happening to him and can anticipate speedy restitution to normality, while the schizophrenic is afflicted with an unknown and unpredictable long-term process. To test whether a drug truly mimics schizophrenia, one should administer the drug surreptitiously every

day for several years, beginning in the subject's early childhood.

This line of reasoning suggests that one should compare drug psychosis to the clinical state displayed by schizophrenic patients during their earliest acute breakdown. There seem to be some striking similarities between the subjective states of some early schizophrenic patients and the effects of psychedelic drugs. Psychedelic drugs elicit feelings of enhanced self-awareness, awe, and ecstasy, with sensations of increased acuity and profundity of all sensory perception. Similarly, in case histories of patients suffering acute schizophrenic breakdowns, Bowers and Freedman (*15*) frequently encountered apparent psychedelic experiences. Perceptual modes were heightened, the patients feeling that they had broken through conventional modes of perceiving, thinking, and feeling to attain a "new creativity." Instead of the flattened affect of chronic schizophrenics, these patients experienced intense joy or dread, which is of interest since with psychedelic drugs one often sees an alternation between extremes of elation and abject terror. Although their thinking was altered, these patients often did not display the typical schizophrenic disturbance of thought or feeling. Moreover, in these acute schizophrenics, changes in visual perception were much more frequent than they were in chronic patients. Snyder and Lamparella (*16*) quantified the presence of various "psychedelic" behaviors in schizophrenia and observed that these were much more frequent in acute patients.

This "psychedelic" phase of schizophrenia seems not to be tolerated for long. Either the acute state subsides and normal mental function is restored, or the bewildering experience is resolved by encapsulation into fixed delusional systems, or restricted modes of interacting, including autistic behavior, altered affect, and a formal thought disorder.

Phenothiazines and Catecholamines

Ascertaining the way in which a drug exerts its therapeutic effects is the pharmacologist's most difficult task. Most drugs elicit a myriad of biological effects, the majority of which are unrelated to the therapeutic action of the drug. Phenothiazines are highly reactive chemicals capable of pi electron donation or acceptance, hydrophobic binding, and ionic links by way of the side-chain amine; they produce biochemical effects on almost every system that has been examined (*17*). How might one decide which of these effects is most relevant to therapeutic efficacy? Of the large number of phenothiazines that have been employed clinically and that are fairly similar in their chemical structure, some are highly effective in the treatment of schizophrenia, others are somewhat less efficacious clinically; while yet others are definitely ineffective. Biochemical actions that correlate with known clinical actions would be the best candidates to mediate the therapeutic actions of the drugs.

Most of the biochemical effects of the phenothiazines do not correlate with clinical potency. The best correlation is in certain effects upon catecholamines in the brain, especially dopamine; this suggests that the therapeutic action of these drugs is related in some way to a blockade of dopamine receptors in the brain (see box).

The catecholamines, norepinephrine and dopamine, are transmitters in a group of well-defined tracts in the brain. Dopamine is best known as the transmitter of a prominent dopamine tract with cell bodies in the substantia nigra and terminals in the caudate nucleus and putamen of the corpus striatum. The nigrostriatal dopamine pathway degenerates in Parkinson's disease, and the attendant dopamine deficiency appears to account, in large part, for the symptoms of the disease. Thus restoration of the depleted dopamine by treatment with L-dopa,

Relations between Drugs, Catecholamines, and Schizophrenia

Phenothiazines (and related antischizophrenic drugs)

Phenothiazines have true antischizophrenic actions:
They are more effective than sedatives.
They act best on fundamental symptoms.
Blockade of dopamine receptors by phenothiazines is closely related to their clinical efficacy.
The ability of phenothiazines to mimic the preferred catecholamine conformation predicts their therapeutic efficacy.

Amphetamines

In small doses, amphetamines specifically activate schizophrenic symptoms.
Amphetamines can evoke a psychosis that is often indistinguishable from acute paranoid schizophrenia.
Phenothiazines appear to be optimal antidotes for amphetamine psychosis.
Behavioral effects of amphetamines are presumably mediated by catecholamines in the brain.

Table 1. The relative affinities of phenothiazines and butyrophenones for muscarinic cholinergic receptor binding in the brain correlate inversely with extrapyramidal side effects.

Drug class	Relative affinity for muscarinic receptor*	Frequency of extrapyramidal side effects† (*27, 28*)
Dibenzodiazepine		
Clozapine	385.0	5
Piperidine phenothiazine		
Thioridazine	66.7	4
Alkylamino phenothiazine		
Promazine	15.2	3
Chlorpromazine	10.0	
Trifluopromazine	10.0	
Piperazine phenothiazine		
Acetophenazine	0.91	2
Perphenazine	0.93	
Trifluoperazine	0.91	
Fluphenazine	0.91	
Butyrophenone		
Haloperidol	0.21	1

* Affinity for the muscarinic receptor is defined as the reciprocal $\times 10^{-5}$ of the molarity of the drug that displaces by 50 percent the specific binding [^{3}H]QNB (1 n*M*) to whole rat brain homogenates (*31*). Effective dose (ED_{50}) values were obtained by log probit plots of the effects of four concentrations of each drug assayed three times. Each experiment was done twice. The same relative affinities were observed in experiments with clozapine, thioridazine, chlorpromazine, and trifluoperazine on specific [^{3}H]QNB binding to homogenates of guinea pig ileum. † Rank by class; 1 indicates the most side effects.

the amino acid precursor of dopamine, has proved to be a veritable "miracle" therapy for Parkinson's disease. There are also prominent dopamine pathways with cell bodies dorsal to the interpeduncular nucleus and terminals in the nucleus accumbens and olfactory tubercle, areas of the limbic forebrain, that have been implicated in emotional behavior (*18*). An extensive network of dopamine neurons has been found in the cerebral cortex (*19*).

Carlsson and Lindqvist (*20*) first suggested that phenothiazine drugs act by blocking dopamine receptors. They observed that chlorpromazine and related antischizophrenic agents elevated concentrations of the methoxylated metabolites of dopamine in the brain, while the antihistaminic phenothiazine, promethazine, which is not effective in treating schizophrenia, did not alter these concentrations. Haloperidol, a butyrophenone drug with antischizophrenic actions similar to, but more potent than, the phenothiazines, was correspondingly more potent in elevating the concentrations of these metabolites. Carlsson and Lindqvist speculated that the phenothiazines block catecholamine receptor sites, whereupon a message is conveyed by means of a neuronal feedback to the cell bodies: "We receptors are not receiving enough transmitter; send us more catecholamines!" Accordingly, the catecholamine neurons proceed to fire more rapidly and, as a corollary, synthesize more catecholamines and release more metabolites. These speculations have been confirmed in

studies showing that phenothiazines and butyrophenones do accelerate catecholamine synthesis in proportion to their clinical efficacy (*21*). The influence of these drugs upon dopamine synthesis correlates much better with clinical effects than their actions on norepinephrine synthesis. Indeed, several extremely potent butyrophenone tranquilizers selectively accelerate dopamine turnover with negligible effects on norepinephrine. Kebabian *et al.* (*22*) have shown that a dopamine-sensitive adenylate cyclase in the caudate nucleus is inhibited by low concentrations of phenothiazines and butyrophenones that are clinically effective in treating schizophrenia, but not by phenothiazines that are ineffective in treating schizophrenia. Aghajanian and co-workers (*23*) have demonstrated an inhibitory effect of iontophoresed dopamine on olfactory tubercle cells receiving dopamine terminals. Very low doses of intravenously administered phenothiazines and butyrophenones block this effect of dopamine in proportion to their clinical efficacy in treating schizophrenia.

How do the phenothiazines, which are complex, multiringed structures, interact with the receptor for dopamine, a simple phenethylamine? Chlorpromazine in its preferred conformation, as determined by x-ray crystallography, can be partly superimposed upon the preferred conformation of dopamine or norepinephrine, providing a molecular mechanism whereby phenothiazines might block dopamine receptors (*24*). In the preferred conformation of chlorpromazine, its side chain tilts away from the midline toward the chlorine-substituted ring (Fig. 1). Presumably the chlorine on ring a is responsible in some way for the "tilt" of the side chain, since if there were no substituent on ring a, both rings a and c would be symmetrical and one would expect the side chain to be fully extended. Accordingly, phenothiazines lacking a substituent on ring a should mimic the conformation of dopamine less efficiently, have less affinity for dopamine receptors, and therefore be less efficacious in the treatment of schizophrenia. Of the numerous phenothiazine tranquilizers that have been widely employed clinically, only two lack a substituent on ring a. Mepazine and promazine, the two phenothiazines lacking a ring a substituent, are significantly less effective as antischizophrenic drugs than the others (*4*). Besides the ring a substituent, another major requirement for therapeutic efficacy is that the side-chain amine of phenothiazines contain three carbons; phenothiazines with two-ringed side chains lack antischizophrenic efficacy. Phenothiazines with two-carbon side chains, such as the antihistamine promethazine and the anti-parkinsonism agent diethazine, are less capable of assuming the dopamine-like conformation than those with three-carbon side chains (*24*).

Besides being associated with antischizophrenic activity, dopamine receptor blockade by phenothiazines and butyrophenones may explain the prominent extrapyramidal side effects of these drugs. By blocking the dopamine receptors in the corpus striatum, these agents produce a functional deficiency of dopamine. One might speculate that, while the parkinsonism-like side effects of the phenothiazine drugs arise by blocking dopamine receptors in the corpus striatum, the antischizophrenic action of the phenothiazines may be related to effects upon dopamine receptors in other areas of the brain, such as the olfactory tubercle, nucleus accumbens, or the dopamine receptor sites in the cerebral cortex.

In most of their biochemical features, dopamine neurons in different parts of the brain and periphery behave quite similarly. Thus the reuptake process of dopamine nerve terminals, which presumably serves to inactivate synaptically released dopamine, appears to be the same in dopamine terminals of the corpus striatum, olfactory

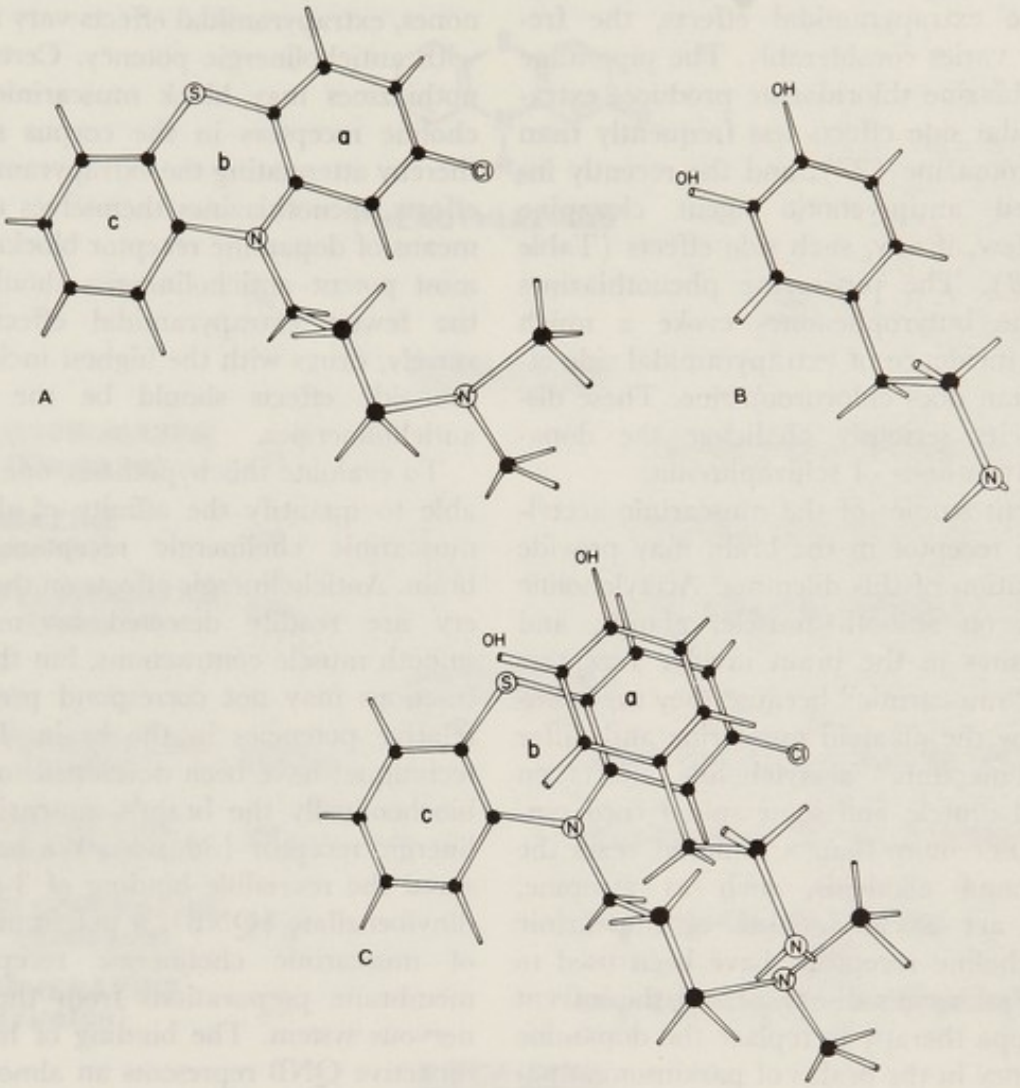


Figure 1. Conformations of chlorpromazine (A), dopamine (B), and their superimposition (C), determined by x-ray crystallographic analysis. The a, b, and c in (A) and (C) designate rings. [Adapted from Horn and Snyder (24)]

tubercle, nucleus accumbens, median eminence, and retina (*25*). Drug responses of dopamine receptors in the olfactory tubercle, corpus striatum, kidney, and superior cervical ganglia are also quite similar (*25, 26*).

Phenothiazines and Acetylcholine Receptors

Since the phenothiazines and butyrophenones act similarly at all dopamine receptors, they should, when given in thera-

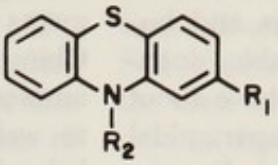
peutic antischizophrenic doses, produce the same incidence of extrapyramidal side effects. Although all antischizophrenic drugs produce extrapyramidal effects, the frequency varies considerably. The piperidine phenothiazine thioridazine produces extrapyramidal side effects less frequently than chlorpromazine (*27*), and the recently introduced antipsychotic agent clozapine elicits few, if any, such side effects (Table 1) (*28*). The piperazine phenothiazines and the butyrophenones evoke a much higher incidence of extrapyramidal side effects than does chlorpromazine. These discrepancies seriously challenge the dopamine hypothesis of schizophrenia.

Recent studies of the muscarinic acetylcholine receptor in the brain may provide a resolution of this dilemma. Acetylcholine actions on smooth muscle, glands, and many sites in the brain involve receptors called "muscarinic" because they are mimicked by the alkaloid muscarine and differ from "nicotinic" acetylcholine effects on skeletal muscle and some spinal cord synapses. For more than a hundred years the belladonna alkaloids, such as atropine, which act as antagonists of muscarinic acetylcholine receptors, have been used to treat Parkinson's disease. Until the advent of L-dopa therapy to replace the dopamine deficiency in the brains of parkinsonian patients, anticholinergic drugs that act on the central nervous system constituted the major drug therapy for this disease. Anticholinergic drugs have been especially effective in combating the extrapyramidal side effects of phenothiazines. Their therapeutic efficacy apparently deflects a balance in the corpus striatum between dopamine and acetylcholine such that antagonizing acetylcholine effects is equivalent to enhancing those of dopamine, and vice versa.

Phenothiazines often produce muscarinic anticholinergic effects, such as dry mouth and difficulty in urination. Clozapine has few extrapyramidal effects, perhaps because it is a fairly potent antagonist of acetylcholine in smooth muscle (*29*). We speculate that, for all phenothiazines and butyrophenones, extrapyramidal effects vary inversely with anticholinergic potency. Certain phenothiazines may block muscarinic acetylcholine receptors in the corpus striatum, thereby attenuating the extrapyramidal side effects phenothiazines themselves evoke by means of dopamine receptor blockade. The most potent anticholinergics should evoke the fewest extrapyramidal effects; conversely, drugs with the highest incidence of the side effects should be the weakest anticholinergics.

To evaluate this hypothesis, one must be able to quantify the affinity of drugs for muscarinic cholinergic receptors in the brain. Anticholinergic effects on the periphery are readily detected by measuring smooth muscle contractions, but these contractions may not correspond precisely to relative potencies in the brain. Recently, techniques have been developed to identify biochemically the brain's muscarinic cholinergic receptor (*30, 31*). We have measured the reversible binding of 3-quinuclidinylbenzilate (QNB), a potent antagonist of muscarinic cholinergic receptors, to membrane preparations from the central nervous system. The binding of highly radioactive QNB represents an almost exclusive interaction with muscarinic cholinergic receptors (*32*).

With a simple, sensitive, and specific assay for the muscarinic cholinergic receptor in the brain, we evaluated the relative affinities of a variety of antischizophrenic drugs (Table 1 and Fig. 2). Their affinity for the muscarinic receptor in the brain correlates inversely with their tendency to elicit extrapyramidal side effects. Clozapine, which is almost devoid of these side effects, has the greatest potency, similar to that of standard anti-parkinsonism drugs. Thioridazine, which next to clozapine elicits the fewest extrapyramidal symptoms, is second



PHENOTHIAZINES

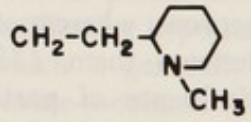
	R_1	R_2
ALKYLAMINO		
CHLORPROMAZINE (Thorazine)	Cl	$CH_2-CH_2-CH_2-N(CH_3)_2$
PROMAZINE (Sparine)	—	$CH_2-CH_2-CH_2-N(CH_3)_2$
TRIFLUPROMAZINE (Vesprin)	CF_3	$CH_2-CH_2-CH_2-N(CH_3)_2$
PIPERAZINE		
ACETOPHENAZINE (Tindal)	$COCH_3$	$CH_2-CH_2-CH_2-N\langle\rangle N-CH_2-CH_2-OH$
FLUPHENAZINE (Prolixin; Permitil)	CF_3	$CH_2-CH_2-CH_2-N\langle\rangle N-CH_2-CH_2-OH$
TRIFLUOPERAZINE (Stelazine)	CF_3	$CH_2-CH_2-CH_2-N\langle\rangle N-CH_3$
PERPHENAZINE (Trilafon)	Cl	$CH_2-CH_2-CH_2-N\langle\rangle N-CH_2-CH_2-OH$
PIPERIDINE		
THIORIDAZINE (Mellaril)	SCH_3	

Figure 2. Structures of different classes of phenothiazines. [Adapted from Snyder (84)]

most potent. The alkylamino phenothiazines, whose moderate incidence of extrapyramidal actions is greater than that of thioridazine, have correspondingly less affinity for the acetylcholine receptor. Piperazine phenothiazines and the butyrophe-

nones, whose frequency of extrapyramidal effects is greatest, have the least affinity for the muscarinic receptor. According to this formulation, when given in antischizophrenic doses, all phenothiazines and butyrophenones produce comparable dopamine receptor blockade, thus all have about the same tendency to elicit extrapyramidal side effects. Blockade of acetylcholine receptors by drugs such as clozapine and thioridazine combats these extrapyramidal effects, while, because of their negligible anticholinergic activity, the piperazine phenothiazines and butyrophenones elicit many more extrapyramidal side effects.

Amphetamines and Catecholamines

While the structural relationship between phenothiazines and the catecholamines was far from obvious, amphetamines, whose chemical structure closely resembles that of the catecholamines, have always been assumed by pharmacologists to act by way of these neurotransmitters. Which of the various dopamine and norepinephrine pathways in the brain mediates particular behavioral effects of amphetamines? In animals, one can make a discrete lesion in individual catecholamine pathways with 6-hydroxydopamine and examine the behavioral consequences. 6-Hydroxydopamine is selectively accumulated into catecholamine neurons, whereupon it autooxidizes and destroys them (*33*). After evaluating the influence of particular lesions on individual behavioral effects of amphetamines, one can make inferences about the tracts mediating the behaviors.

In relatively high doses, amphetamines elicit stereotyped compulsive behavior in animals, the exact pattern varying with different species, but often resembling a searching form of behavior. Rats, whose major means of exploring their environment is olfactory, tend to stay in one portion of the cage, sniff, lick, and especially gnaw (*34*). Cats confined to their cages become involved in repetitive sniffing motions, while less confined cats develop constant, purposeless side-to-side looking movements that may be a response to fear (*35*). Chimpanzees intoxicated with amphetamines display side-to-side looking patterns, as well as self-picking and self-grooming behavior (*36*). These effects of amphetamines closely resemble the stereotyped compulsive behavior frequently observed in addicts who consume large amounts of the drug (*37*). Amphetamine addicts have a compulsion to take objects apart, to sort the parts, and occasionally to put them back together again. Like the monkeys who, under the influence of amphetamines, constantly pick at their skin, amphetamine addicts indulge in "grooming" behavior; this behavior is generally associated with tactile hallucinations that bugs or amphetamine crystals are creeping beneath their skins. Of particular interest is a report that the stereotyped compulsive behavior appears to be an invariable concomitant of psychosis and does not occur in amphetamine addicts who do not develop psychosis (*38*).

An abundance of evidence suggests that stereotyped compulsive behavior of rodents is mediated by way of dopamine pathways in the brain. Thus, making a lesion in the substantia nigra with 6-hydroxydopamine, with complete degeneration of the nigrostriatal dopamine pathway and some loss of dopamine terminals in the nucleus accumbens and olfactory turbercle, abolishes amphetamine-induced stereotyped compulsive behavior, while locomotor stimulation by the drug continues (*39*). Lesions in the corpus striatum can abolish stereotyped behavioral effects of amphetamines (*40*). However, since the nucleus accumbens and the olfactory tubercle are adjacent to the corpus striatum, it is possible that one or the other of these areas is involved in mediating certain components of the stereotyped behavioral syndrome (*41*). Injecting

dopamine or apomorphine (which is thought to stimulate dopamine receptors) into the vicinity of the corpus striatum, nucleus accumbens, and olfactory tubercle elicits stereotyped behavior in rats (*42*).

In lower doses, amphetamines stimulate locomotor activity of rodents, an effect that has been thought to mirror the actions of amphetamines in man. Intraventricular administration of norepinephrine produces a similar locomotor activation, but dopamine is much less effective (*43*). Since the naturally occurring (−)− isomer of norepinephrine is much more potent in stimulating locomotor activity after intraventricular administration than is the (+)− isomer, it would seem that locomotor stimulation is dependent on a stimulation of norepinephrine receptors. Postsynaptic dopamine receptors differentiate less well between the isomers of norepinephrine (*44*). Drugs that block the conversion of dopamine to norepinephrine diminish the locomotor stimulant, but not the stereotyped behavioral effects of amphetamines, again suggesting that norepinephrine rather than dopamine is responsible for mediation of this behavior (*45*).

Another dramatic behavioral effect of amphetamines is their ability to greatly facilitate hypothalamic self-stimulation. Animals with electrodes in the lateral hypothalamus will press levers at astronomical rates to obtain electrical stimulation, which suggests that these areas are pleasure centers. This action of amphetamines may be related to the euphoric effects of the drug in man. Several findings indicate that norepinephrine fibers may be responsible for hypothalamic self-stimulation, as Stein suggested (*46*). The "map" for hypothalamic self-stimulation correlates with norepinephrine fiber distribution (*47*). In addition, drugs that block conversion of dopamine to norepinephrine depress hypothalamic self-stimulation (*48*). The depressed self-stimulation rates are restored to normal by intraventricularly administered (−)− norepinephrine, but not by its physiologically inactive (+)− isomer or by dopamine (*48*). There appear to be at least two distinct self-stimulation systems in the brain. Self-stimulation can also be obtained from the area of the substantia nigra, which is rich in dopamine cell bodies (*49*).

Brain lesions, which provide powerful tools for delineating neurochemical mediation of drug effects in animals, can hardly be applied to human beings. Unfortunately, there are no faithful animal models for human conditions such as schizophrenia and amphetamine psychosis. Attempts have been made to draw inferences about the involvement of individual catecholamines in human behavior by using isomers of amphetamines. Such efforts are based on the differences in relative affinities of norepinephrine and amphetamine isomers for dopamine and norepinephrine neuronal uptake systems and for norepinephrine depletion (*25, 50, 51*), although there are discrepant biochemical observations (*52*). In several studies, behavior generally thought to involve primarily norepinephrine is elicited much more efficiently by (+)− amphetamine than by (−)− amphetamine, whereas the two isomers have more similar potencies in enhancing dopamine-mediated behaviors. Thus (+)− amphetamine is seven to ten times as potent as (−)− amphetamine in facilitating hypothalamic self-stimulation, which is generally thought to be norepinephrine-mediated (*46, 53*). By contrast, the two isomers are about equal in facilitating self-stimulation in the dopaminergic substantia nigra (*49*). (+)− Amphetamine is only about twice as potent as (−)− amphetamine in evoking stereotyped behavior in rats (a dopamine-mediated behavior), whereas (+)− amphetamine is ten times as potent as (−)− amphetamine in facilitating locomotor activity (*50*). The rotating behavior of rats following unilateral lesions of the substantia nigra, a motor

activity that is determined by dopamine neuronal pathways, is facilitated to an equal extent by (+)− and (−)− isomers of amphetamine (*54*).

Behavioral effects of amphetamine isomers have been explored in man. (+)− Amphetamine is known to be about five times as potent as (−)− amphetamine in its alerting and euphoric effects, which accordingly might be hypothesized to involve predominantly norepinephrine neurons. Amphetamine isomers have been evaluated in studies of amphetamine psychosis (*10*) and schizophrenia (55) in human volunteers. In both situations, (+)− amphetamine is less than twice as potent as (−)− amphetamine in the precipitation of amphetamine psychosis in nonschizophrenics and in the florid exacerbation of schizophrenic symptoms; this suggests that both phenomena are dopamine-mediated. However, complex and conflicting biochemical data (*51, 52*) preclude firm conclusions. Interestingly, physostigmine, which inhibits acetylcholinesterase and thus increases the effects of acetylcholine, can prevent the psychosis-worsening action of the amphetamine analog methylphenidate (*55*). This suggests a balance between catecholamines and acetylcholine in modulating psychotic symptoms.

There is other evidence pointing to a primary role for dopamine in amphetamine psychosis and amphetamine exacerbation of schizophrenia. The stimulant methylphenidate is more active than amphetamine in exacerbating schizophrenic symptoms (*55*), and in certain biochemical systems it seems to have a more selective effect upon dopamine, as compared to norepinephrine, neuronal disposition (*25, 56*). L-Dopa, whose administration is followed by a considerable formation of dopamine with very little norepinephrine synthesis, exacerbates schizophrenic symptoms in a selective fashion, much like amphetamines (*57*). Although L-dopa does produce psychiatric side effects in parkinsonian patients, there are few reports of anything resembling amphetamine psychosis (*58*). It is conceivable that these results are related to the enormous doses of amphetamine (300 to 500 milligrams) required to elicit a psychosis in nonschizophrenic subjects. To obtain comparable catecholamine-enhancing effects with L-dopa would probably require much higher doses than are generally administered to parkinsonian patients. Cocaine, which facilitates the actions of both norepinephrine and dopamine, produces a psychosis that is virtually identical to amphetamine psychosis (*59*).

Amine-Related Enzymes in Schizophrenics

The relationships among the catecholamines, phenothiazines, amphetamines, and schizophrenia are tantalizing. However, one should be cautious before arguing that these relationships bear upon the hypothetical biochemical lesion in schizophrenia. None of the studies cited presents any direct evidence of a biochemical abnormality in schizophrenic patients. The effects of drugs could well be exerted at a locus extraneous to the fundamental schizophrenic abnormality. What direct evidence is there of abnormal brain chemistry in schizophrenics? Are there biochemical pathways in mammalian brains that could under any circumstances give rise to "psychotomimetic" substances?

Many reports of "abnormal" chemicals, such as adrenochrome and taraxein, in body fluids of schizophrenics have not been confirmed (*8, 60*). The reported selective occurrence of dimethoxyphenylethylamine in urine of the schizophrenics, although confirmed by some workers, has been attributed by others to drugs and diet (*60, 61*).

With reference to biogenic amines, two observations are relevant. Murphy and

Wyatt (*62*) observed a highly significant reduction in the activity of monoamine oxidase in platelets of both chronic and acute schizophrenic patients. Concentrations of this enzyme in patients were only about half those in control subjects. Platelet monoamine oxidase concentrations were uninfluenced by drug treatment, and the schizophrenic abnormalities were present in some patients who had never received these drugs. Depressed patients possessed normal enzyme activity, although some bipolar manic-depressive patients displayed monoamine oxidase levels intermediate between those of chronic schizophrenics and controls. Of particular interest is the finding that platelet monoamine oxidase activity was highly correlated in monozygotic twins, only one of whom was schizophrenic (*62*). Thus the reduction in enzyme activity is not a product of the schizophrenic illness; rather, it may provide a genetic marker for vulnerability to schizophrenia. If monoamine oxidase in the brain has the same genetic determinants as the platelet enzyme, then, on the basis of these findings, there should be decreased monoamine activity in the brains of individuals vulnerable to schizophrenia. Preliminary investigations, however, have not revealed abnormalities in monoamine oxidase in the brains of schizophrenics (*63*, *64*). The data on amphetamines and phenothiazines are consistent with an excess of dopamine-like activity in the brain, which could conceivably result from reduced monoamine oxidase activity.

Wise and Stein (*64*) have observed lower dopamine β-hydroxylase activity in the brains of schizophrenic patients than in the brains of nonschizophrenic patients. They conducted control experiments to rule out the possibility that their findings resulted from postmortem changes or from the effects of drugs ingested by the patients. As a result of lowered dopamine β-hydroxylase activity, dopamine concentrations might build up in the brains of schizophrenic patients, which again is consistent with what is known of drug actions in schizophrenia. One might also predict, based on observations of Wise and Stein, that net accumulation of norepinephrine would be deficient in the brains of schizophrenics; however, this prediction does not accord with the histochemical data of Olson (*65*), which indicate that norepinephrine fluorescence is the same in the brains of control subjects and schizophrenics.

Amine-Methylating Enzymes that Synthesize Psychotomimetic Drugs

Rather than search for quantitative changes in normal metabolic pathways in schizophrenia, one might search for enzyme systems capable of synthesizing psychotogenic compounds. The known psychedelic drugs are either *O*-methylated (for example, mescaline) or *N*-methylated (for example, dimethyltryptamine). Pollin *et al.* (*66*) observed that, of several amino acids administered to schizophrenic patients, only methionine, and sometimes tryptophan, reliably exacerbated schizophrenic symptoms. As with amphetamines, methionine appeared to worsen the actual schizophrenic symptoms rather than superimpose a toxic psychosis.

Several other investigators have confirmed these findings (*67*). Nonetheless, it is difficult to determine whether the "methionine effect" involved a stimulation of biogenic amine methylation or other quantitatively more prominent pathways of this amino acid. Axelrod (*68*) has described an enzyme in the lungs of rabbits that can transfer the methyl of *S*-adenosylmethionine (AMe) to a variety of phenethylamines and indoleamines. Unfortunately, this enzyme can only be found in rabbit lungs. Relatively feeble enzyme activities have been reported in other mammalian tissues,

Table 2. Characteristics of 5-methyltetrahydrofolic acid (MTHF) mediated amine methylation. Substrates: (i) *N*-methylation utilizes phenethylamines and indoleamines with primary or secondary amine groups (*71, 72*) (tyramine, amphetamine, dopamine, epinine, norepinephrine, normetanephrine, mescaline, tryptamine, *N*-methyltryptamine, 5-methoxytryptamine); and (ii) *O*-methylation utilizes 5-hydroxyindoleamines (*72*) [serotonin, *N,N*-dimethylserotonin (*bufotenin*)]. Affinity for substrates (*72*): MTHF, $K_m = 1 \times 10^{-5} M$; tyramine, $K_m = 1 \times 10^{-3} M$; serotonin, $K_m = 2 \times 10^{-4} M$.

	Distribution of *N*- and *O*-methylation of indoleamines in rat		
Tissue*	*O*-methylation	*N*-methylation	Ratio of *N*-methylation to *O*-methylation
Brain	97	16	0.16
Heart	145	15	0.10
Intestine	85	37	0.44
Kidney	259	31	0.12
Liver	66	60	0.91
Lung	65	0	0.0
Spleen	52	20	0.38

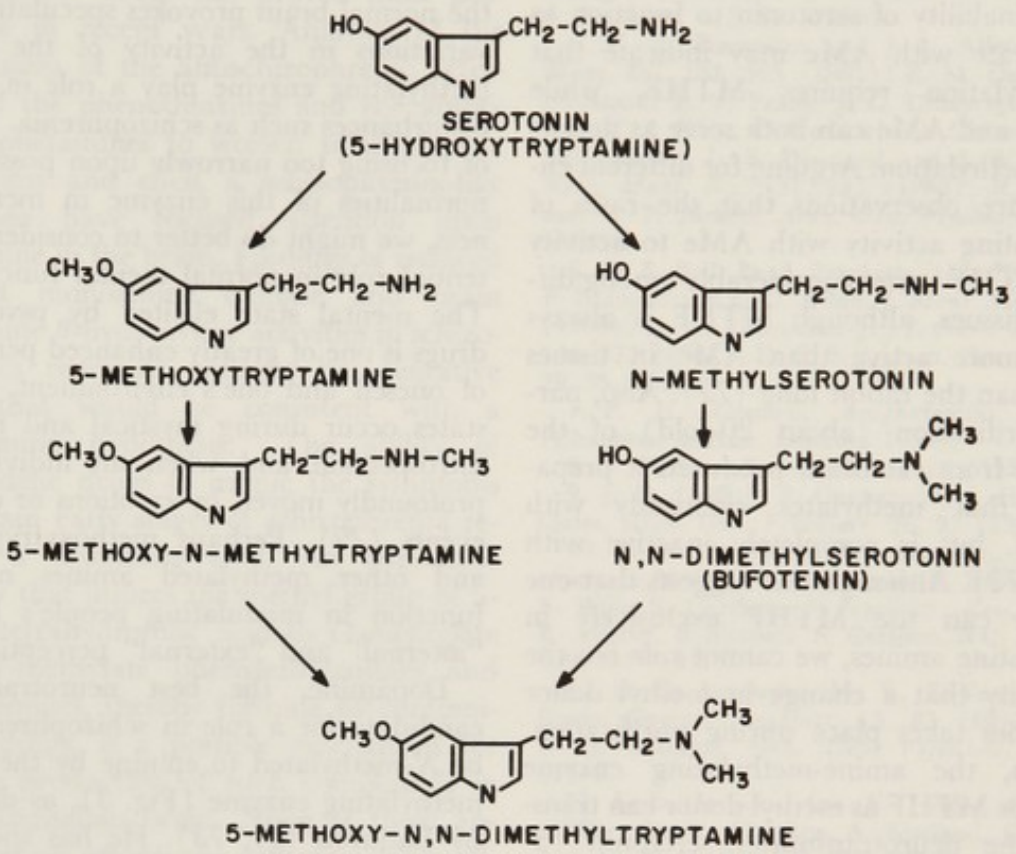
* Tissues were homogenized in ten volumes of 5 m*M* sodium phosphate buffer (*p*H 7.9). After dialysis, the solutions were centrifuged at 100,000g and the supernatants were assayed for enzyme activity. Bufotenin (5 m*M*) and 5-methoxytryptamine (5 m*M*) were substrates for *O*-methylation and *N*-methylation, respectively. [^{14}C]MTHF (20 μM) was the methyl donor. Data are presented as the mean of three experiments. Enzyme activity is expressed as picomoles of methylation per milligram of protein per hour.

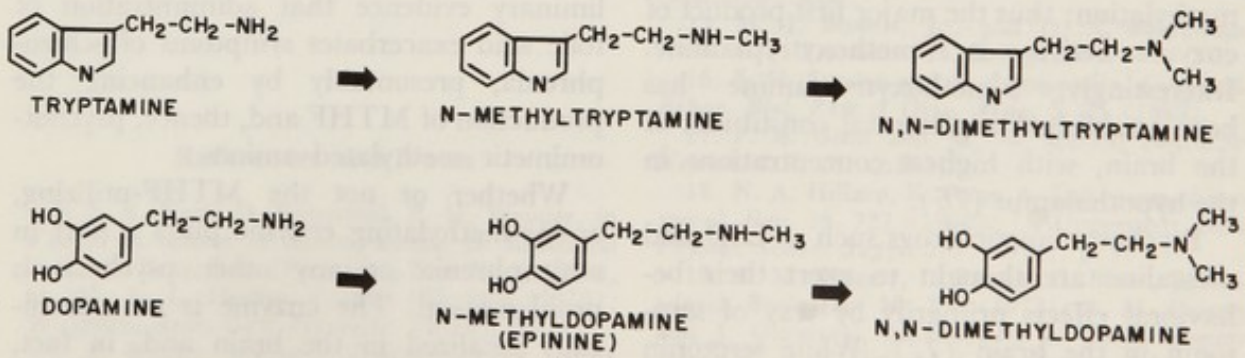
including the brain, which can *N*-methylate indoleamines and phenethylamines (*69, 70*). Saavedra *et al.* (*70*) observed that serotonin, which might be anticipated to be the naturally occurring substrate, is not methylated.

All these *N*-methylations utilize AMe as a methyl donor, although 5-methyltetrahydrofolic acid (MTHF) can serve as the methyl donor in the methylation of dopamine to epinine (*71*). We have found (*72*) that MTHF can serve as a methyl donor in the methylation of a variety of indoleamines, as well as phenethylamines (*73*) (Table 2 and Fig. 3). With MTHF as the methyl donor, this enzymatic activity is much more vigorous than it is with AMe, suggesting a more important biological role for the MTHF reaction than was evident from earlier studies with AMe. We have found amine-methylating activity in a variety of mammalian tissues, including liver and heart. The enzyme in rabbit lungs differs from that in other tissues, since it is the only one that prefers AMe as methyl donor. Both indoleamines and phenethylamines are methylated by the enzyme. No methylation of serotonin can be demonstrated with AMe, whereas with MTHF, serotonin is the best amine substrate.

Studies with AMe had revealed only *N*-methylation of biogenic amines (*68–70*). Our thin-layer chromatographic analyses in several systems showed that with MTHF, while phenethylamine, tryptamine, and 5-methoxytryptamine are methylated on the amine nitrogen, serotonin is predominantly methylated on the 5-hydroxyl group to form 5-methoxytryptamine. We confirmed the *O*-methylation of indoleamines by showing that bufotenin, in which the amine nitrogen is already fully methylated, is an active substrate and is methylated to form 5-methoxy-*N,N*-dimethyltryptamine. This is interesting because 5-methoxy-*N,N*-dimethyltryptamine is a very potent psychotomimetic drug (*74*), considerably more active than bufotenin, from which it is formed by *O*-methylation.

Figure 3. Methylation reactions of naturally occurring biogenic amines mediated by MTHF: (A) Serotonin can be both O-methylated and N-methylated: (B) N-methylation of dopamine and tryptamine.


HO
CH2-CH2-NH2
N
SEROTONIN
(5-HYDROXYTRYPTAMINE)
CH3O
CH2-CH2-NH2
5-METHOXYTRYPTAMINE
HO
CH2-CH2-NH-CH3
N-METHYLSEROTONIN
CH3O
CH2-CH2-NH-CH3
5-METHOXY-N-METHYLTRYPTAMINE
HO
CH2-CH2-N
CH3
CH3
N,N-DIMETHYLSEROTONIN
(BUFOTENIN)
CH3O
CH2-CH2-N
CH3
CH3
5-METHOXY-N,N-DIMETHYLTRYPTAMINE


CH2-CH2-NH2
TRYPTAMINE
CH2-CH2-NH-CH3
N-METHYLTRYPTAMINE
CH2-CH2-N
CH3
CH3
N,N-DIMETHYLTRYPTAMINE
HO
HO
CH2-CH2-NH2
DOPAMINE
HO
HO
CH2-CH2-NH-CH3
N-METHYLDOPAMINE
(EPININE)
HO
HO
CH2-CH2-N
CH3
CH3
N,N-DIMETHYLDOPAMINE

Indeed, it is questionable that bufotenin is a psychotomimetic drug at all, although its failure to produce psychotomimetic effects may be related to difficulty in passing the blood barrier in the brain (*75*).

The inability of serotonin to function as a substrate with AMe may indicate that *O*-methylation requires MTHF, while MTHF and AMe can both serve as donors for *N*-methylation. Arguing for different enzymes are observations that the ratio of methylating activity with AMe to activity with MTHF varies considerably among different tissues, although MTHF is always much more active than AMe in tissues other than the rabbit lung (*72*). Also, partial purification (about 20-fold) of the enzyme from rat brain produced a preparation that methylates vigorously with MTHF, but is completely inactive with AMe (*72*). Although this suggests that one enzyme can use MTHF exclusively in methylating amines, we cannot rule out the possibility that a change in methyl donor properties takes place during purification.

Thus, the amine-methylating enzyme that uses MTHF as methyl donor can transform the neurotransmitter serotonin (5-hydroxytryptamine) into psychotomimetic compounds by *O*-methylation and *N*-methylation (Fig. 3). With the enzyme preparation studied in our laboratory, *O*-methylation of serotonin greatly exceeds *N*-methylation; thus the major first product of enzyme activity is 5-methoxytryptamine. Interestingly, 5-methoxytryptamine has been established as a normal constituent of the brain, with highest concentrations in the hypothalamus (*76*).

Psychotomimetic drugs such as LSD and mescaline are thought to exert their behavioral effects primarily by way of serotonin in the brain (*77*). While serotonin is largely *O*-methylated, tryptamine, which also occurs naturally in the brain (*78*), is *N*-methylated. One of the products of this reaction, *N,N*-dimethyltryptamine (Fig. 3), is a potent psychotomimetic drug.

The fact that serotonin and tryptamine have been definitively shown to be converted to psychedelic-like compounds in the normal brain provokes speculation that variations in the activity of the amine-methylating enzyme play a role in mental disturbances such as schizophrenia. Instead of focusing too narrowly upon possible abnormalities of this enzyme in mental illness, we might do better to consider its potential role in normal mental functioning. The mental state elicited by psychedelic drugs is one of greatly enhanced perception of oneself and one's environment. Similar states occur during mystical and religious introspection and when an individual is profoundly moved by emotions or external events (*79*). Perhaps methoxytryptamine and other methylated amines normally function in modulating people's level of "internal" and "external" perception.

Dopamine, the best neurotransmitter candidate for a role in schizophrenia, can be *N*-methylated to epinine by the amine-methylating enzyme (Fig. 3), as described by Laduron (*71, 73*). He has speculated that schizophrenia arises from a defect in MTHF destruction, resulting in abnormally high MTHF levels and the resulting formation of excess amounts of psychotomimetic, methylated biogenic amines. He cites preliminary evidence that administration of folic acid exacerbates symptoms of schizophrenia, presumably by enhancing the production of MTHF and, thence, psychotomimetic methylated amines.

Whether or not the MTHF-utilizing, amine-methylating enzyme plays a part in schizophrenia or any other psychosis is problematical. The enzyme is not specifically localized in the brain and, in fact, concentrations of it in the brain are lower than those in several other tissues (*72*) (Table 2).

Concluding Remarks

Of various biochemical approaches to the study of schizophrenia, the investigation of brain neurotransmitter interactions with psychotropic drugs has proved most productive in recent years. Analyses of the mechanism of the antischizophrenic activities of the phenothiazines and the ability of amphetamines to worsen schizophrenic symptoms and elicit a schizophrenia-like psychosis have focused attention upon dopamine in the brain. Findings of reduced platelet monoamine oxidase and brain dopamine β-hydroxylase activities in schizophrenics represent enticing but tentative data that would be consistent with a "dopamine hypothesis." The ability of psychedelic drugs to mimic the symptoms of certain early stages of schizophrenia remains a promising lead. An enzymatic activity that utilizes the methyl group of 5-methyltetrahydrofolic acid to *O*-methylate and *N*-methylate phenylethylamines and indoleamines, thereby forming psychotomimetic drugs, is a possible mechanism for for the production of such compounds in the mammalian brain. None of these approaches yet affords the definitive "answer" to the riddle of schizophrenia, and roles for other neurotransmitters, such as acetylcholine (*55*) and γ-aminobutyric acid (*80*), are possible.

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prefers the naturally occurring (−)—norepinephrine isomer (*25*). In all peripheral sympathetic nervous tissues of the rat and in the iris-ciliary body of the rabbit, (+)—amphetamine, the isomer with greater stimulating effects on the central nervous system, blocks norepinephrine uptake more efficiently than (−)—amphetamine. However, in cardiovascular tissues of the rabbit, stereoselectivity is reversed, and uptake is affected more by (−)— than by (+)—amphetamine and more by (+)— than by (−)—norepinephrine (*81*). Studies in our laboratory in synaptosomal (isolated nerve terminal) preparations showed a tenfold greater affinity of (+)— than of (−)—amphetamine for the uptake process of norepinephrine neurons in the brain. Other laboratories have not detected this stereoselectivity (*52*) for reasons that are unclear but that might conceivably relate to difficulties in tissue preparation, since demonstration of stereoselective effects requires careful attention to linearity of uptake with tissue and time and the use of nonsaturating catecholamine concentrations. Dopamine neurons in the brain and retina (*25, 81*) show much less stereoselectivity than norepinephrine neurons in experiments with isomers of norepinephrine, amphetamine, or ephedrine, although distinct stereoselective effects with amphetamines and ephedrines can be demonstrated (*52, 56, 82*). Effects of amphetamines on norepinephrine uptake in vivo are more clear-cut. Inhibition of the initial accumulation of intraventricularly administered [^{3}H]-norepinephrine into norepinephrine-rich brain regions is inhibited by (+)— but not by (−)— amphetamine, while the two isomers are equally effective in reducing uptake in the corpus striatum, which is primarily dopaminergic (*50*). Since amphetamine is thought to act as much (or more) by facilitating catecholamine release as by blocking uptake, the effects of amphetamine isomers on processes presumably related mostly to release have been studied (*50, 83*). In rat and mouse brain, (+)—amphetamine is much more potent than (−)—amphetamine in depleting norepinephrine (*50*). Changes in methoxylated metabolites of norepinephrine that may be related to the release process are not affected as differentially by amphetamine isomers (*83*).

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Possible Etiology of Schizophrenia: Progressive Damage to the Noradrenergic Reward System by 6-Hydroxydopamine

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Single or repeated intraventricular injections of 6-hydroxydopamine caused marked and long-lasting deficits in brain self-stimulation and other rewarded behaviors in the rat. The behavioral deficits, as well as the depletion of brain norepinephrine induced by 6-hydroxydopamine, were prevented by prior treatment with chlorpromazine. Episodic or continuous formation of endogenous 6-hydroxydopamine in man as a result of a genetically determined enzymatic error could selectively damage the binding capacity and, eventually, the structural integrity of the noradrenergic reward mechanism. Such damage might cause the fundamental symptoms and long-term downhill course of schizophrenia.

We propose in this report a novel physiological and chemical etiology for schizophrenia. Our work is based on Thudichum's (*1*) concept that "many forms of insanity" are caused chemically by "poisons fermented within the body." The essential properties of the offending chemical have been outlined by Hollister (*2*): "In short, what is required is an endogenous toxin, highly active and highly specific in its action at minute doses, continuously produced, for which tolerance does not develop."

Current biochemical theories, which use mescaline or LSD (lysergic acid diethylamide) as a model, generally attribute hallucinogenic or psychotomimetic properties to the toxic metabolite (*3, 4*). Such formulations may be criticized on two grounds. First, in view of the chronic and even lifelong duration of schizophrenia, it seems unlikely that a mescaline-like substance would be produced in adequate quantities con-

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tinuously over many decades without the development of tolerance. Second, many authorities now question the assumption that hallucinogenic drugs induce a "model psychosis." These agents do not reproduce the fundamental symptoms of schizophrenia, and the differences between the drug states and schizophrenic reactions are easily distinguished (*5*). The wide variety of mental changes caused by the drugs, such as hallucinations and delusions, tend rather to resemble the accessory symptoms of schizophrenia.

According to Bleuler (*6*), "the fundamental symptoms consist of disturbances of association and affectivity." Specifically, this author suggests that schizophrenic associations lose their continuity because the thoughts "are not related and directed by any unifying concept of purpose or goal." At the same time, emotional responsivity is diminished and eventually reduced to indifference, so that "many schizophrenics in the later stages cease to show any affect for years and even decades." In Rado's (*7*) view, the disturbance of affect stems from the fact that the "pleasure resources are inherently deficient." Finally, Blueler and others emphasize that the course of the disease "is at times chronic, at times marked by intermittent attacks, and which can stop or retrograde at any stage, but does not permit a full *restitutio ad integrum*." A distinctive feature of our theory is that it explains both the fundamental symptoms of schizophrenia and its long-term downhill course.

Physiological (*8*), histochemical (*9*), and psychopharmacological (*10*) work has led to the suggestion (*11*) that rewarded or goal-directed behavior is controlled by a specific system of norepinephrine-containing neurons in the brain. The cells of origin of this system are localized in the lower brain stem, and the axons ascend via the medial forebrain bundle to form noradrenergic synapses in the hypothalamus, limbic system, and frontal cortex. Electrical stimulation of the medial forebrain bundle serves as a powerful reward and also elicits species-typical consummatory responses, such as feeding and copulation, which produce pleasure and permit the satisfaction of basic needs (*8*). Electrolytic lesions of the medial forebrain bundle, or pharmacological blockade of its noradrenergic function, cause severe deficits in goal-directed behavior and the loss of consummatory reactions (*12*). There is some evidence that these findings in animals may be extrapolated to man (*13*). If so, one could speculate that the two primary symptoms of schizophrenia—both the deficit in goal-directed thinking and the deficit in the capacity to experience pleasure—may be due to a chronic and at least partially irreversible impairment of the nonadrenergic reward system.

Genetic studies provide indirect support for the idea that an impairment of noradrenergic function may be involved in schizophrenia. The early impression that schizophrenia is inherited has been verified by systematic family studies and studies of adopted children (*14, 15*), which establish "the importance of genetic factors in the development of schizophrenia . . . beyond reasonable dispute" (*15*). Several modes of inheritance have been proposed, but many authorities currently favor the idea that a main gene of large effect, modified either by a second gene (*16*) or by multiple factors (*15*), is responsible for schizophrenia and borderline schizoid disorders. In any case, the conclusion that schizophrenia is hereditary necessarily implies a biochemical aberration, since no other mechanism is known for the expression of genetic traits.

Several lines of biochemical evidence suggest that 6-hydroxydopamine (2,4,5-trihydroxyphenethylamine) is the aberrant

metabolite that causes schizophrenia (*17*). This compound is an autoxidation product and metabolite of dopamine, and "its formation can occur to a significant extent in the intact animal" (*18*). 6-Hydroxydopamine induces a specific degeneration of peripheral sympathetic nerve terminals with a marked and long-lasting depletion of norepinephrine (*19*). When injected intraventricularly into the rat brain, 6-hydroxydopamine similarly causes a prolonged or permanent depletion of brain catecholamines. Only catecholamine-containing neurons are affected, and brain norepinephrine is more severely depleted than is dopamine (*20*). Electron microscopic evidence reveals that norepinephrine (but not dopamine) nerve terminals in the brain degenerate and eventually disappear after repeated doses of 6-hydroxydopamine (*21, 22*).

Surprisingly, despite the profound damage to central noradrenergic neurons, rats treated with 6-hydroxydopamine are reported to the "grossly indistinguishable" from controls "except for a slight decrease in body weight and a lack of self-grooming" (*23*). If sensitive behavioral tests are used, however, marked deficits are obtained after single or repeated doses of 6-hydroxydopamine (*24*). Behavioral tests in the unanesthetized rat also may be made more sensitive by use of permanently indwelling cannulas, which permit injection of solutions into the lateral ventricle with minimum disturbance.

In our experiments, 6-hydroxydopamine as a hydrochloride salt is dissolved in 10 μl of Ringer-Locke solution containing 0.1 percent ascorbic acid (*p*H 4.5). Control animals are injected intraventricularly with 10 μl of the vehicle solution. Under these conditions, large deficits in behavior are readily observed after administration of 6-hydroxydopamine, either in acute experiments with small doses (Table 1) or in chronic experiments with larger or repeated doses.

Most directly relevant to the present argument are studies of the chronic effects of 6-hydroxydopamine on "self-stimulation" (*8*) behavior maintained by rewarding electrical stimulation of the medial forebrain bundle (at the level of the ventromedial nucleus). A single 200-μg dose of 6-hydroxydopamine reduced the rate of self-stimulation by 58.9 percent on the first day after the injection; recovery of the rate before drug administration was incomplete over the next 5 days (Table 2). In a related experiment, seven daily doses of 25 μg caused progressive suppression of the self-stimulation rate to 67 percent of control. The suppression persisted for at

Table 1. Acute suppressant action of 6-hydroxydopamine on feeding. Rats were trained to drink milk from a graduated tube in a 45-minute test until intakes stabilized. Tests were made 3 hours after injections of 6-hydroxydopamine or the vehicle solution. First and second tests were separated by 1 week. The suppressant effects of lower doses showed evidence of tolerance in the second test.

Rat No.	Dose (μg)	Milk intake (ml)				
		No drug		Ascorbic acid vehicle	6-Hydroxydopamine	
		1st test	2nd test		1st test	2nd test
W-31	6.3	13	14.5	16	6	17
W-36	12.5	24	21.5	23	18.5	22.5
W-35	25	17	13.5	13.5	12	17.5
W-34	50	17.5	19.5	19	6	20*
W-32	100	26	22.5	30	12	13.5

* Received 6.3 μg rather than 50 μg.

Table 2. Suppressant effect of 6-hydroxydopamine on self-stimulation. A single dose of 200 μg: was injected intraventricularly 23 hours before the start of a series of six daily tests.

Treatment	Rats (No.)	Mean self-stimulation rate (% of control before drug)					
		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
6-Hydroxydopamine	5	41.1 ± 12.7*	71.2 ± 8.8*	69.2 ± 14.3	71.0 ± 18.3	65.6 ± 21.1	65.7 ± 10.9
Ascorbic acid vehicle (10 μl)	3	96.5 ± 25.3	98.6 ± 11.5	99.4 ± 8.9			

least 5 days after dosing was discontinued (Fig. 1). In a third study, an intraperitoneal injection of the monoamine oxidase inhibitor pargyline potentiated the suppressive action of a series of 400-μg doses for several days; during most of this time, the rat displayed a catatonic-like syndrome of "waxy flexibility" (Fig. 2). It is evident from these results that 6-hydroxydopamine markedly impairs self-stimulation and other rewarded behaviors. Furthermore, because the drug-induced impairment is long-lasting, it probably is caused at least in part by a selective destruction of the noradrenergic binding sites and, eventually, of the terminals of the medial forebrain bundle. It thus seems reasonable to assume that, if 6-hydroxydopamine were formed endogenously in sufficient amounts in the immediate vicinity of noradrenergic nerve endings, it would cause progressive and at least partially irreversible damage to the reward mechanism. As noted, such damage could produce the primary symptoms of schizophrenia.

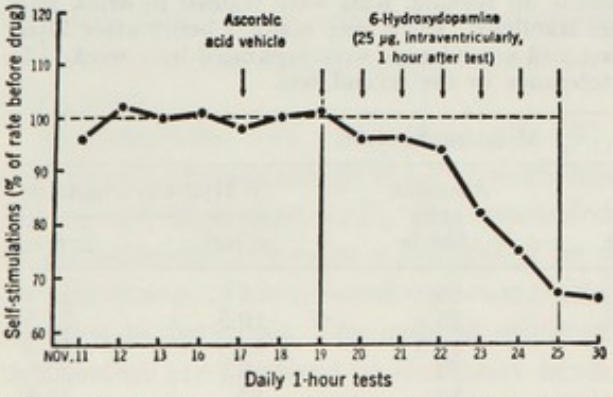

Figure 1. Suppression of self-stimulation by repeated doses of 6-hydroxydopamine (averaged data of three rats).

The isolation and identification of a specific odorous substance [*trans*-3-methyl-2-hexenoic acid (*25*)] in the sweat of schizophrenics provides a second thread of evidence that links 6-hydroxydopamine to schizophrenia. H. Smith of Wyeth Laboratories has suggested hypothetical pathways for the formation of this substance by known biochemical reactions from 6-hydroxydopamine or 2-hydroxydopamine (Fig. 3).

A third line of evidence is suggested by recent studies of Shulgin and his associates (*3*) on mescaline-like psychotomimetics. This work reveals that phenethylamine derivatives with the same 2,4,5-substitution pattern as 6-hydroxydopamine have consistently high hallucinogenic activity in man. Indeed, Shulgin *et al.* postulate that 6-hydroxydopamine may be an intermediate metabolite in the formation of a possible endogenous psychotogen, 2-hydroxy-4,5-dimethoxyphenethanolamine. Although it is not inconceivable that metabolites of 6-hydroxydopamine are hallucinogenic and therefore may contribute to the accessory symptomatology, our theory emphasizes the role of 6-hydroxydopamine itself as the agent that causes the fundamental symptoms of schizophrenia (*26*).

The fourth line of biochemical evidence derives from the observation that chlorpromazine, the drug of choice in the treatment of schizophrenia (*27*), antagonizes the norepinephrine-depleting action of 6-hydroxydopamine (*28*). Chlorpromazine

Figure 2. Induction of catatonic-like behavior ("waxy flexibility") after seven intraventricular injections of 6-hydroxydopamine (400 μg) and a single intraperitoneal injection of pargyline (100 mg/kg). In the upper portions of parts A and B, the animal was molded in the indicated postures, which were retained for at least several minutes.

is an inhibitor of the neural norepinephrine uptake process [see (*29*)]; hence, it has been assumed that chlorpromazine norepinephrine by limiting the access of 6-hydroxydopamine to the noradrenergic nerve terminal (*28*). The drug may exert its central antipsychotic effect by the same mechanism. According to this idea, chlor-

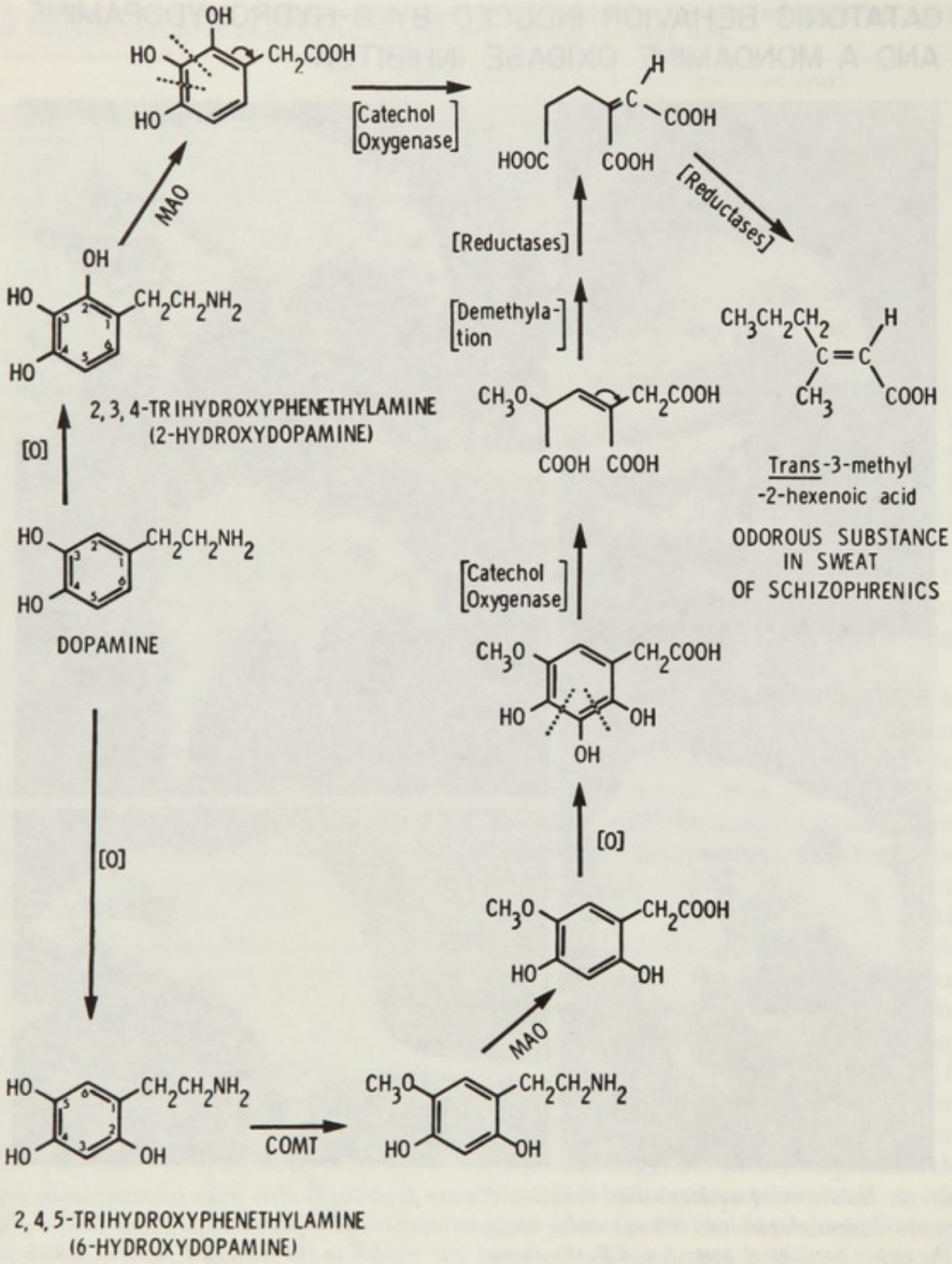

Figure 3. Hypothetical pathways for the formation of trans-*3-methyl-2-hexenoic acid from either 6- or 2-hydroxydopamine. The postulated steps involving reductases are unlikely to occur in man but may be mediated by bacteria in the skin. MAO, monoamine oxidase; COMT, catechol-O-methyl transferase.*

promazine protects the reward system of the schizophrenic by blocking the uptake of endogenously formed 6-hydroxydopamine into the noradrenergic nerve ending. Hence, although formation of 6-hydroxydopamine may continue in the chlorpromazine-treated schizophrenic, the toxic substance no longer would have entry to the vulnerable site.

As a first test of this idea, we attempted to protect self-stimulating rats from the toxic action of 6-hydroxydopamine by prior treatment with chlorpromazine. One week before the start of a 6-hydroxydopamine test series, four rats received daily intraperioneal injections of chlorpromazine hydrochloride (3 mg/kg) immediately after the self-stimulation test. Three controls were given injections of saline solution. During the next 7 days, 6-hydroxydopamine (25 μg) was administered intraventricularly to all rats 1 hour after injection of chlorpromazine or saline solution. Injections and self-stimulation tests were discontinued for a 5-day interval and were then reinstated during a second 3-day test period. Self-stimulation rates in the chlorpromazine group were not significantly reduced in either test period, whereas the rates of unprotected control animals declined progressively with successive doses of 6-hydroxydopamine (Fig. 4). We assume that the behavioral deficit in the unprotected group is due to depletion of brain norepinephrine after administration of 6-hydroxydopamine and that the absence of a deficit in the chlorpromazine group is evidence that norepinephrine levels remained substantially unchanged. These conclusions are supported by biochemical experiments, which demonstrate that chlorpromazine largely prevents the depletion of brain norepinephrine by 6-hydroxydopamine (Table 3).

The present hypothesis of the mode of action of chlorpromazine may explain why the antipsychotic effect of the drug usually takes weeks to develop and why its abrupt withdrawal usually does not cause immediate deterioration (*30*). In animal studies, after electrolytic lesions of the medial forebrain bundle (*12*) or after chemical damage by 6-hydroxydopamine (Fig. 1 and Table 2), recovery of feeding and goal-directed behavior takes place

Table 3. Prevention by chlorpromazine of 6-hydroxydopamine-induced depletion of brain norepinephrine. Chlorpromazine was injected intraperitoneally in two doses (15 and 30 mg/kg, respectively) 24 hours and 1 hour before intraventricular injection of 6-hydroxydopamine (200 μg). Control animals received two injections of saline solution before the injection of 6-hydroxydopamine. Animals were killed 5 days later.

Treatment	Rats (No.)	Mean concentration in diencephalon and forebrain			
		Norepinephrine		Dopamine	
		μg/g	% of control	μg/g	% of control
Control (no drug)	3	0.314 ± 0.024		0.923 ± 0.066	
Chlorpromazine + vehicle	3	0.329 ± 0.013	104	0.938 ± 0.183	101
Chlorpromazine + 6-hydroxydopamine (200 μg)	3	0.251 ± 0.048	80	0.812 ± 0.314	88
Saline + 6-hydroxydopamine (200 μg)	4	0.093 ± 0.007	29	1.550 ± 0.127	168
*Saline + 6-hydroxydopamine (100 μg)	4	0.103 ± 0.001	33	0.982 ± 0.025	106

* Animals received 100 μg of 6-hydroxydopamine and were killed 2 days later.

gradually over days or weeks. By analogy, recovery of normal behavior in schizophrenic patients may take weeks to develop after the toxic action of endogenous 6-hydroxydopamine has been blocked by chlorpromazine; in this regard, it is of interest to note that several days may be required for the synthesis and transport down into the terminals of new noradrenergic vesicles (*31*). Furthermore, after chlorpromazine is discontinued, deterioration should become manifest only gradually as the 6-hydroxydopamine regains entry to the noradrenergic storage sites. Finally, the hypothesis explains why chlorpromazine has reduced efficacy in "burnt-out" schizophrenics (*30*), if it is correct to assume that in these cases the noradrenergic reward terminals have suffered irreversible damage.

Taken together, the foregoing lines of evidence provide reasonable support for the theory that chemical damage to the noradrenergic reward system by endogenous 6-hydroxydopamine causes schizophrenia. If this hypothesis is correct, it would be logical to ask (i) how 6-hydroxydopamine gains access to the noradrenergic nerve endings of the reward system, and (ii) why toxic quantities of the substance are formed only in the schizophrenic and not in the normal individual.

Although one can only speculate in the absence of data, the answer to the first question may be relatively straight-forward: 6-Hydroxydopamine has access to the noradrenergic reward terminal because it is formed from dopamine in the noradrenergic nerve. After its release into the synaptic cleft, dopamine could be converted (by autoxidation or by an enzymatic reaction) to 6-hydroxydopamine, which could then be taken up by the norepinephrine uptake mechanism. In the normal brain, only negligible amounts of 6-hydroxydopamine would be formed in this way. The conversion of dopamine to norepinephrine by dopamine-β-hydroxylase normally is not

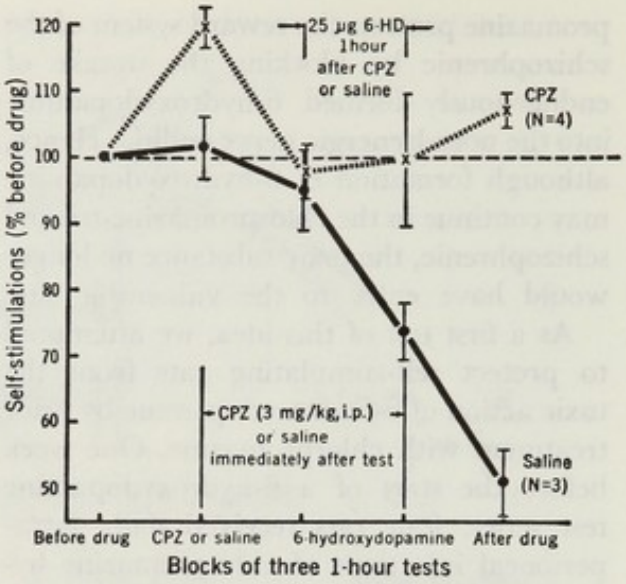

Figure 4. Prevention by chlorpromazine (CPZ) *of suppression of self-stimulation induced by 6-hydroxydopamine* (6-HD). *The means of the chlorpromazine and saline groups after drug administration differ significantly at* $P = .005$. (i.p., *intraperitoneal*).

the rate-limiting step in the synthesis of norepinephrine (*32*); hence, only a negligible amount of dopamine would be stored in noradrenergic binding sites under ordinary physiological conditions. In the schizophrenic brain, however, the step from dopamine to norepinephrine could be rate-limiting if dopamine-β-hydroxylase activity, or the capacity to induce the enzyme under stress, were drastically reduced by a pathological gene. In such a case, dopamine would be released from noradrenergic nerve endings into the synaptic cleft and converted into 6-hydroxydopamine. Continuous uptake of this substance over a long period of time could damage the binding capacity and, eventually, the structural integrity of the noradrenergic terminal (*33*) (Fig. 5).

Needless to say, other enzymatic errors also could lead to the formation of 6-hydroxydopamine in the schizophrenic brain (*34*). Some support for the dopamine-β-hydroxylase assumption is provided by the

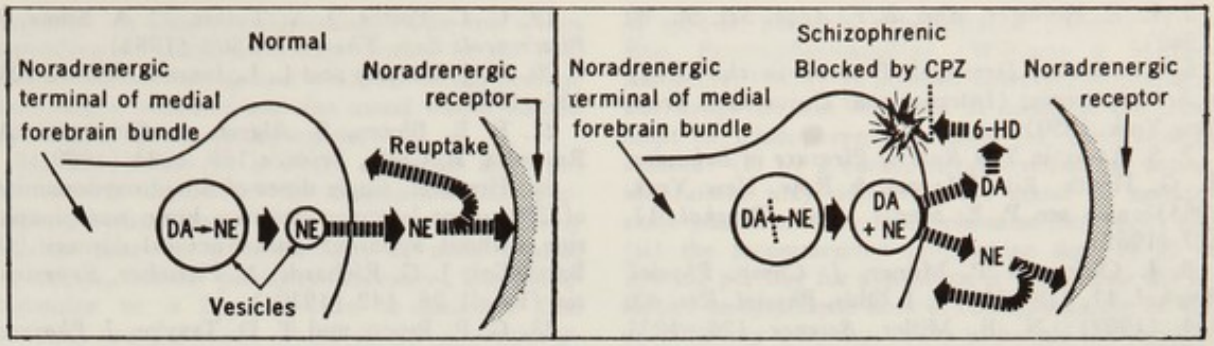

Figure 5. Postulated etiology of schizophrenia–diagram of noradrenergic transmission in normal and schizophrenic brain based on the assumption that a pathological gene for schizophrenia causes reduced activity, or synthesis, of dopamine-β-hydroxylase (34). Normal: Virtually all dopamine (DA) is converted to norepinephrine (NE) by dopamine-β-hydroxylase. Schizophrenic: Dopamine is only partially converted to norepinephrine. After release into synapse, some of the dopamine is autoxidized to 6-hydroxydopamine. When this toxic substance is taken up by the nerve terminals, it gradually destroys the vesicles and eventually the nerve endings.

observation of psychosis in alcoholics after overdoses of the dopamine-β-hydroxylase inhibitor disulfiram. According to Angst (*35*), disulfiram psychosis can be symptomatically indistinguishable from schizophrenia.

A similar process of neural damage by 6-hydroxydopamine also may be operative in endogenous depressions and Parkinson's disease. Manic-depressive psychosis has a close similarity to schizophrenia with many overlapping symptoms (*16*). Recent histochemical studies suggest that central noradrenergic neurons form two important ascending systems: a dorsal pathway, which mainly innervates the cerebral cortex and the hippocampus; and a ventral pathway, which mainly innervates the hypothalamus and the ventral parts of the limbic system (*36*). It is possible that primary damage to the dorsal system leads to thought disorders (schizophrenia), whereas primary damage to the ventral system produces affective disorders (manias and depressions). In any case, the therapeutic use of tricyclic antidepressants in endogenous depression parallels the use of phenothiazine antipsychotics in schizophrenia, and their mechanism of therapeutic action might similarly depend in part on a capacity to block the uptake of 6-hydroxydopamine into noradrenergic terminals (*28*). Moreover, as in the case of phenothiazines, the well-established delay in the onset of the therapeutic action may be explained by the time that would be required to synthesize new vesicles and transport them to active sites (*37*). Finally, in Parkinson's disease, the normal resistance of dopamine neurons to the toxic action of 6-hydroxydopamine may be weakened after viral infection or as a result of a pathological gene.

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17. Closely related compounds, such as 6-hydroxynorepinephrine and 2-hydroxydopamine, cannot yet be ruled out with certainty. 6-Hydroxynorepinephrine is extremely reactive and difficult to prepare. The biochemistry and pharmacology of 2-hydroxydopamine and other analogs of 6-hydroxydopamine are currently under investigation in collaborative studies with H. Smith and R. P. Stein of Wyeth Laboratories.

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26. Hallucinations, and possibly other accessory symptoms, might be caused by a relative predominance of serotonin systems after impairment of the norepinephrine system by 6-hydroxydopamine. See, for example, the work of G. K. Aghajanian and M. H. Sheard [*Commun. Behav. Biol.* 1, 37 (1968)] on the reduction in habituation to auditory signals after increases in serotonin activity.

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33. Early in the process, reward function may be paradoxically augmented by various mechanisms: 6-Hydroxydopamine may displace norepinephrine from its storage sites, it may potentiate the release of norepinephrine by nerve impulses, or it may promote the development of receptor supersensitivity. In this phase, one might see manic and agitated states, euphoria, paranoid delusions of grandeur, and so forth. This phase would not necessarily occur in all cases. However, in all cases, the lesioning process would progressively destroy reward capacity—sometimes intermittently, as the

formation of 6-hydroxydopamine waxes and wanes depending on stress and other factors. In the end, goal-directed thinking and behavior would become increasingly impaired and the mood would flatten, resulting in apathy or depression.

34. The theory as a whole obviously does not rest on the validity of the assumption that dopamine-β-hydroxylase is deficient. The theory merely requires that the schizophrenic, by some genetic aberration, either produces excessive 6-hydroxydopamine or is hypersensitive to amounts that normally are produced. Proof of the dopamine-β-hydroxylase assumption would require the demonstration of reduced activity (or reduced induction) of this enzyme in the schizophrenic brain relative to that of other enzymes involved in the metabolism of norepinephine.

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37. These considerations suggest that antipsychotics and antidepressants could be used interchangeably or in combination in schizophrenia and manic-depressive psychosis. In certain types of depression, such combinations (for instance, perphenazine and amitriptyline) have in fact become the treatment of choice. Tricyclic antidepressant drugs are used in schizoaffective and cyclophrenic psychoses and in the depressive hypochondriacal states of chronic paranoid schizophrenic patients [T. A. Ban, *Psychopharmacology* (Williams & Wilkins, Baltimore, 1969)]. In general, however, imipramine-like drugs are not regarded as useful in the treatment of schizophrenia, possibly for the following reasons: (i) by a noradrenergic-facilitating action, imipramine may potentiate the manic or agitated early phases of some schizophrenias [see (*33*)] and (ii) the recommended imipramine dose of 75 to 250 mg per day for depression is well below the effective antipsychotic dose of chlorpromazine of 400 to 1000 mg per day (*27*), although the median effective dose (ED_{50}) for blockade of norepinephrine depletion by 6-hydroxydopamine in mouse heart is 2.8 mg/kg for imipramine versus 1.8 for chlorpromazine (*28*). In this regard, it is interesting to note that the norepinephrine uptake inhibitor cocaine fails to antagonize the norepinephrine-depleting action of 6-hydroxydopamine (*28*).

38. We thank Herchel Smith for suggesting a pathway from a catecholamine to *trans*-3-methyl-2-hexenoic acid. His suggestion of a trihydroxydopamine intermediate helped to stimulate the idea that 6-hydroxydopamine may be the chemical cause of schizophrenia. We also thank R. P. Stein for useful discussions and the preparation of trihydroxydopamines, E. Buckley for editorial assistance, and A. T. Shropshire, N. S. Buonato, W. J. Carmint, H. C. Goldman, H. Morris, J. D. Noblitt, and L. E. Wehren for expert technical assistance.

3. Affective Disorders

Each of us has experienced depression, related either to a specific event such as the loss of a loved one or as a feeling of gloom not obviously associated with any specific life event. Most individuals are only briefly, if at all, incapacitated by such feelings. Similarly, we have all experienced feelings of elation or euphoria, usually without loss of control over our behavior. In contrast to the range of emotional states that are considered to fall within normal limits, some individuals experience marked alterations of moods that may be disabling. A profoundly depressed person may be driven to suicide by feelings of loneliness, worthlessness, and guilt. At the other extreme the overoptimistic and unrealistically self-confident manic may suffer pronounced social dysfunction. These severe and incapacitating mood states (affective disorders) will be discussed in this section.

Classification

Affective disorders are usually classified on the basis of symptoms that tend to cluster together and by the natural history of the illnesses. The two major categories of symptom-complexes associated with affective disease are depression and mania.

Depression. Depressive states are characterized by a decrease in energy and interest, feelings of worthlessness and guilt, and a sense of helplessness to alter the course of one's life. These symptoms can be accompanied by either a marked decrease in behavioral activity (psychomotor retardation) or a restlessness characterized by anxious pacing and handwringing (psychomotor agitation). Depressive states may be accompanied by reproachful delusional thoughts and hallucinations that reflect the guilt and worthless self-image of the individual. To such people the anguish may be so overwhelming that suicide appears to be a welcome avenue of escape. Severe depressions are often accompanied by bodily (somatic or vegetative) symptoms, including disturbed sleep, diminished appetite, constipation, and loss of sexual urge.

Mania. Manic states present a sharp contrast to depression. The manic usually experiences an exalted feeling of well-being and enhanced sexual interest. Thought and speech flow rapidly, as if under pressure, and ideas frequently seem superficially connected to one another (flight of ideas). The manic is often easily distractable and is,

therefore, unable to give sustained attention to a task. Perhaps the most functionally damaging aspect of this disorder is that the afflicted individual often becomes involved in grandiose plans or schemes that may assume delusional proportions. Manics characteristically have little insight into their condition and often do not recognize their behavior as unusual and potentially damaging until the episode has subsided.

Although mania and depression have frequently been conceived as opposites, a notion perhaps reinforced by the term bipolar, they may not be opposites in every respect. While certain behaviors do contrast the two states, for instance, the lack of energy in depression and the overabundance of it in mania, some evidence suggests that mania and depression can coexist at the same time in the same patient. One possibility is that these two disorders reflect different degrees of the same underlying neurochemical aberration. For example, certain findings indicate that depressed patients have an excess of intracellular sodium, and that this abnormality is even more marked in mania than in depression.[14]

The classification of affective disorders, particularly syndromes of depression, is the subject of considerable controversy. For a variety of reasons, different investigators prefer one system of classification over another. Therefore, it is necessary to become acquainted with the various diagnostic categories currently employed and their relationships to one another.

Two sets of dichotomous terms have been in common use: endogenous/exogenous (reactive) and psychotic/neurotic. Endogenous episodes of depression seem to arise spontaneously, without precipitation by any known external stress. These episodes are usually more severe than those called reactive, are marked by greater numbers of somatic symptoms, are more responsive to treatment by drugs and electroconvulsive therapy, and are less influenced by changes in the social environment and psychotherapy. Reactive (exogenous) depressions are thought to result from evident life stresses. These episodes are less frequently accompanied by severe somatic symptoms and are more responsive to changes in the social environment. The difficulty with the endogenous/reactive dichotomy is that the classification presumes that we know more about the causes of these forms of depression than we actually do. In fact, rather than being distinct entities, these disorders might better be conceived as being on a continuum.

The terms psychotic depression and neurotic depression, too, lack specificity. Generally, psychotic refers to the more severe cases (usually those called endogenous), and neurotic to the less severe cases (usually those termed reactive).

Several attempts have been made to improve the classification of affective disorders. One, in which computers were used to distinguish natural groupings of symptoms, has produced four distinct syndromes of depression: those in (1) older, psychotically depressed persons with good premorbid histories; (2) younger patients with lifelong histories of neurotic problems, least severely ill; (3) older patients with predominantly hypochondrial symptoms; and (4) a younger group with poor premorbid history, which include some schizophrenics and hysterical features.[15] Types 1 and perhaps 3 include cases usually referred to as "endogenous," while Types 2 and 4 include those frequently termed "reactive."

Another attempt at classification has involved the differentiation of primary* and

* Because the term depression is frequently used to describe a normal mood, a component of another psychiatric syndrome, or a distinctive psychiatric disorder, it has been suggested by some that the term melancholia be used exclusively for primary depression of psychiatric significance.[17,18]

secondary affective disorders.[16] Primary affective disorders are those that occur without the preexistence of other diagnosable psychiatric disorders such as schizophrenia, alcoholism, neurosis, or character disorder. No claim is made about etiology. Both "endogenous" and "reactive" are included in this category. Before the diagnosis is made, specified criteria for symptoms and their duration must be met. Within the broad category of primary affective disorder, subcategories have been distinguished, the most important of which are "bipolar," indicating that the patient has both manic and depressive episodes, and "unipolar," indicating that the patient has only one type of episode, usually depression (unipolar mania occurs rarely). Subtypes within these designations are based on course, family history, and other clinical features. Bipolar types I and II have been designated, type I referring to alternating episodes of depression and mania, and type II referring to a course of depression and hypomanic episodes.[17] Unipolar depressions have been subdivided into pure depressive disease and depressive spectrum disease on the basis of age of onset and the prevalence of other problems such as alcoholism in family members.

Secondary affective disorder refers to depression that occurs in the wake of another psychiatric problem. Thus an episode of depression in a schizophrenic person or in an alcoholic would be termed secondary affective disorder.

The major classification system used in the United States is the nomenclature of the American Psychiatric Association (*Diagnostic and Statistical Manual,* ed 2) currently under revision. The present version includes three categories of severe affective disorders: (1) manic-depressive psychosis; (2) psychotic depressive reaction; and (3) involutional melancholia.[19]

Manic-Depressive Psychosis. Manic-depressive psychosis is a mood disorder with recurring (cyclical) periods of severe depression or elation. A family history of affective disorder is frequently present. Persons with manic-depressive disease may have only periods of depression or, rarely, of elation (unipolar), or may exhibit both mood states (bipolar) during the course of the illness. Episodes of depression or mania may last for weeks or months. In rare cases depression alternates with mania as frequently as every 24 hours with clocklike precision. The intervals between episodes may be very short or may last for years. With advancing age there seems to be an increase in the frequency and severity of the episodes. In the untreated depressive phase suicide is not uncommon.

The depressive phase may be of the agitated or, more commonly, of the retarded type. In a retarded depressive phase the symptoms may range from simple psychomotor retardation to stupor. Severe depressive attacks require hospitalization.

The manic phase can also occur with varying degrees of severity. In the most severe attacks the patients may not eat or sleep for a long period of time and, if untreated, may die from exhaustion. As a result of this behavioral excitation and accompanying impairment of judgment, severe manic attacks necessitate hospitalization for appropriate medical management.

Psychotic Depressive Reaction. The characteristic feature of this category is that the onset of depression is preceded by one or more precipitating events. This usually involves a significant loss or disappointment, such as the death of a loved one, the termination of an important social relationship, or an occupational setback. Suicidal risk is

high in psychotic depressive reactions and, as a consequence, most cases require hospitalization. Without treatment the depression can last for many months, or even years.

Involutional Melancholia. This disorder occurs in the involutional period of life, between 50 and 70 years of age. The agitated form of depression is usually present and is frequently accompanied by vague bodily complaints and paranoid thinking. Life changes associated with middle age may contribute to the precipitation of this syndrome in predisposed individuals. Since there is a high suicidal risk in this disorder, most patients with involutional melancholia require hospitalization. This condition can become chronic if untreated; however, with proper treatment the prognosis is excellent.

Treatment

The treatment chosen for a patient with affective disorder depends on the nature and severity of the syndrome. Typically milder cases of depressive disorders are treated with psychological therapies, including individual, family, and group psychotherapy aimed at helping a person to understand and better cope with the psychological and environmental factors that contribute to the depression. The large majority of mildly depressed people benefit from such therapy and do not require medication or electroconvulsive therapy. The exact role of psychotherapy is hard to evaluate since many mild depressions remit spontaneously. However, there is evidence that patients receiving professional help do better than those who do not.[20] The role of medications in milder forms of depression is also difficult to evaluate. In one carefully conducted study drugs and psychotherapy each added to the improvement of depressed neurotic female outpatients. Drugs seemed to contribute mostly to the alleviation of specific symptoms, while psychotherapy improved social function.[21]

For the severe depressions—the melancholias—the consensus is that psychological treatments are inadequate by themselves, and that drugs or electroconvulsive therapy should be employed. The class of drugs most commonly used is the tricyclic antidepressants, which include imipramine (eg, Tofranil®), amitriptyline (eg, Elavil®) and their respective derivatives, desipramine (Norpramin®, Pertofane®) and protriptyline (Vivactil®). In appropriate doses these drugs will usually bring about a remission of severe depression in a period of two to three weeks in about 70% to 80% of patients. There is wide variability in the ways individuals metabolize these drugs, which may partly account for the differences in effective dosage and explain why some patients don't respond to them at all. The fact that the drugs are not clinically effective until they have been administered for two or three weeks is of both practical and theoretical importance. Theoretical implications are discussed in the following section. In practical terms more rapidly acting drugs would be desirable, as would methods that could predict whether or not a given patient would respond favorably to a course of tricyclic antidepressant medication. While amphetamine-like drugs are by themselves inadequate to treat these severe depressions effectively, they are sometimes used as adjuncts to treatment. It has also been suggested that patients who feel improved with stimulants like amphetamines will respond favorably to tricyclics.[22]

Monoamine oxidase inhibitors (MAOIs) are also clinically useful in the treatment

of depression, but appear to be effective in a smaller percentage of cases than are tricyclic antidepressants. Moreover, there are risks involved in their use, for instance, patients who eat foods containing large amounts of tyramine (such as certain cheeses) while being treated with MAOIs may develop severe headaches, elevated blood pressure and/or intracranial bleeding. In spite of the prevalent belief that the combination is particularly risky, tricyclic antidepressants and MAOIs have been used with safety and success in the treatment of very resistant depressions.[23] Certain phenothiazines may also be clinically effective antidepressants.[24]

Electroconvulsive therapy is a proved, effective method for the treatment of severe depression. Small amounts of electric current are administered either bitemporally or to the nondominant hemisphere of an anesthetized patient who has been given a muscle relaxant drug such as succinyl choline. The convulsive movements are minimal, and the risk of serious adverse effects is small. Patients usually receive a total of 8 to 12 treatments, administered every other day. In most cases improvement is evident after the fifth or sixth treatment. Memory disturbances during the period of treatment are common and may persist for several weeks or longer.[25] In some cases electroconvulsive therapy may be less risky than medication. Electroconvulsive therapy alone will result in substantial symptomatic improvement for about 80% to 90% of patients with severe depression, a higher percentage than will improve with tricyclic antidepressants (70% to 80%).

Manic episodes require pharmacological treatment or electroconvulsive therapy. The most commonly used drugs are phenothiazines such as chlorpromazine (Thorazine®), butyrophenones such as haloperidol (Haldol®), and simple salts of lithium such as lithium carbonate (Eskalith®, Lithane®). Phenothiazines and butyrophenones seem to be less specific than lithium for mania; lithium appears to have a true antimanic effect, and the underlying manic irritability and hyperarousal disappears in the responsive patient. About 70% of manic patients will respond to lithium after five to ten days of treatment.

Lithium is also effective against subsequent attacks in bipolar patients. In some cases continued lithium treatment eliminates subsequent clinically significant attacks of either mania or depression. In other cases the severity of the attacks is greatly diminished although mood swings may still be evident. Lithium is also useful in the prophylaxis of some recurrent unipolar depression.[26]

Reading Selections

The evidence for a biochemical defect or "lesion" in affective illness comes from research in a number of areas including behavioral genetics, neurochemistry, and clinical pharmacology.

Genetics. There is general agreement that a significantly higher incidence of affective disorders occurs in the relatives of afflicted individuals than in the general population. Although such evidence is provocative, it does not unequivocally indicate a genetic role because closely related individuals are likely to be exposed to similar environments.

In spite of the difficulty in separating genetic from environmental factors, recent research strongly supports the view that there is a genetic component associated with at least some forms of affective illness. Much of this evidence is reviewed in the article entitled *Toward a Biology of Affective Disorders* by Gershon, Dunner, and Goodwin. Classifications of illness that take into account inherited behavioral patterns may prove useful from

the point of view of clinical prediction and therapy. In this regard Gershon et al discuss evidence suggesting that unipolar and bipolar affective diseases are genetically separate entities.

Much of this evidence is discussed in terms of heritability. Heritability (h^2) is a measure of the contribution of genetic factors to the variability in the expression of a trait in a given population: $h^2 = 1.00$ implies that heredity is the sole determinant of the illness. Conversely, $h^2 = 0$ means that only environmental factors are relevant in determining the presence or absence and severity of a disorder. Gershon et al conclude that certain types of affective disorders are due primarily to genetic differences, the heritability having been calculated at relatively close to 1.

Currently, considerable attention is given to the possibility that manic-depressive disease involves sex-linked inheritances in at least some instances. In a number of families a high concordance for manic-depressive disease has been demonstrated between mothers and their sons or daughters, but not between fathers and their sons,[27] suggesting transmission through the X chromosome. Moreover, associations have been demonstrated between transmission of manic-depressive disease and other genetic markers on the X chromosome, specifically Xg blood type, and, in some families, protan or deutan forms of colorblindness.[28] Other studies have demonstrated different patterns of transmission of manic-depressive disease, including transmission from father to son.[29] It may be that several distinct genotypic patterns exist for manic-depressive disease.

Catecholamines (CAs). Following the suggestion by W. B. Cannon in the early 1900s that adrenalin (epinephrine) was secreted in response to stimuli that provoked affective reactions in experimental animals, numerous scientists have studied the relationship between biogenic amines and emotional state. The putative brain neurotransmitters dopamine (DA) and norepinephrine (NE)—both CAs—and the indoleamine serotonin (5HT) are the biogenic amines that have been most extensively studied. The study of NE has been facilitated because NE also functions as a transmitter in the peripheral sympathetic nervous system, which is more accessible than the brain to experimental analysis.

Localization of the CAs and 5HT in specific central nervous system (CNS) neuronal pathways has been made possible by fluorescence microscopy, a technique that involves conversion of these neurotransmitters to fluorescent derivatives, which can be directly visualized under the microscope. Three well-defined DA pathways have been mapped in the CNS, the most extensively studied being the nigrostriatal, which appears to be involved in the regulation of motor activity. Damage to the substantia nigra in which the cell bodies for this pathway are located has been shown to result in Parkinson's disease.[30] Pathways consisting of NE-containing neurons originate in compact cell body groups in the brainstem and give rise to diffuse projections that ascend to the hypothalamus and other areas of the limbic system, as well as to the cerebral and cerebellar cortices. The diffuse projections of noradrenergic neurons suggest that these systems modulate such generalized functions as levels of arousal or consciousness. Moreover, since there are apparently a number of separate DA and NE pathways, each may subserve different behavioral functions.

The CAs are synthesized from the amino acid L-tyrosine, which is actively transported into the brain from the general circulation. Tyrosine is hydroxylated by the enzyme tyrosine hydroxylase (the rate-limiting step in CA biosynthesis[31]) to dihydroxyphenylala-

nine (DOPA). DOPA is decarboxylated to DA by L-aromatic amino acid decarboxylase in both DA and NE neurons. In NE neurons, DA is further hydroxylated on the β carbon of the side chain by dopamine-β-hydroxylase to form NE. Norepinephrine that is not protected by storage in vesicles is deaminated by the mitochondrial enzyme monoamine oxidase (MAO) and eventually converted to vanillymandelic acid (VMA) (for schematic of biosynthetic pathway, see page 170).

When an electrical impulse reaches the nerve ending, the CA neurotransmitter is released from storage vesicles into the space between two adjacent neurons, the synaptic cleft. The released CAs initiate electrical impulses by activating receptors on the postsynaptic neuron. After release NE can be inactivated by several routes. It can diffuse away from the area of the synapse, be reabsorbed from the synaptic cleft into the nerve ending by a process called reuptake inactivation, or converted into normetanephrine by the enzyme catechol-*O*-methyltransferase (COMT). Normetanephrine in the CNS is further metabolized by MAO to 3-methoxy-4-hydroxyphenyl-glycol (MHPG), which is considered a major brain metabolite of released NE. A metabolite of released DA, homovanillic acid (HVA), has often been used as a measure of functional DA activity in the brain (for schematic of CA metabolism, see pages 171 and 183).

The research strategy underlying many studies of the relationship between brain CA or 5HT metabolism and behavior, called the pharmacological bridge,[32] involves an examination of the effects of psychoactive drugs on the brain chemistry of animals. It is assumed that these effects reflect similar biochemical changes in humans and could thus provide insight into changes in brain metabolism underlying emotional illness. Psychoactive drugs used in such studies include reserpine, lithium, monoamine oxidase inhibitors, tricyclic antidepressants, and amphetamine.

Reserpine can produce a clinical syndrome resembling endogenous depression and has also been used to treat mania. Lithium is the most effective drug available for the treatment of mania. Both of these drugs appear to decrease CA activity.[33,34] In contrast, monoamine oxidase inhibitors, tricyclic antidepressants, and amphetamine, all of which possess antidepressant properties and in some cases produce elation, appear to facilitate central catecholaminergic transmission.[35]

Because the psychoactive drugs that appear to decrease the functional level of CAs produce depression or have an antimanic effect, whereas drugs that increase catecholaminergic activity have an antidepressant effect or produce elation, it has been suggested that depression may be caused by a deficiency and mania by an excess of CAs.[33] This hypothesis, an historical milestone in the evolution of biochemical psychiatry is discussed at length in the article by Schildkraut entitled *The Catecholamine Hypothesis of Affective Disorders.*

In spite of the evidence in support of this hypothesis, some findings are inconsistent with the view that NE produces behavioral stimulation. A number of studies have reported that direct administration of NE into the brain results in a behavioral state variously described as somnolence, anesthesia, or depression.[36] However, in those studies the behavioral depression was observed after single injections of large doses of NE, so the effects may not reflect the natural role of NE in behavior. In fact, in one study in which relatively low doses of NE were gradually administered into the brains of animals, the NE produced a dose-related increase in behavioral activity,[37] a finding consistent with the proposal that an increase in functional NE in the brain produces behavioral excitation.

Support for the CA hypothesis has also been obtained from clinical studies. For ex-

ample, Rosenblatt and Chanley[38] found a significant correlation between inhibition of NE reuptake inactivation (as measured by increases in urinary normetanephrine) and antidepressive response to imipramine. In another study Nies, Robinson, Ravaris et al[39] observed significantly higher levels of blood platelet MAO in patients with endogenous depression. If platelet MAO activity accurately reflects the activity of this enzyme in brain CA neurons, then an increase in MAO activity would produce a decrease in the level of CAs. However, since the correlation between platelet MAO activity and central nervous system MAO activity is not clear, cautious interpretation of these data is warranted.

Data from some clinical studies have challenged various aspects of the original CA hypothesis. In the article entitled *L-DOPA, Catecholamines, and Behavior: A Clinical and Biochemical Study in Depressed Patients,* Goodwin, Murphy, Brodie, and Bunney show that a procedure that presumably increased brain CA levels, alleviated depression in only a small subgroup of depressed patients. These investigators used the "precursor load" strategy to increase central nervous system CA levels (see Mendels, Stinnett, Burns et al[40] for a review of studies using the precursor load strategy). This strategy is based on the fact that L-DOPA, the amino acid precursor of DA and NE, crosses the physiological blood-brain barrier to a significantly greater extent than the neurotransmitters themselves.[41] Therefore, systemic administration of L-DOPA is much more effective in increasing brain CA levels than is the administration of DA or NE. The data from Goodwin et al suggest that (1) the CA hypothesis may be applicable to only a subgroup of depressed patients; and (2) mania and depression can coexist.

Other investigators have questioned the original CA hypothesis on conceptual and methodological grounds, as discussed in the article by Shopsin, Wilk, Samananthan, Gershon, and Davis, entitled *Catecholamines and Affective Disorders Revised: A Critical Assessment.* For example, these authors discuss evidence for elevated plasma CA concentrations in depressed patients. However, because the correlation between peripheral and central CA activity is uncertain, interpretation of all such data is open to question.

Measurements of HVA and MHPG in cerebrospinal fluid (CSF) are currently accepted as the most accurate indices of central DA and NE activity. Yet Shopsin et al suggest that low levels of HVA in the CSF of depressed patients cannot be interpreted as specific for depression because low HVA levels occur in a number of other illnesses such as Parkinson's disease and amytrophic lateral sclerosis. Moreover, Shopsin and his colleagues found no correlation between MHPG in the CSF and urine of patients with amphetamine-induced mood changes, and they point out that urinary MHPG in patients with affective illness probably does not accurately reflect central CA activity.

Nevertheless, some evidence indicates that depressed patients with low levels of MHPG in the urine respond well to imipramine or desmethylimipramine, whereas patients with high urinary MHPG levels respond better to another tricyclic, amitriptyline.[42–44] Therefore, urinary MHPG levels might prove to be valuable in predicting responses to tricyclic compounds and, in fact, may serve as an index of different kinds of depression, only certain of which may be caused by a deficiency in CAs.

Some recent data indicates that although acute administration of antidepressant drugs may facilitate catecholaminergic activity, chronic administration of these drugs (typically required for therapeutic efficacy) may have an opposite effect. One group reported a significant decrease in urinary MHPG excretion after three to four weeks of tricyclic therapy.[44] This observation is consistent with animal data that show chronic tricyclic administration decreases the activity of brain tyrosine hydroxylase, the rate-limiting

enzyme in CA biosynthesis. On the basis of this evidence, Segal and his colleagues have suggested (contrary to the original CA hypothesis) that antidepressant effects may result from a decrease in central catecholaminergic activity.[45–47] Whybrow and Mendels[48] present neurophysiological evidence for a state of hyperexcitability and hyperactivity in depression that is also consistent with this interpretation.

Serotonin (5HT). The cell bodies of 5HT-containing neurons are located in specific brainstem nuclei (raphe nuclei). Diffuse axonal projections of the raphe nuclei extend to many regions of the CNS, including hypothalamus, forebrain, and spinal cord. In general, the distribution of 5HT in the brain is similar to that of NE. The diffuse axonal projections suggest that 5HT, like NE, subserves such generalized functions in the brain as modulating levels of arousal or consciousness.

Serotonin is synthesized from the amino acid L-tryptophan, which, like L-tyrosine, is actively transported into the brain. This amino acid is subsequently hydroxylated by tryptophan hydroxylase to 5-hydroxytroptophan (5HTP); 5HTP is decarboxylated to 5HT. Serotonin is metabolized to 5-hydroxyindoleacetic acid (5HIAA) by MAO and, as with CAs, reuptake appears to be the primary means of inactivation after 5HT release (for schematic of 5HT biosynthesis and metabolism see page 223).

Pharmacological studies suggest that 5HT may also be involved in the regulation of emotional state. For example, reserpine reduces 5HT levels, presumably by impairing its storage.[33] Although the nature of the lithium effect on 5HT is still controversial, several groups have presented evidence consistent with increased 5HT activity in the brains of lithium-treated animals.[49, 50] Monoamine oxidase inhibitors increase 5HT by blocking its metabolism to 5HIAA, while imipramine and the related antidepressant amitriptyline have been reported to block reuptake inactivation of 5HT. On the basis of these and other pharmacological effects of psychoactive drugs on central 5HT mechanisms, a hypothesis has evolved that postulates that at least some forms of depression may be caused by a decrease in central serotonergic activity. This view is supported by recent evidence of a decrease in CSF 5HIAA in a subgroup of depressed patients.[51,52] Some data indicate that a decrease in central serotonergic activity may also be responsible for mania.[51,53]

In the article entitled *Indoleamines and Affective Disorders,* Coppen reviews clinical evidence consistent with a role for 5HT in affective illness. Much of this evidence, obtained by measuring 5HIAA levels in the CSF of depressed patients and 5HT in the autopsied brains of individuals who had committed suicide, indicates that central 5HT activity is decreased in depression and possibly in mania as well. However, measures of 5HIAA in the CSF also suggests that the activity of 5HT neurons may remain low after recovery from the affective illness. In an effort to explain these observations and to speculate on the possible interaction between 5HT and CAs, it was proposed that in the presence of low CNS 5HT activity an excess of CA activity might produce mania, whereas a deficit might produce depression.[51,54] However, some recent evidence is not consonant with this hypothesis. Friedman and his coworkers[55] reported that patients whose depressions improved during treatment with imipramine again became depressed when synthesis of 5HT, but not CAs, was inhibited. From their data it could be argued that decreased 5HT activity may be pathogenetically more important than CAs in some types of affective illness.

If there is a deficiency in brain 5HT in affective disease, then L-tryptophan might

be an effective antidepressant. The administration of L-tryptophan to increase central 5HT (the precursor load strategy) is necessary because 5HT, like NE, does not readily cross the blood-brain barrier. L-tryptophan has been reported in some studies to have an antidepressive effect alone or to potentiate the antidepressant action of the MAOIs.[56] One group has also reported a reduction in manic symptoms in patients treated with L-tryptophan.[51]

Evidence for a functional deficiency in brain 5HT and an antidepressive and perhaps an antimanic effect for L-tryptophan is consistent with a role for 5HT in the etiology of affective illness. However, some investigators have failed to confirm these findings.[41,57] Therefore, conclusions regarding the involvement of 5HT in all forms of depression and mania would be premature at this time.

Acetylcholine (ACh). Acetylcholine is a naturally occurring compound that fulfills all the criteria for a transmitter substance at neuromuscular junctions and in the autonomic nervous system.[58] In addition, ACh probably functions as a transmitter substance in the brain.[59] Evidence of a role for central cholinergic systems in the regulation of emotion is reviewed by Janowsky, El-Yousef, Davis, and Sekerke in the article entitled *A Cholinergic-Adrenergic Hypothesis of Mania and Depression.* For example, the drug physostigmine increases ACh levels by inhibiting acetylcholinesterase, the degradative enzyme in ACh metabolism. This drug has been found to decrease mania and increase depression in some psychiatric patients and to produce an anergic syndrome consisting of apathy, slowed thought processes, and decreased locomotion in nonpsychiatric controls. These effects appear to be mediated centrally since they could not be reproduced by the acetylcholinesterase inhibitor neostigmine, which cannot cross the blood-brain barrier to any significant extent. Therefore, Janowsky and his colleagues suggest that increased central cholinergic activity may be etiologically significant in depression.

These investigators postulate that a disturbance in the balance between central catecholaminergic and cholinergic systems may be responsible for mania and depression. In support of this view is the observation that physostigmine reverses the manic-like symptoms (increase in talkativeness and social interactions) produced by the stimulant methylphenidate; methylphenidate allegedly increases catecholaminergic activity by releasing CAs. Conversely, methylphenidate reverses the depression and psychomotor retardation produced by physostigmine. In addition, some reports suggest that such anticholinergic compounds as atropine have an antidepressive effect and may also produce euphoria. A relationship between ACh and NE is also supported by animal data that indicate behavioral excitation results from increased central CA activity, and behavioral suppression results from increased cholinergic activity.

It is not apparent how this model as originally proposed would deal with the clinical observation that mania and depression may coexist. Furthermore, since central 5HT systems appear to have some role in the regulation of mood states, the concept of CA-ACh balance needs expansion to integrate the possible influence of brain 5HT. Still, the suggestion that affective illness may be due to an imbalance between two or more brain neurotransmitter systems is of considerable heuristic value and is currently the focus of much research.

Toward a Biology of Affective Disorders

Genetic Contributions

Elliot S. Gershon, MD; David L. Dunner, MD; and Frederick K. Goodwin, MD

The role of heredity in the major psychiatric disorders and the incorporation of genetic knowledge into related clinical and biologic research continue to be problematic issues for contemporary psychiatric thought. The purpose of this communication is to outline the current status of genetic knowledge in the affective disorders and to apply this knowledge to recent developments in the phenomenology, etiology, and treatment of these disorders. Four areas will be considered: First, the evidence for a genetic factor in affective illness; second, the relative contribution of genetic and nongenetic factors in determining who will manifest an affective disorder ("heritability"); third, genetic contributions to nosology and to the clinical and biological phenomenology of affective illness; and fourth, the mode of genetic transmission of the predisposition to these disorders. Some implications of genetic knowledge for future biologic research in affective disorders will be discussed.

Evidence for a Genetic Factor

A genetic hypothesis in human disorders is supported by evidence of excessively high rates of illness in persons with a specifiable genetic relationship to known patients, for which nongenetic explanations do not appear tenable. The available data from family history studies in affective disorders have been the subject of recent reviews.[1-6] A consistently high lifetime prevalence of affective disorders has been found in first degree relatives (parents, sibs, and children) of patients with affective disorder, as compared with the general population.[1,4] As would be expected in a genetically determined disorder, comparisons of the rate of concordance in twin studies have consistently revealed a much higher concordance rate for affective disorders in monozygotic (MZ) twins than in dizygotic (DZ) twins. In the six twin studies reviewed by Zerbin-Rudin,[4] the overall concordance was 74% for MZ twins and 19% for DZ twins (Table 1). The recent report of preliminary findings by Pollin, et al[7] is not included in Table 1 because their sample has not yet passed through a major part of the age of risk. At ages 38 to 48, only one of 23 MZ pairs were concordant for affective illness. The definitive results of this study are awaited with interest.

The use of twin data as evidence for a genetic factor depends on certain assumptions: First, that being a twin does not it-

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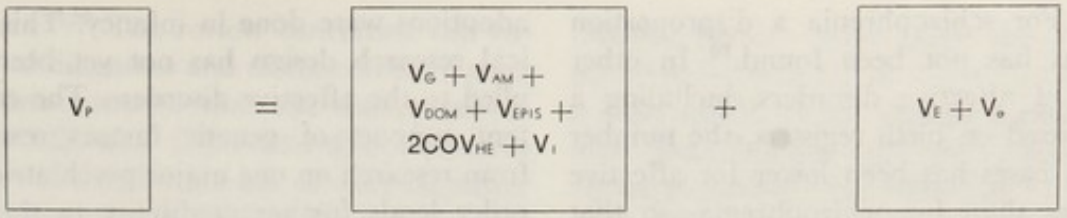

V_P = phenotypic variance in the population
V_G = genic (additive, polygenic) variance
V_{AM} = variance due to assortative mating ($V_{AM} = 0$ if mating is genetically random)
V_{DOM} = variance due to dominance
V_{EPIS} = epistaxis (interaction among genes at two or more loci)
V_E = environmental variance
COV_{HE} = covariance of heredity and environment
V_I = true statistical interaction of genetic and environmental factors
V_e = error of measurement (unreliability)

Heritable and nonheritable components of phenotypic variance in a population (adapted from Jensen[33]).

Table 1. Heritability of affective disorders*

Investigator	Monozygotic Pairs	Monozygotic % Concordant	Dizygotic Pairs	Dizygotic % Concordant	Heritability
Luxenberger (1930)	4	75.0	13	0	1.74
Rosanoff (1935)	23	69.6	67	16.4	1.08
Kallmann (1954)	27	92.6	55	23.6	1.16
Slater (1953)	7	57.1	17	23.5	0.70
Da Fonesca (1959)	21	71.4	39	38.5	0.56
Harvald & Hauge (1965)	10	50.0	39	2.6	1.23

* Twin data adapted from Zerbin-Rudin; (4,11,25,26,42,102,154) calculation of heritability by twin method of Jensen. Data not corrected for age.

self make one more liable to affective disorder; second, that the increased similarity between members of an MZ twin pair (as opposed to a DZ pair) is due to genetic rather than other factors; and third, that the methodological problems inherent in twin data do not significantly distort the concordance rates. These general assumptions have been the subject of several criticisms. It has been argued that being an MZ twin might itself increase the liability to major psychiatric disorders.[8] If so, one would expect a disproportionate representation of such twins in schizophrenic and in affective samples. An excess of twins was found in one study of hospitalized patients with affective illness, as compared with controls.[9] Because of the incidence of death in infancy in the co-twins, however, the number of twin patients with co-twins who reached the age of risk for affective disorder was not different from the control

group. For schizophrenia a disproportion of twins has not been found.[10] In other studies of affective disorders, including a study based on birth registers, the number of twin cases has been lower for affective disorders than for schizophrenia, so that twins are not disproportionally represented.[1,11]

Second, there are similarities in the environment of twins which could lead to psychological similarities independent of genetic factors. An attempt to demonstrate socioenvironmental factors in MZ-DZ differences in twins reared together was inconclusive.[12] Although similarities in environment do exist, it is difficult to explain the difference in concordance rates between MZ and DZ twins on this basis, in view of data that parents commonly misidentify MZ and DZ twins, and in view of high concordance of abilities and personality traits in twins, even when reared apart.[13–15] Valuable evidence of familial environment is contained in studies of MZ twins reared apart. A collation of case reports in the literature of affective disorder in 12 MZ twin pairs reared apart indicates a concordance rate similar to that in the other reported series of MZ twins.[3] Similar data have been reported for schizophrenia[16] and for intelligence.[14] These data indicate that psychiatric disorders and psychological variables can be very similar in related individuals as a result of genetic factors. The psychiatric similarities between MZ twins with affective disorder are compatible with this principle.

Critical evidence has recently been presented for schizophrenia which may differentiate genetic factors from postinfancy environmental factors in producing the disorder.[17–21] A consistently high rate of schizophrenia and related disorders is found in adopted children whose biologic parents are schizophrenic, as compared with adopted children of controls. Presumably this is due to genetic factors, since the adoptions were done in infancy. This critical research design has not yet been applied to the affective disorders. The consistent support of genetic factors resulting from research on one major psychiatric disorder lends further credibility to the evidence for a genetic factor in the other.

It is generally accepted that twin concordance studies represent crucial evidence for accepting or rejecting the genetic hypothesis. Consequently, the studies reporting these data in affective disorders and in schizophrenia have been the subject of critical methodologic review. It has been suggested that the high MZ concordance rates might reflect artifacts introduced by: (1) use of the proband method, ie, concordant twin pairs may be counted twice, (2) use of age correction, (3) incorrect diagnosis of zygosity or of psychiatric disorder, or (4) weighting of samples with severe (hospitalized) cases.[22–24] Although these criticisms have merit, the quantitative effect of these factors is small. Shields,[21] reviewing each of these criticisms, makes several observations. (1) Use of the proband method, which occurs only in the studies of Luxenberger and Slater,[25,26] had the effect of increasing the monozygotic concordance rates for schizophrenia only slightly (from 58% to 64% and from 65% to 68% in the two studies respectively). (2) Nonage-corrected data, which represents a minimal estimate of concordance, still show very high monozygotic concordance. (Age corrections are not used in statistical calculations in the present paper.) (3) Diagnosis of zygosity or of affective disorder apparently does not present a statistically important difficulty in those studies where the investigators did a careful review of the clinical features of the reported cases.[27,28] For example, the original case material of Kallmann (who reported uncorrected MZ concordance of 92.6% in affective disorders and 69% in schizophrenia) has been recently reviewed by other prominent inves-

tigators.[16,29] The review concerned the validity of diagnoses and of concordance rates and demonstrated that the difference between MZ and DZ concordance rates is preserved despite the use of very stringent diagnostic criteria applied by independent investigators. (4) Concordance may be higher in the more severely ill (hospitalized) cases in schizophrenia.[22,23] This would limit the applicability of the schizophrenia concordance rates to the severe (hospitalizable) cases in a population. In affective disorders, the relation of severity to concordance has not been investigated.

The use of birth register data avoids sampling artifacts introduced in generalizing from hospital samples to the population served by the hospital. The Harvald and Hauge study,[11] which is based on all registered male twin births in Denmark between 1870 and 1910, shows a large difference between MZ and DZ concordance rates in affective disorders (50.0% vs 2.6%). The MZ concordance of 50% is lower, but of the same order of magnitude as in several studies of hospital admissions (Table 1). Slater concludes from this that the use of samples of hospitalized patients does not produce misleading concordance rates for testing the genetic hypothesis, since the great excess of MZ concordance over DZ concordance is preserved.[16] The true concordance rates, however, may be lower than reported in the earlier studies.

It is in the nature of genetic studies in human characteristics that the initial demonstration of genetic etiology will often rest on epidemiologic and statistical studies of sets of relatives, which are then tested for congruence with genetic models. The data on affective disorders in twins and relatives of probands are compatible with a genetic factor in affective disorders according to accepted models, although the issue is not yet resolved.[2,30,31] Further goals in the development of the genetic hypothesis include demonstration of genetic markers which identify persons who carry the affective genotype(s) or parts of it, establishment of a valid model of the genetic transmission, and identification of the abnormality (pathophysiologic or psychologic) that is genetically transmitted.

Heritability

Since genetic factors apparently do play a role in the etiology of affective disorders, the question of how much of a role becomes of much interest. The relative contribution of genetic and nongenetic factors in accounting for the probability of an individual developing affective illness during his lifetime may be referred to as the heritability of affective illness.[32–36]

Measurement of the heritability of affective disorder would allow quantitative estimation of the maximum possible independent contribution of nongenetic factors. As is discussed below, heritability in the affective disorders is apparently quite high, accounting for at least one half of the total variance. One important implication is that, to the extent to which the type of relationship with the parents and other life experiences are not genetically determined, they can play only a relatively limited independent role in determining who will develop affective illness.

Heritability refers only to the relative contribution of existing genetic and environmental factors in the particular population studied. If there were a treatment in use which could prevent the development of affective illness, the heritability of the illness would be diminished in that population. In a sample which contains a mixture of disorders, such as inherited and noninherited forms of the same disorder, the heritability estimated would be a mean value, weighted by the relative contribution of the several disorders to the sample studied.

Two methods for estimating heritability

of a trait in a population have been recently developed. Jensen's method is based on twin concordance rates, and Falconer's is based on the difference between the population incidence and the incidence in relatives of probands.[32,37,38] These methods can be applied to the existing data on twin concordance, although several assumptions are necessary in making this computation.

A polygenic model serves as a convenient initial approximation for calculating heritability. The estimates presented here, following Jensen and Falconer, have a common underlying model of a population in which an illness is found to which genetic factors are contributing. In this model population there is random distribution of genes which could lead to affective illness. Each member of this population has a liability to affective disorder which is directly proportional to the number of "affective genes" which he possesses. The variability in who actually manifests the illness also reflects factors other than genetic, and these other factors may vary independently of the genetic factors, or may interact with them. Mating occurs at random with respect to persons carrying the genes of interest (that is, no assortative mating occurs).

This model is an additive variance polygenic model of affective illness. Heritability is defined as the proportion of phenotypic variance within that population which is attributable to genotypic variance.[32–36] That is, if heritable factors account for a quantifiable fraction of the total variance in affective illness within the population, then independent environmental and random influences account for the remaining fractions of the variance.

The components which make up the total phenotypic variance are depicted in the Figure, which is adopted from Jensen.[33] Each of the components represents a specific and quantifiable contribution to the total variance. The data needed to quantify the contribution of each component could be assembled by existing research techniques, but most of this data collection remains to be done. To calculate heritability in this communication, we have used computational models which are applicable to existing data on affective disorders (from twin studies, family history studies, and studies of population incidence) although these models do not separate out each of the components of heritability. For example, interaction and covariance between genetic and environmental factors are accounted for as part of the heritable variance in the computational models used here. The most rigorous definition of the genetic variance in a population would also account for nonpolygenic nonadditive factors, such as the presence of major genes, dominance, assortative mating (genetically nonrandom mating), and epistaxis (interaction between genes) as components of total genetic variance.[32,33] In presenting data on heritability, we have assumed that none of these factors is making a significant

Table 2. Heritability of affective disorders in several types of relatives*

Investigator	Population Incidence	MZ Twins	DZ Twins	Parents	Sibs	Children
Slater (1953)						
Incidence	0.8% (Max estimate)	57.1%	23.5%	10.2%		12.8%
Heritability		0.94	1.23	0.83		0.93
Kallmann (1954)						
Incidence	0.4%	92.6%	23.6%	23.4%	22.7%	
Heritability		1.38	1.30	1.31	1.28	

* Calculation of heritability by method of Falconer. Data not corrected for age.

contribution to the total variance. The possible effects of this assumption are discussed below.

As noted by Jensen, the conceptually most direct estimate of heritability of a trait would be the correlation between MZ twins reared apart in uncorrelated environments.[32] The rarity of MZ twins reared apart makes such a study unfeasible. The difference between MZ and DZ concordance rates is a function of the differing amounts of shared genes, assuming that the environment for each type of twin varies randomly and that being an MZ or DZ twin does not itself alter the probability of developing affective illness. A concordance rate per se cannot be used to estimate the relative contribution of genetic factors, since it is not a population statistic.[39] An intraclass correlation coefficient can be derived from the concordance rate and from the population incidence which allows statements to be made about a population. Comparison of the intraclass correlation in MZ twins with the correlation in DZ twins thus can be used to provide an indication of the relative contribution of genetic and non-genetic factors.

Jensen's formula [32] for heritability is

$$h^2 = \frac{{}^{r}MZ - {}^{r}DZ}{1 - P\infty}$$

where r_{MZ} = intraclass correlation coefficient for MZ twins, and $P\infty$ = genetic correlation between sibs in a population, which is a function of the degree of assortative mating in the parents, and other variables. The quantity $[P\infty]$ cannot be estimated in the available data; it is 0.5 in a random mating population, and approaches 0 in a population with complete negative assortative mating. $[r_{MZ} - r_{DZ}]$ is thus less than or equal to heritability $[h^2]$. The expression $[r_{MZ} - r_{DZ}]$ is a minimum estimate of heritability.

The studies of affective illness in twins reported to date have found high concordance rates for monozygotic twins and lower rates for dizygotic twins.[4] Using Jensen's twin method and assuming random mating, the median of the heritability estimates derived from six reported twin studies (Tables 1 and 2) is between 1.08 and 1.16. That is, with regard to presence or absence of affective disorder, virtually all of the variance in the sampled population is due to heritable factors.

Falconer has developed an alternate method of calculating heritability, derived as a function of the difference between the incidence of disorder in the population and the incidence in relatives of probands of a given degree of relationship.[37,38,40] Heritability can then be estimated independently from MZ twins, first degree relatives, second degree relatives, etc. Because of the differing diagnostic criteria, it seems appropriate to calculate heritability only from data in which a complete set of incidences, including population incidence and incidence in several degrees of relatives, is produced by a single investigative effort. The studies of Slater [26] and of Kallmann [41,42] contain such data, and heritability estimates may be derived from their data on several types of relatives (Table 2). The heritability estimates are fairly close to the estimates calculated from the same data by Jensen's method. The preliminary data reported by Pollin, et al [7] yields a heritability of 0.32 for MZ twins by this method; this lower figure may reflect the fact that the population sampled has not yet passed through the age of risk.

The heritability figures presented here are rough estimates because the extent to which the affective disorders deviate from the assumptions of the additive variance model is not yet established. Values of h^2 greater than 100% do not fit the additive variance model of genetic factors since variance must be positive and $H^2 + E^2 + e^2 = 1$. Such data imply that the disorder is heritable and that a nonadditive genic fac-

tor such as dominance, presence of a single major gene, or assortative mating is present.[32,37,38] These factors can inflate heritability estimates although even if our figures are greatly distorted the high heritability is still quite high. For example in the model discussed above, random mating was assumed; negative assortative mating (people with the same genes avoiding marriage with each other) would considerably reduce the heritability. Heritability would reach a minimum if there were complete negative assortative mating. From Jensen's formula it is evident that this minimum is half of the value calculated for random mating or between 54% and 58%. Another source of overly high heritability estimates may be the sampling biases of the concordance rates. As noted above, studies which are not based on prospective study of valid population samples may produce somewhat inflated concordance rates. For example if the true average MZ concordance rate in the studies reviewed by Zerbin-Rudin were 37% (rather than the reported 75%) and the population lifetime prevalence is 1%, then the heritability would be 0.75 according to the Falconer method. Thus, the heritability remains high even though minimal estimates are derived.

The heritability estimates derived from the incidences of affective disorder in different types of relatives are consistent with each other (Table 2) (DZ twins in the Slater study are the only exception). It is of particular interest that the heritability as calculated from the data on MZ twins is about the same as that estimated from data on first degree relatives.

(Falconer's definition of heritability is $h^2 = \frac{b}{r}$ where b is a normalized expression of the difference between the population rate and the rate in the relatives studied, and r is the degree of relationship ([for MZ twins $r = 1$, for sibs $r =$ one half, for aunt or uncle, $r =$ one fourth, etc]).

This suggests that the experience of twinship, with its unique psychological and other environmental experiences, is *not* producing an excess of concordance in the MZ twins. Looked at another way, the heritabilities found in more distant relatives are so high that the expected age-corrected MZ concordance rate approaches 100%, so there is hardly "room" for nonheritable factors to be operating.

Thus, heritable factors account for an important proportion of population variance in the affective disorders. Further clinical genetic studies of pertinent population parameters may lead to greater precision in the quantitative estimation of heritability.

Role of Environment

A great deal of clinical and demographic research has been directed toward documenting an association between environmental events and the development of affective disorders. Experiences of loss, bereavement, and social marginality have been found in people who subsequently develop depressive illness[43–51] although not all investigators agree.[52–55]

In an illness with significant heritability, these observations could be understood as manifestations of inherited personality traits which result in affective disorders in response to normal or stressful life events. An inherited vulnerability to loss, with increased likelihood of development of pathological loss reactions, as described by Bowlby, would fit such a model.[56,57] This hypothesis could be tested by family history studies of reactors and nonreactors to these events. However, other possible interpretations need to be ruled out by future investigation. For instance, heritable factors might be operating to produce apparently environmental events. Dennehy has reported an excess of parental bereavement in childhood for persons with depressive ill-

ness, as compared to the expected rate of bereavement predicted by census data.[51] However, because of the higher mortality rate in affective disorder due to suicide and other causes, excess bereavement in these families is to be expected.[58–67] Thus, early bereavement may be a manifestation of the illness or an etiologic factor in which there is genetic-environmental interaction, rather than an independent cause of affective disorder in the population studied.

More generally, the contribution of genetic-environmental interaction and covariance can be quantified within the additive variance model of heritability. In a complete analysis of variance, one can determine the relative contribution of main effects (that is, independent effects of major variables) and interaction effects (where the effect of one variable depends on the status of other variables). In the computational techniques of Jensen and of Falconer, genetic-environmental interaction is included within heritability and is not determined separately. The relative contributions of independent genetic variability and of genetic-environmental interaction to heritability can be estimated by existing research techniques, and need not be a matter of conjecture. For example, studies of adopted children represent a method of controlling genetic variables while randomizing environmental effects after birth.[17–20] If one studied the offspring of probands with affective disorder, a comparison of the heritability in adopted children with the heritability in children raised by their biologic parents would indicate the magnitude of genetic-environmental interaction. Parenthetically, it should be noted that genetic-environmental interaction does not include the effects of every conceivable event, such as the severe interactional deprivation described by Spitz,[68] unless the event actually contributed to the environmental variance in the studied population. That is, this interaction describes the effects of the *existing* range of environmental variability interacting with the *existing* genetic variability.

Phenomenology, Nosology, and Genetics

Among the first degree relatives of patients with affective illness, several psychiatric disorders are found with a higher lifetime prevalence than in the general population. In view of the high heritability of affective disorders, we can make the working assumption that the illness in the first degree relatives may be manifestations of the same heritable factors which lead to affective illness. On the basis of these relationships, a set of affective and related illnesses can be defined which may share some common etiologic genetic factors with each other (Table 3).[1,69]

This grouping may represent a biologi-

Table 3. Major groupings of psychiatric illnesses*

Affective and Related Disorders
Unipolar disorders
Manic-depressive illness, depressed
Psychotic depressive reaction
Bipolar disorders
Manic-depressive illness, circular type
Manic-depressive illness, manic
Neurotic depressive reaction
? Antisocial personality
? Alcoholism
Involutional melancholia
"Cycloid personality"
Schizophrenia and Related Disorders
Schizophrenia spectrum
Chronic schizophrenia ("process schizophrenia")
Schizoid personality or schizoid tendencies
Paranoid character
Borderline schizophrenia
Pseudoneurotic schizophrenia
Inadequate personality
? Involutional psychosis (late-onset and paranoid types)
Genetically Independent or Mixed Disorders
Schizoaffective disorder
Acute schizophrenic reaction
? Antisocial personality
? Alcoholism
? Some forms of mental retardation

* Groupings based on genetic overlap suggested by family history studies. 17–21, 26, 41, 67, 70–72, 77.

cally more accurate nosology of affective disturbances than nosologies based solely on symptomatology and psychodynamics, and may thus offer new research opportunities in clinical understanding, pharmacology, and areas of biologic interest. Similar groupings of several diagnostic entities on the basis of family history studies have recently been proposed by several authors; these are incorporated into Table 3.[17–21,26,41,42,70–72]

For our definition of affective disorder we use Winokur's concept of "primary affective disorder," which is defined as an illness characterized by depressions or manias, or both, seen in an individual who lacks a history of preexisting psychiatric illness, exclusive of uncomplicated episodes of depression or mania.[2] The disorders found in the relatives of persons with primary affective disorder include neurotic depressive reaction, involutional melancholia, alcholism, antisocial personality, and cycloid personality. These are referred to as "related illnesses," and are presented in Table 3.

Hospitalized *neurotic depressive reactions,* distinguished by the presence of clinically clear psychogenic causes, were studied by Stenstedt.[73] In that study, the morbid risk for affective disorder in first degree relatives was 3.4%, and this figure is higher than he found in the general population but smaller than the risk in relatives of affective probands. However, a study of eight MZ and 16 DZ twin pairs in which one twin had neurotic depressive reaction did not show significant concordance within pairs.[74] Hospitalized neurotic depressions may thus represent an intermediate degree of genetic predisposition in the patients affected or else may represent a mixed group of people, some without genetic predisposition to affective illness and some who are genetically predisposed. The choice between these possibilities is related to the choice between single genes and polygenic models, with the polygenic model postulating varying degrees of genetic load in each person in a population.

Involutional melancholia and involutional psychosis are diagnostic categories which have been applied with some overflap by different investigators. Those investigators who consider involutional melancholia a depressive disorder (with agitation, obsessions, and paranoid ideation often the predominant symptoms) report fairly consistent findings. In these studies, increased morbidity risk for affective illness and for involutional melancholia, but not for schizophrenia, are found in relatives of involutional probands.[1,67,75–77] Relatives of affective probands had an increased incidence of involutional melancholia in several studies [1,75] although not all investigators found this.[66] Kallmann [41,42] defined involutional psychosis to include most functional psychoses and nonperiodic affective disorders (including involutional melancholia) with onset after age 50. He found schizophrenia, but not affective disorder, in the relatives of his involutional probands. Also, he found involutional psychosis to be a heritable disorder in itself. His findings are discrepant from those of other investigators, apparently because of the diagnostic definition.[4] In one study, which considered the age at which involutional melancholia first appeared, the younger patients (50 to 60) had an excess of relatives with affective disorder but not schizophrenia, whereas the older patients had fewer relatives with affective disorder and an increased incidence of schizophrenia.[67] It appears to us that late-onset cases of affective disorder account for a significant number of patients with involutional melancholia and that some late-onset cases of schizophrenia are also included in this classification. Cerebrovascular disease may also account for a number of patients presenting with involutional melancholia.[67] It is

not clear if there is also a genetically independent illness giving rise to depression or psychosis in this age group.

Alcoholism has been found to be related to affective disorder in several studies. First degree relatives of alcoholics had elevated risks for affective illness[64] which are consistent with the risks in relatives of affective probands as reported by these same investigators.[2] Among relatives of probands with affective disorder, an excess of alcoholism has been reported,[65,78] although not all studies agree.[79] An overlap of alcoholism and affective disorder in the same individual has also been reported.[64,78] It should be noted, however, that this association may apply to only a limited proportion of all alcoholics and that it was not found in a non-Western culture.[80,81]

Increased *sociopathy* is found in relatives of patients with early onset of depressive disorders[82] and affective disorders is slightly increased in relatives of sociopaths.[83] The relationship of affective disorder, alcoholism, and sociopathy is quite complex, and apparently includes assortative mating of persons with family histories of alcoholism and sociopathy.[82–84] Each type of patient has a somewhat increased prevalence of the other disorders in their relatives (with the exception of late onset depression in males, see below). At this time it cannot be determined whether this overlap is due to common genes, assortative mating, or, biologically different disorders with similar clinical features.

Kallmann has used the term "*cycloid personality*" to refer to the many relatives of patients with affective disorder who had mild affective changes and related personality traits but did not have ascertainable illness.[41,42] Kallmann finds 0.7% in the general population but 13%–31% in the relatives of his probands. This grouping has been noted in relatives of patients with affective disorder by several investigators, but has not been the subject of intensive investigation.[25,26,41,42,58] These people may represent a clinically mild expression of some (or all) of the genetic factors in affective disorders.

Unrelated Disorders. The incidence of *schizophrenia* in first degree relatives of affective illness probands is about the same as in the general population, except that the risk for children was somewhat elevated in some of the studies reviewed.[1,2] The implication is that affective and schizophrenic illnesses are genetically independent.

Schizo-affective disorder represents a mixture of affective and schizophrenic symptoms, and this same mixture has been carried over into the results of family history studies of this syndrome. An association with affective disorders has been reported by some investigators[85] but an association with schizophrenia has also been reported,[75] and a mixed set of manic depressive and schizophrenic family histories has also been found.[86,87] At present, these disorders with mixed clinical pictures seem to have a complex and unclear relation to schizophrenia and to affective illness, and may include atypical cases of more than one psychiatric illness,[86,87] or be entirely independent of other entities.[88]

The possibility of genetic heterogeneity within affective disorders must also be considered. Several genotypes might independently cause the same manifestations of psychiatric illness but might be separable by the prevalence of the illnesses found in relatives or by biologic variables. This has been investigated only for unipolar and bipolar illness, and for subdivisions within unipolar illness.

Unipolar and Bipolar Illness. Recent studies have demonstrated genetic, clinical, pharmacologic, and neurophysiologic support for distinguishing between unipolar and bipolar affective disorder. These

studies represent the most developed set of investigations in the affective disorders which draw correlations between all these disciplines. Patients with episodes of mania (or hypomania) and depression may be considered bipolar (BP) and those with depressive illness only considered unipolar (UP).[89] Relatives of UP patients show a high prevalence of UP illness and depressive personalities, and a low prevalence of BP illness.[58,75,90] Conversely, relatives of BP patients have a higher prevalence of BP illness and of cyclothymic personality than UP patients. Very divergent figures for UP illness in relatives of BP patients have been obtained, possibly due to the somewhat different definitions of UP illness that have been employed.[58,75,91] The reported risks range from nearly 0% to 11%.[58,75,89,90,92]

Distinguishing whether a proband with UP illness belongs to the UP or BP genetic populations is problematic. Winokur et al, reviewing the data assembled by Zerbin-Rudin, find that 25% of monozygotic twins concordant for affective illness are discordant for types of illness (unipolar or bipolar).[2,4] This suggests that the genes for manic illness have incomplete penetrance and that at least some of the UP relatives of BP patients have the BP genotype. Angst's findings of high prevalence of UP illness in relatives of BP probands is compatible with this concept.[75] Clinical, pharmacologic, and physiologic comparisons among patients with affective illness, in which the proband's family history is used in assigning him to a BP or UP category, have recently begun.[93]

If two disorders are genetically distinct, there should be demonstrable clinical and biologic differences between them, despite their similarities. Such differences have recently been demonstrated between UP and BP depressions, although the observed clinical intensity of depressions did not appear to differ between the two groups of patients.[46,90,94] The median age of onset for BP patients is about 30 years, whereas for UP patients it is about 45 years.[2,58] The overall mortality due to suicide in affective illness is about 15%; apparently it does not differ between BP and UP patients.[58,63–65] However, there was an excess mortality in BP patients from causes other than suicide, with a considerable shortening of life expectancy in one study.[58] The cause of the excess mortality was not clear in the sample studied. The suicide rate in *relatives* of BP patients appears higher than in relatives of UP patients, although not all investigators agree.[58,66,90] One study reported a subgroup of BP patients with an unusually high suicide rate.[90] These patients required hospitalization for depression and also had episodes of mild hypomania never requiring treatment, but they never had a full-blown manic episode. It is possible that the excess suicide rate reflects a greater morbidity of depressions in certain BP patients.

Comparison of the response to pharmacologic treatment for depression in BP and UP illness also shows marked differences between them. In one study, depressed BP patients had an antidepressant response to lithium carbonate more frequently than did UP patients.[95] Bipolar patients, but not UP patients, exhibited episodes of hypomania while being treated for depression with tricyclic antidepressants or with levodopa.[95–97] These differences in pharmacologic response may be due to the underlying differences in the genes which are predisposing the probands to affective illness.

Neurophysiologic differences in evoked cortical potentials have recently been demonstrated between BP and UP patients.[98] Differences in urinary 17-hydroxycorticosteroid excretion have also been found.[89] Erythrocyte catechol-D-methyltransferase has recently been reported to be lower in UP women than in BP women.[99]

Although much genetic knowledge remains to be developed, it is worth noting

that the demonstration of the presumably genetic differences between UP and BP illness preceded the discovery of the biologic, clinical, and pharmacologic differences, and that the genetic findings may have led to the other findings. The genetic relationship of the two illnesses to each other remains to be clarified. Of particular interest are whether they are entirely independent or share some common gene(s) and what the mode of genetic transmission is in each case.

A recent study reports differences in family history among patients with UP illness.[82] Relatives of female patients with onset before age 40 had markedly increased prevalence of depression in female relatives, whereas male relatives had only slightly increased depression but markedly increased alcoholism and sociopathy. In contrast to these findings, male patients with onset after 40 had an increased prevalence of depression in their relatives, which was the same for male and female relatives. Alcoholism and sociopathy were not increased in the relatives of these patients. As noted by the authors, further research is needed to determine whether this distinction will be supported by biologic and pharmacologic studies.

Mode of Genetic Transmission

Attempts have been made by several investigators to fit mendelian models of inheritance to the affective disorders. Beginning with Slater, several authors have suggested the possibility of a single dominant autosomal gene with low penetrance.[100–102] The main support for this hypothesis was the similar morbid risks (9% to 12%) in parents, sibs, and children in several studies,[1] although not all studies agree.[58] The hypothesis of low penetrance may be tested using the intraclass correlation between monozygotic twins as a measure of penetrance. The overall correlation of the 92 monozygotic twin pairs reviewed by Zerbin-Rudin is 0.83, a figure which is difficult to reconcile with the hypothesis of low penetrance.[4] However, correlations based on studies with less susceptibility to sampling bias may eventually give a better estimate of penetrance.

Kallmann[41,42] applied the single autosomal dominant hypothesis to his data, and included sibs with "cycloid" personalities as being positive for affective disorder. He found an age-corrected ratio of approximately 1:1 of well to ill sibs, which supported the single gene dominant hypothesis. His finding of age-corrected MZ twin concordance of 100% supported the hypothesis that the gene had a high penetrance. Support for a dominant gene is also found in the investigations of bipolar affective disorder by Winokur and his associates.[2,100] They found that sibs and parents of BP probands had nearly equal age corrected incidence rates for affective disorder (35% and 34%), which is compatible with a single penetrant dominant gene.

A single recessive gene would produce greatly increased incidence of illness in sibs as compared with other first degree relatives, which is not present, so this mode of inheritance is not likely.[103]

A polygenic inheritance is consistent with the reported studies in which the incidence of affective illness are nearly equal in different types of first degree relatives. In a disorder which is inherited polygenically, there should be a gradual regression of the rate in relatives toward the population mean as one examines relatives further and further removed from the patient. Falconer's heritability statistic for the different types of relative is corrected for the degree of relationship to the proband, so the heritability estimate would remain constant. Stable heritability estimates for several types of relatives were noted above, using the method of Falconer, which are compatible with the polygenic hypothesis. More

data are needed, however, especially on rates in more distant observable relatives, such as cousins. As noted above, the calculated heritabilities tend to be quite high, implying that factors such as nonpolygenic inheritance, dominance, or assortative mating are important in the inheritance of affective disorders.

Simple dominant and polygenic modes of inheritance may be difficult to distinguish from one another.[104,105] In an uncommon trait with dominant inheritance, one would expect a significant number of probands to have unilateral rather than bilateral family history. Slater[104] has calculated a rough estimate of the expectation of unilateral vs bilateral family histories in a polygenic system, with random mating in the parental generation. Based on his calculation, he estimates that the ratio of bilateral to unilateral family histories should be 10:22. The ratio should be lower for dominant inheritance. Slater's data on affective disorders in general, and Winokur's data on bipolar affective disorder, do not differ significantly from this expected ratio, which is compatible with the null hypothesis of polygenic inheritance. This does not demonstrate polygenic inheritance, however, and further study is needed, particularly with regard to the assumption of random mating.

The evidence on mode of genetic transmission presented by all investigators is based on the number of relatives with affective disorders of the classical types. This may not be an appropriate genetic marker, since relatives with related disorders (such as involutional melancholia or alcoholism) are generally not included, and since some persons with the genetic predisposition may not manifest any disorder. A second problem is that BP and UP affective disorders were not considered separately until recent years, and therefore older studies may be misleading if the true modes of inheritance of these two disorders are very different from each other. It is not surprising, then, that a mode of genetic transmission is not yet established.

At present, dominant or polygenic gene hypotheses, or both, are consistent with much of the data, and neither can now be ruled out. So far, it has not been possible to integrate into a single genetic model the various behavioral manifestations of affective geneotype(s) and the effects of penetrance or assortative mating. Further progress in identifying modes of transmission appèars to depend on developments in two areas; first, incorporation of the knowledge on genetically related psychiatric disorders and personality types into studies and models of the behavioral genetics of affective disorder,[70,106] and second, identification of genetic markers for persons with the genotype or with discrete parts of the genotype. Testing of complex models of transmission, such as the model of two dominant genes, apparently must await development of such markers.

Interestingly, the genetic grouping of affective and related illnesses cuts across the usual distinctions between functional psychoses and personality disorders. The genetic overlap of these entities calls into question the value of the exclusiveness of diagnostic criteria in several genetic studies. Some studies required that each person have three depressive episodes for the proband or relative to be included.[26,58,101] A large number of ill relatives in these studies were excluded because they could not be easily classified. As noted by several authors, decreasing the exclusiveness of the diagnostic criteria greatly increases the percentage of positive relatives.[58,66] This may account for the relatively higher percentage of affected relatives in the Kallmann and Winokur et al studies than in other studies. In view of the high heritability and the large number of relatives with somewhat abnormal personalities (but without clearcut major illness), it would appear most valid

to use *less* exclusive diagnostic criteria and to include the several related illnesses in genetic and in other biologic studies. Including a broader range of affective disturbances within a specifically defined illness does not lead to findings of universal affective illness: Winokur et al, who find the highest prevalence of affective illness in the relatives of probands, find a population lifetime prevalence of slightly more than 2%.[2,107] This is somewhat higher than the estimates of slightly less than 1% that are generally found, but still shows a great difference in prevalence between the general population and the relatives of patients with affective illness.

A great deal of investigation of the family histories of patients with affective and related disorders is now needed to further study the genetic relation of these disorders to each other and to expand our understanding of their etiology and treatment. One possible interpretation of the genetic overlap between different disorders is that they are equivalent manifestations of the same genotype, with the same penetrance, between men and women. It would then follow that the risks for these disorders in relatives of probands with affective disorder might be additive, so that the sum of (alcoholic + affective disorder) male relatives might equal the (alcoholic + affective disorder) female relatives. Winokur and Clayton investigated whether such an equivalence might explain the differences in incidence of affective and related disorders between men and women, since men have higher rates for alcoholism and lower rates for affective disorder than do women.[106] Their data were not consistent with the straightforward additive concept of equivalence. In a later study UP patients with early onset (before age 40) did show this equivalence, in that the prevalence for depression in the female relatives was equal to the sum of depression, alcoholism and sociopathy in the male relatives.[82] Studies into the heritability, penetrance, male-female differences, and genetic heterogeneity of the related disorders are required for further investigation of the equivalence hypothesis.

Sex Distribution and Sex Linkage. In the major affective disorders the overall rate of hospital admissions is higher for females than for males. This has led to the conclusion that females are more liable to these disorders than males.[58,66,103,108] Several studies of population incidence have also reported a higher incidence for females than for males, although not all of the reported studies are in agreement.[26,66,107,109–111]

The higher rate of female admissions could be due to a higher suicide rate in males or to earlier onset of illness in females. A higher suicide rate for males was not supported by recent investigations.[58,75] The age of onset is earlier for women than for men, and women are more likely to be hospitalized when they have affective illness.[46,109] Even when these variables are taken into account, in several studies the incidence of new cases is still higher in females.[46,107,108,110]

In view of these data, the hypothesis of sex-linked dominant transmission in these disorders has long been of interest.[2,100,102] In a disorder with X-linked dominant transmission there is an excess of female relatives affected (for probands of either sex) and a very low number of affected father-son pairs, as compared with affected mother-son pairs. These expected findings were not present in two studies which did not distinguish among types of affective illness.[66,107] However, when UP and BP probands have been considered separately, differences suggesting sex linkage have been found. For example, Perris and Angst noted an excess of illness in female relatives of unipolar cases.[90] An excess of mother-son pairs, as compared with father-son pairs, was found by Perris for unipolar, but not for bipolar, illness.[91] These data are con-

sistent with the hypothesis that *unipolar* illness is associated with an X-linked dominant gene and that bipolar illness is not.

Very different data have recently been reported by Reich et al and Winokur et al.[2,100] Bipolar patients were noted to have an excess of females among affected first degree relatives. There were no father-son pairs with the illness, but 14 ill mother-son pairs were found. The Winokur data are consistent with an hypothesis opposite to that of Perris and Angst: that an X-linked dominant transmission in *bipolar* illness is present. Winokur's group have also presented data on bipolar illness in two families in which color blindness could be used as an X-chromosome marker.[2] In 12 cases in these two families affective disorder was consistently associated with the X-chromosome marker. The reconciliation of these apparently inconsistent sets of data remains for future investigations. The number of cases reported in each study is small, and the possibility of fortuitous associations of certain genes in isolated populations remains to be ruled out.

More complex sex-linked hypotheses, such as the hypothesis in bipolar illness of an autosomal dominant and a sex-linked dominant [100,102] do not appear testable with currently available samples.[112] To test for two dominant genes when the separate genes can not be identified with markers, one needs a large number of offspring of marriages with both parents phenotypically dominant.[112] Such marriages are uncommon, and we have seen none in our clinical experience.

Research Design in a Heritable Psychiatric Disorder

Studies of Twins and Other Relatives. Strategies of research in psychiatry which incorporate genetic relationships into biological investigations have recently aroused much interest.[2,113–115] Comparisons of monozygotic twins with each other may not reveal major genetic factors since they are genetically identical whether they are concordant or discordant for the disorder. Even if a given trait is found in all concordant MZ twin pairs and not found in discordant MZ twins, it would not reflect a genetic variance, and therefore would not be one of the major etiologic genetic factors. Of course, such a finding would be of much interest, either as a manifestation of affective illness or as a nongenetic etiologic factor.

It is clear from twin studies and from studies of other relatives that many people have the genotypes for an affective or related illness and manifest either no illness or only some manifestations of illness. Monozygotic twins can be discordant for affective illness and can be discordant for bipolar or unipolar forms of affective illness. Relatives of BP patients who manifest UP illness may have the BP genotype. The existence of this type of relative implies that illness not only in probands but also in his relatives should be carefully considered in the definition of experimental and control groups in biologic research.[70,93]

In studies of DZ twins (or other relatives who differ genetically), comparison between discordant and concordant pairs could reflect a genetic factor which is itself important in causing the illness, or which is chromosomally linked to important genes. The advantage of DZ twin comparisons over other sib-pair comparisons is that within-pair environments presumably vary less. An ideal study of a large number of DZ twins could include all twins from sib-ships in which affective illness was present (that is, including twin pairs who themselves do not have affective illness but who have a third sib who does). The number of pairs studied should be large enough so that fortuitous genetic linkage in a few families would not be misleading. A positive

genetic finding would be that twins concordant for the illness were both positive (+, +) for a given finding, discordant twins were (+, −) or (+, +) and twins concordant for no illness were generally (−, −).

Polygenic or dominant gene models, or both, are compatible with much of the data on genetic transmission reviewed above. For such models, one would expect a gradual regression of mean trait value or frequency toward the population mean, as one studied relatives progressively further removed from the proband. These relatives could thus constitute additional control groups for demonstrating association of a genetically determined characteristic with affective illness.

Variables suitable for genetic investigations of this kind would be those in which there are demonstrable differences between probands and normals, and in which these differences could be demonstrated while the proband is in a normal state. Only a few such differences have been found,[98,116] possibly because of the preference for longitudinal rather than cross-sectional designs in biological psychiatric investigations. Recently, the use of MZ twins and other relatives as controls in biologic investigations has begun to be reported.[98,114,117–120] This design may be considered as an intermediate between the longitudinal investigation and the cross-sectional design using normal controls.

Study of discordant and normal relatives might also prove useful in establishing markers for the genotypes of interest. For example, provocative pharmacologic testing with amphetamines or other psychoactive drugs might identify persons with an affective genotype, in view of the possibly genetic determination of mood response to several drugs[92,115,121,122] and in view of the reports that amphetamine response distinguishes depressions that are treatable with electroconvulsive therapy or tricyclic antidepressants from depressions that are not.[123,124] This type of hypothesis could be tested most directly in discordant MZ twins. A similar response in a series of discordant twins, and a negative response in a suitable control group, would establish the positive response as identifying the genotype.

Extension of Biological Findings in Affective Illness into Genetically Related Disorders. The major biologic findings in affective illness of current interest include the pharmacology of antidepressant and antimanic drugs,[125,126] findings of altered catecholamine metabolite excretion during illness,[116,127] changes in cerebrospinal fluid serotonin metabolism,[128–130] elevated steroid excretion during periods of acute turmoil,[131–135] altered glucose tolerance,[136–138] altered electrolyte excretion and retention patterns,[139–141] altered sleep, and distinctive neurophysiologic patterns (cortical evoked potentials.[98,142] It would be of much genetic interest if these findings could be replicated in the disorders which may be genetically related to affective illness; involutional melancholia, alcoholism, neurotic reactive depression, and schizoaffective disorder. The practical clinical value of extending the usefulness of antidepressant pharmacology has long been apparent, but the clinical usefulness of tricyclic antidepressants in these disorders has been somewhat variable. Treatment selection of patients with related disorders on the basis of family history of affective illness would seem a rational step which would provide important genetic information and might prove clinically useful.

In Vitro Genetics. Recent advances in cell culture techniques have demonstrated that some fully differentiated mammalian and avian cells can be successfully cultured in vitro[143–145] and others, including neuronal cells, can be cultured in the hybridized form.[146–149] The demonstration of a characteristic found in successive serial clones from a single source would be proof

that the characteristic is genetically determined. The current state of this field [150–154] suggests that further progress in techniques of cell culture and in the biology of the cell types found in the central nervous system may be needed before significant applications to the affective disorders are developed. Eventually, this type of study may supplant some of the clinical genetic studies described in this paper.

Summary and Conclusion

We have discussed the evidence for the role of genetic factors in the etiology of the affective disorders and have discussed application of the concept of heritability to these illnesses. In view of the high incidence of several psychiatric states in relatives of patients with affective disorders, we have suggested that these states (neurotic depressive reaction, involutional melancholia, alcoholism, and cycloid personality) may be associated forms of the affective disorders. This relationship may need to be considered in future genetic studies of affective disorders in the calculation of morbidity rates in relatives and in biologic and pharmacologic studies in the related disorders. The data on the mode of genetic transmission of the affective disorders were briefly reviewed; the hypotheses that there is a dominant gene or that there is a polygenic inheritance are compatible with the existing data. Sex-linkage has also been suggested in some recent studies. The division of affective disorders into unipolar and bipolar illness was discussed as an example of a well supported genetic and phenomenological differentiation among patients with the affective disorders.

Genetic factors are of great importance in determining who will manifest affective illness. Whatever the major etiologic factors are, they are largely heritable; this inheritance needs to be demonstrated in probands and their relatives to confirm any hypothesized etiology. The extension of biologic research in affective illness to include genetic knowledge is a major current challenge.

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The Catecholamine Hypothesis of Affective Disorders: A Review of Supporting Evidence

Joseph J. Schildkraut, MD

During the past decade there has been a gradual accumulation of evidence suggesting a possible link between the affective disorders (depressions and elations) and changes in central nervous system catecholamine metabolism. Most of this evidence is indirect, deriving from pharmacological studies with drugs such as reserpine, amphetamine and the monoamine oxidase inhibitor antidepressants which produce affective changes in man (15, 16, 34, 43, 53, 57, 109).

These studies have shown a fairly consistent relationship between drug effects on catecholamines, especially norepinephrine, and affective or behavioral states. Those drugs which cause depletion and inactivation of norepinephrine centrally produce sedation or depression, while drugs which increase or potentiate brain norepinephrine are associated with behavioral stimulation or excitement and generally exert an antidepressant effect in man. From these findings, which are summarized in Table 1, a number of investigators have formulated a hypothesis about the pathophysiology of the affective disorders (25, 50, 56, 77, 81, 87). This hypothesis, which has been designated the "catecholamine hypothesis of affective disorders," proposes that some, if not all, depressions are associated with an absolute or relative deficiency of catecholamines, particularly norepinephrine, at functionally important adrenergic receptor sites in the brain. Elation conversely may be associated with an excess of such amines.

Although the hypothesis may not be directly testable by currently available experimental methods, this formulation is nonetheless of considerable heuristic value. In this paper we shall review the findings which have led to the formulation of the "catecholamine hypothesis" and consider the significance of this hypothesis for contemporary research in psychopharmacology and psychiatry.

Biology of Brain Monoamines

Various aspects of the extensive literature on monoamine metabolism and its possible relationship to behavior have been well reviewed by several authors (3, 18, 25, 30, 46, 52, 56, 77, 87). In this section,

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TABLE 1. Summary of the pharmacological observations consistent with the "catecholamine hypothesis of affective disorders."

Drug	Effects on Mood in Humans	Effects on Behavior in Animals	Effects on Catecholamines in Brain
Reserpine	Sedation Depression in some patients)	Sedation	Depletion (intracellular deamination and inactivation)
Tetrabenazine	Sedation Depression (in some patients)	Sedation	Depletion (intracellular deamination and inactivation)
Amphetamine	Stimulant	Stimulation Excitement	Release NE* (? onto receptors) Inhibits cellular uptake (and inactivation) of NE*
Monoamine oxidase (MAO) inhibitors	Antidepressant	Excitement Prevents and reverses reserpine-induced sedation	Increase
Imipramine	Antidepressant	Prevents reserpine-induced sedation Potentiation of amphetamine effects	Inhibits cellular uptake (and inactivation) of NE* ? Potentiates action of NE* (as in periphery)
Dihydroxyphenylalanine (DOPA)	? Reverses reserpine effects	Excitement Reverses reserpine effects	Increase

* NE = Norepinephrine.

however, we shall briefly summarize some of the basic biology of brain monoamines pertinent to the catecholamine hypothesis.

The catecholamines, norepinephrine and dopamine, and the indole amine serotonin, are the brain monoamines on which interest has focused. Norepinephrine is present in many areas of the brain but highest concentrations are found in the hypothalamus. Highest concentrations of dopamine are found in the caudate and lentiform nuclei and only minimal concentrations of this amine are found in most other brain areas. Epinephrine, present peripherally in the adrenal medulla, occurs in the brain in low concentrations and may not be of functional importance centrally. Serotonin, while found in large concentrations in various peripheral tissues, is also present in the brain in appreciable concentration and is generally similar to norepinephrine in its distribution (11, 21, 22).

While norepinephrine functions as the transmitter substance of the peripheral sympathetic nervous system, the role of this and other amines in the central nervous system is less clear. Some investigators have suggested that norephinephrine, dopamine and serotonin may each function directly as a transmitter substance, while others have postulated that one or more of these amines may act as modulators or regulators of synaptic transmission mediated by some other direct transmitter, e.g., acetlycholine (2, 9, 22, 28, 67, 110).

The biosynthetic and metabolic pathways for norepinephrine are diagrammed in Figures 1 and 2. Current concepts of norepinephrine storage and metabolism suggest that synthesized norepinephrine is stored in a bound form in intraneuronal granules. This norepinephrine exists in at least two metabolic pools which are in a dynamic equilibrium. One of these is labile and may be released in active form by sympathomimetic drugs, while the other, released by reserpine, is presumed to function as a storage reservoir (76). Norepinephrine released from the nerve in active form either by nerve stimulation or sympathomimetic drugs is inactivated by cellular reuptake or by conversion through

0-methylation to normetanephrine (Figure 2). Norepinephrine released from the "reservoir pool" either spontaneously or by reserpine-like drugs is inactivated mainly by mitochondrial monoamine oxidase before leaving the cell (61, 62) [Figure 2] (4, 9, 19, 60). Secondary 0-methylation or deamination reactions involved in the formation of 3-methoxy-4-hydroxymandelic acid (Vanillylmandelic acid or VMA), the major urinary metabolite of norepinephrine and epinephrine, presumably can occur in the liver or kidney as well as in the nervous system (Figure 2). Monoamine oxidase also functions in the oxidative deamination of the other brain amines, including serotonin and dopamine. While most of these findings derive from studies utilizing peripheral nervous tissue, similar mechanisms have also been demonstrated to occur in the brain (9, 36, 38).

Studies with Antidepressive Agents

Although the role of the central sympathetic system and the catecholamines in affective disorders had been a subject of investigation for many years (29, 31, 32, 79, 99, 107), contemporary research interest in this area was largely stimulated by the crucial discovery that iproniazid, a monoamine oxidase inhibitor, was also a therapeutically effective antidepressant agent (15, 20, 66, 68).

Subsequent studies on experimental animals have shown that iproniazid and the other clinically effective antidepressant monoamine oxidase inhibitors produced both behavioral excitation and elevated brain levels of norepinephrine and serotonin in many species. This elevation of brain monoamines presumably results from the direct inhibition of intracellular deamination by the monoamine oxidase inhibitor. The observed behavioral stimulation is better related to the rise in brain norepinephrine than to the elevation of serotonin and has been postulated to result from the spillover of free norepinephrine onto receptor sites (95, 96).

Amphetamine is a short-acting sympathomimetic psychic stimulant, which has been used for many years with variable results in the treatment of depression (39). Amphetamine is believed to act both by releasing active norepinephrine from nerve cells and by blocking the subsequent inactivation of this released norepinephrine by cellular reuptake (36, 48). It has been observed clinically that the period of acute amphetamine stimulation, particularly after large doses, is often followed by a "rebound period" of mental depression and fatigue (39). This period of depression following amphetamine stimulation may reflect a temporary depletion of norepinephrine stores available for continued release. Consistent with this interpretation is the finding that large doses of amphetamine significantly lower the concentration of brain norepinephrine in animals (69, 94).

The discovery that imipramine, a drug which does not inhibit monoamine oxidase, was an even more effective antidepressant than the monoamine oxidase inhibitors (55, 63, 68), initially cast doubt upon the catecholamine hypothesis of affective disorders. In one of the earliest explicit formulations of the catecholamine hypothesis recorded in the literature, Jacobsen said, in 1959: "Where the effect of imipramine stands in this matter is still a complete riddle which must await elucidation. Here our present ignorance is such that not even a preliminary hypothesis can be offered" (50). In the ensuing five years, however, the considerable advance in our knowledge of the pharmacology of imipramine has brought us close to the solution of this riddle.

Although imipramine does not chemically inhibit either of the enzymes involved in the metabolic inactivation of norepineph-

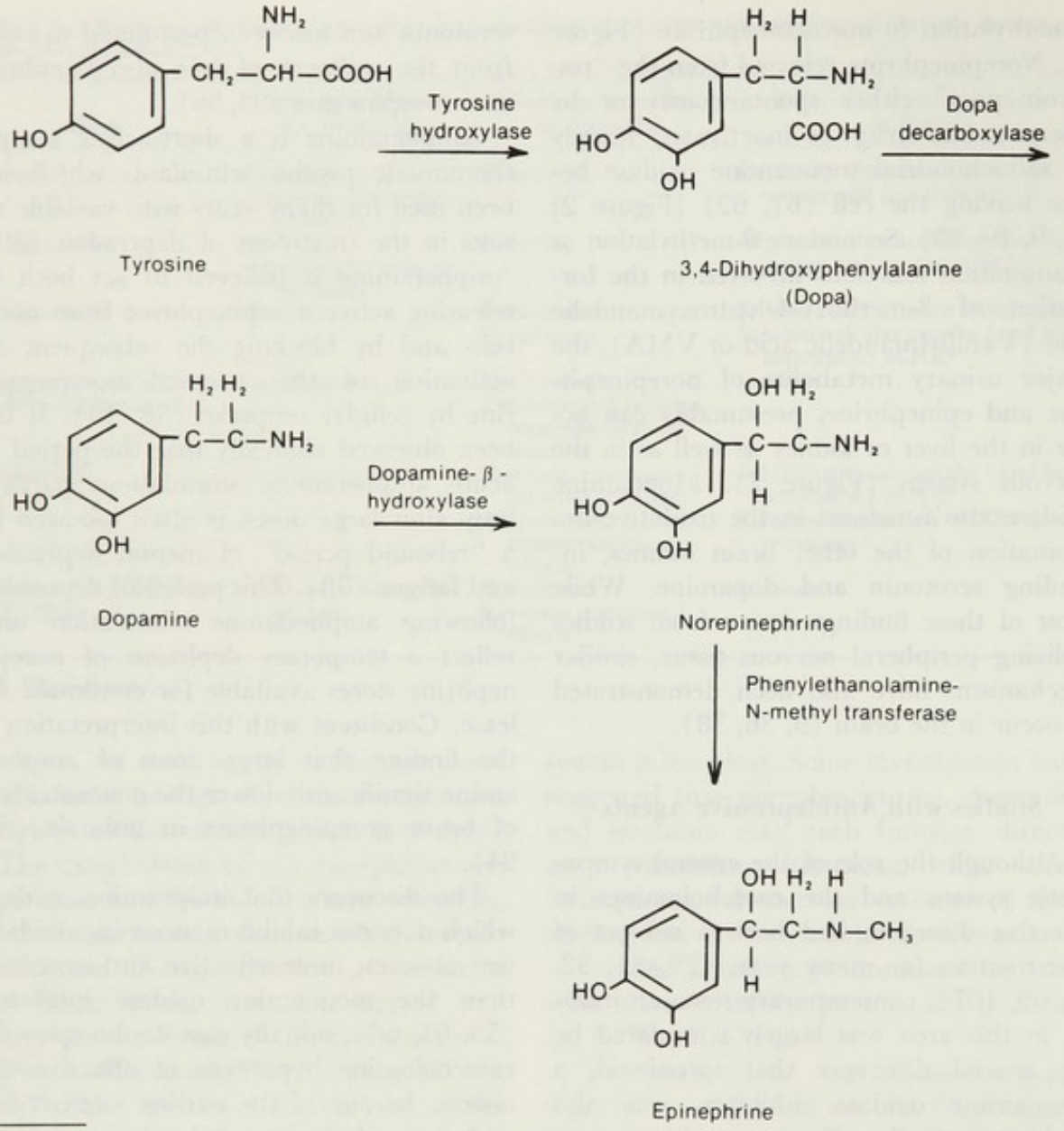

Figure 1. Pathways of Biosynthesis of the Catecholamines—Dopamine, Norepinephrine and Epinephrine (Schematic).

rine, it has been found to potentiate both the response to sympathetic nerve stimulation in several experimental systems and many of the peripheral effects of exogenously administered norepinephrine in animals and in man (33, 82, 91, 92, 103). Axelrod's group, moreover, has found, in animals, that imipramine interferes with the uptake of infused norepinephrine into peripheral tissues, suggesting that imipramine may decrease the cell or storage granule membrane permeability to this amine. Potentiation of the effects of norepinephrine by imipramine may thus result, in part, from impairment of the inactivation of free norepinephrine by cellular reuptake (45). This provides a mechanism for the "sensitization of central adrenergic synapses" which Sigg had proposed to account for the antidepressant action of imipramine (91). Experimental evidence that imipramine inhibits norepinephrine uptake in

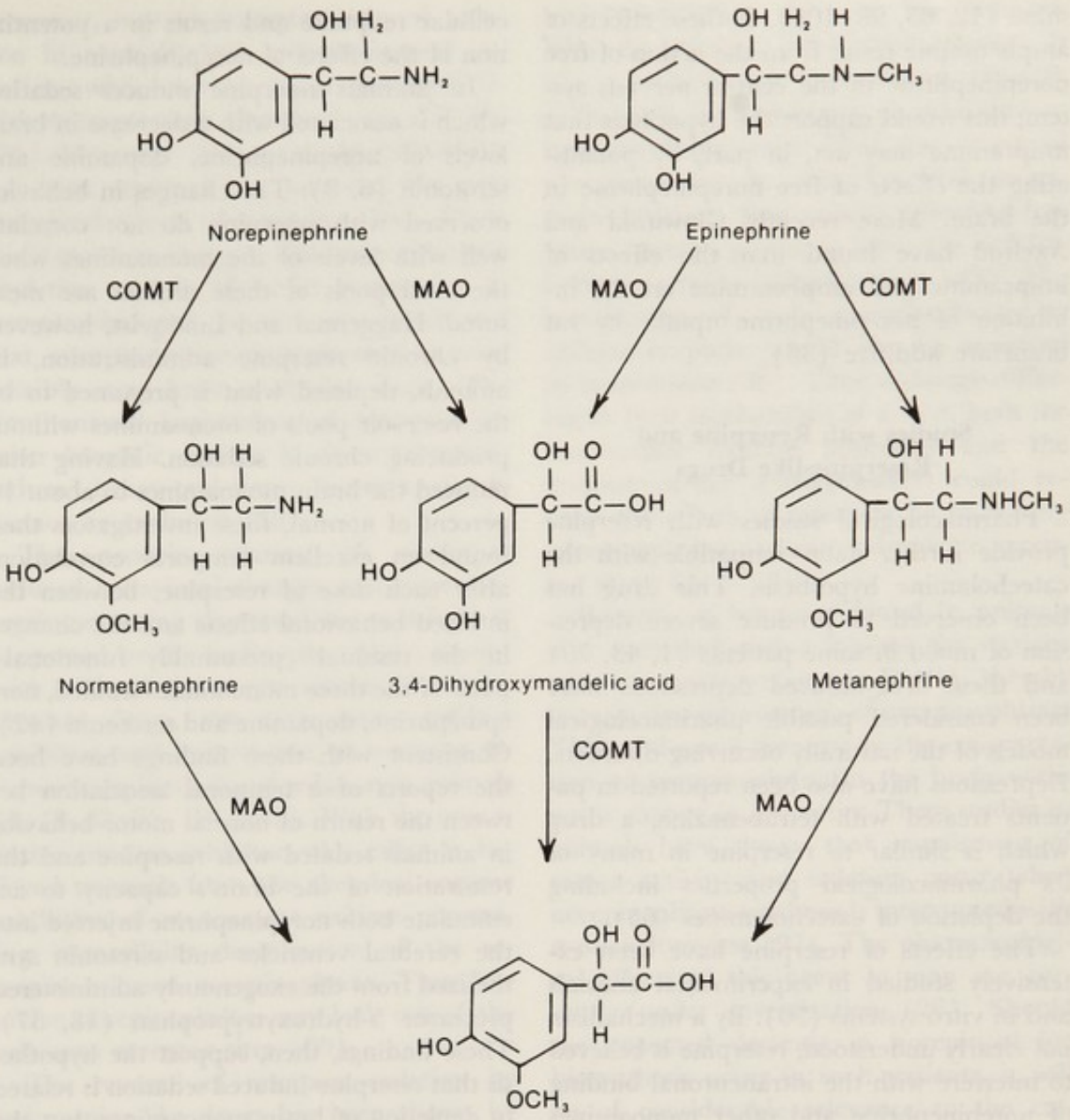

Figure 2. Pathways of Metabolism of Norepinephrine and Epinephrine (Schematic).

the brain as it does peripherally has been reported recently. Moreover, it was found that the chemically related antidepressants desmethylimipramine and amitriptyline also inhibited norepinephrine uptake in the brain while the tranquilized chlorpromazine did not (35).

Stein and other investigators have found, in animals, that many behavioral effects of amphetamine are potentiated by imipra-

mine (12, 83, 98, 108). If these effects of amphetamine result from the action of free norepinephrine in the central nervous system, this would support the hypothesis that imipramine may act, in part, by potentiating the effects of free norepinephrine in the brain. More recently Glowinski and Axelrod have found that the effects of imipramine and amphetamine on the inhibition of norepinephrine uptake by rat brain are additive (36).

Studies with Reserpine and Reserpine-like Drugs

Pharmacological studies with reserpine provide further data compatible with the catecholamine hypothesis. This drug has been observed to produce severe depression of mood in some patients (1, 43, 70) and these drug-induced depressions have been considered possible pharmacological models of the naturally occurring disorders. Depressions have also been reported in patients treated with tetrabenazine, a drug which is similar to reserpine in many of its pharmacological properties including the depletion of catecholamines (65).

The effects of reserpine have been extensively studied in experimental animals and in vitro systems (90). By a mechanism not clearly understood, reserpine is believed to interfere with the intraneuronal binding of norepinephrine and other monoamines (49, 90). With impairment of the binding mechanism by reserpine, norepinephrine may diffuse freely onto mitochondrial monoamine oxidase, resulting in the inactivation of norepinephrine by intracellular deamination and thus depletion of norepinephrine stores. It is essential to an understanding of the different behavioral or clinical effects of these drugs that this mode of action of reserpine be clearly distinguished from the action of the imipramine-like antidepressants which inhibit inactivation of extracellular norepinephrine by cellular reuptake and result in a potentiation of the effects of norepinephrine.

In animals reserpine induces sedation which is associated with a decrease in brain levels of norepinephrine, dopamine and serotonin (6, 8). The changes in behavior observed with reserpine do not correlate well with levels of the monoamines when the total pools of these amines are measured. Haggendal and Lindqvist, however, by chronic reserpine administration, in animals, depleted what is presumed to be the reservoir pools of monoamines without producing chronic sedation. Having thus reduced the brain monoamines to about 10 percent of normal, these investigators then found an excellent temporal correlation, after each dose of reserpine, between the induced behavioral effects and the changes in the residual (presumably functional) pools of the three monoamines studied, norepinephrine, dopamine and serotonin (42). Consistent with these findings have been the reports of a temporal association between the return of normal motor behavior in animals sedated with reserpine and the restoration of the brain's capacity to accumulate both norepinephrine injected into the cerebral ventricles and serotonin synthesized from the exogenously administered precursor 5-hydroxytryptophan (18, 37). These findings, then, support the hypothesis that reserpine-induced sedation is related to depletion of brain monoamines, but the data do not allow separation of the effects of catecholamine depletion from serotonin release or depletion.

Further relevant data, however, come from studies in which the amino acid precursors of catecholamines and serotonin have been administered to reserpinized animals. These precursor amino acids, unlike the monoamines, can cross the blood-brain barrier in animals and raise the concentrations of the respective monamines in the brain (10). Administration of dihydroxyphenylalanine (DOPA), the catecholamine

precursor, reverses reserpine-induced sedation in animals, and restores normal behavior, while the serotonin precursor 5-hydroxytryptophan does not (10, 27, 67, 105). Moreover, in human subjects, DOPA has been reported to counteract the psychological effects of reserpine (24). These findings, then, suggest that catecholamine depletion may be of major importance in reserpine-induced sedation in animals and that reserpine-induced depression in man possibly may have a similar basis. The simultaneous importance of serotonin or other biogenic amines in these reserpine-induced behavioral states, however, clearly cannot be excluded (18).

The possible relation of reserpine-induced behavioral changes and some naturally occurring depressed states is further supported by the finding that pretreatment with both of the major classes of antidepressant drugs, the monoamine oxidase inhibitors and imipramine, prevents or reverses reserpine-induced sedation in animals (8, 13, 83, 95, 101, 102). With the monoamine oxidase inhibitors this effect is believed to result from the chemical enzyme inhibition of monoamine oxidase preventing intracellular deamination of the reserpine-released norepinephrine. Thus free active norepinephrine may leak out of the cell onto receptor sites (60).

The reversal of reserpine sedation by imipramine-like drugs has been shown by Sulser and associates to depend upon the availability of catecholamine stores and the rate of release of these stores by reserpine. These investigators found that in animals selectively depleted of catecholamines with α-methylmetatyrosine, imipramine-like agents did not reverse the effects of reserpine (101). Although imipramine does not chemically inhibit monoamine oxidase, Schildkraut and associates have inferred from changes in norepinephrine metabolism observed in patients treated with imipramine (see below), that imipramine may nonetheless decrease the intracellular deamination of norepinephrine. It was proposed that imipramine, through a decrease in membrane permeability to norepinephrine, may limit the access of norepinephrine to mitochondrial monoamine oxidase, thus possibly allowing free active norepinephrine to leave the cell following reserpine administration (87). The inactivation of such norepinephrine by cellular reuptake would also be impaired by imipramine (35). Thus, although differing in their mechanisms of action, both the monoamine oxidase inhibitors and the imipramine-like antidepressants could reverse the effects of reserpine by increasing norepinephrine at brain adrenergic receptor sites (83, 87, 101).

Recently it has been found in animals that α-methyltyrosine inhibits the enzyme which converts tyrosine to DOPA, thereby interrupting the synthesis of norepinephrine. This produces a decrease in the concentration of norepinephrine in the brain without a change in serotonin. These studies in animals have shown that impairment of motor activity and sedation occur when norepinephrine synthesis is interrupted with α-methyltyrosine (97). The pharmacological effects of this agent in man are currently under investigation (26). Should the expected decrease in norepinephrine biosynthesis occur in such patients, it will be of considerable relevance to the catecholamine hypothesis to observe whether these patients also become depressed.

Studies in Patients with Affective Disorders

Clinical studies which are relevant to the catecholamine hypothesis of affective disorders are limited and the findings are inconclusive. Strom-Olsen and Weil-Malherbe have reported urinary excretion of norepinephrine to be increased during mania and decreased during retarded depres-

sion both in cycling manic-depressive patients studied longitudinally and in cross-sectional studies comparing groups of patients (99). Bergsman has reported similar findings in mania but not in depression (5), and increased urinary excretion of norepinephrine in depression has also been reported (23).

Urinary excretion of normetanephrine, the metabolite which derives from norepinephrine released from the nerve in active form, may better reflect adrenergic activity than urinary norepinephrine excretion. Preliminary results from a longitudinal study of affective disorders now in progress in our laboratory indicate that urinary normetanephrine is significantly increased in some patients with retarded depression following successful treatment with imipramine, when values obtained under pretreatment and posttreatment placebo conditions are compared. Moreover, an even greater increase in normetanephrine excretion was observed in one of these patients, during a subsequent hypomanic episode, which occurred without drug administration (84, 85). Caution must be exercised, however, in interpreting such data on the urinary excretion of norepinephrine and metabolites to imply central changes specifically related to mood. Factors other than affective state, e.g., muscular activity or peripheral sympathetic activity secondary to various changes in the central state also may significantly alter norepinephrine excretion (51). Moreover, a blood-brain barrier to normetanephrine, similar to that known to exist for norepinephrine, has recently been described in animals (38). It is therefore possible that only a small fraction of urinary norepinephrine or normetanephrine derives from the brain. All data on normetanephrine excretion must furthermore be considered tentative since there is no general agreement regarding the chemical methodology involved in the determination of normetanephrine and there is considerable disparity in the range of values reported by different investigators. In a study of the urinary metabolites of infused radioactive norepinephrine in psychiatric patients and normal controls, Rosenblatt and Chanley have observed an elevated ratio of amines to deaminated metabolites in a subgroup of patients with retarded depression whom they classified as manic-depressive (80).

A number of studies have shown that clinically effective doses of the monoamine oxidase inhibitors decrease VMA excretion and cause other alterations in catecholamine metabolism in human subjects (86, 88, 100). Schildkraut and associates have found that VMA excretion is decreased in depressed patients during treatment with imipramine or with monoamine oxidase inhibitors (87), and these findings with imipramine have been confirmed in the current study (84, 85). Since most urinary VMA may derive from norepinephrine which has been synthesized but inactivated by intracellular deamination without necessarily having been utilized, decreased VMA excretion may reflect a decrease in the intracellular deamination of norepinephrine. With the monoamine oxidase inhibitors this probably occurs through direct inhibition of the enzyme. Imipramine, which is not a monoamine oxidase inhibitor, however, may act through a decrease in membrane permeability to impair the spontaneous intracellular release and deamination of the "reservoir" norepinephrine as well as to inhibit the inactivation of free extracellular norepinephrine by cellular reuptake. Thus, imipramine and the monoamine oxidase inhibitors, by different mechanisms, may both increase the active norepinephrine available at adrenergic receptor sites (87). This hypothesis is compatible with our more recent preliminary finding of a gradual rise in normetanephrine excretion during the period of definitive clinical improvement in a small

number of depressed patients studied longitudinally during treatment with imipramine (84, 85).

Results of studies on the administration of the amino acid precursors of norepinephrine and serotonin are difficult to interpret with respect to the catecholamine hypothesis of affective disorders. Several studies have indicated a mood-elevating effect of tryptophan and a possible synergism with monoamine oxidase inhibitors in the treatment of depression (17, 64, 71, 75, 93). This therapeutic synergism has also been reported for 5-hydroxytryptophan, but the group initially reporting this phenomenon could not replicate their original observations in a double-blind study (58, 59). These clinical effects with the serotonin precursors may nonetheless be compatible with the catecholamine hypothesis, since it has been reported recently that, in animals, administration of 5-hydroxytryptophan in doses which produce excitement causes a release of norepinephrine from the brain (18).

DOPA, the precursor of norepinephrine, administered alone or with a monoamine oxidase inhibitor, was not found to be effective in the treatment of depression either by Pare and Sandler or Klerman and associates (56, 73). The latter study was undertaken as an indirect test of the catecholamine hypothesis and the negative findings raised some question about the validity of the hypothesis. Since the patients studied, however, were unusually refractory to other antidepressant treatment as well as to DOPA, and because one could not be certain that adequate amounts of the orally administered DOPA permeated the brain, one could not reject the catecholamine hypothesis on the basis of these findings (56). More recently Turner and Merlis have reported mood elevation in a group of patients treated with a monoamine oxidase inhibitor and DOPA (104). The possible therapeutic efficacy of DOPA and monoamine oxidase inhibitors in the treatment of depression therefore merits further careful study. It must be cautioned, however, that this combination of drugs may produce severe hypertension and cardiac arrhythmias (86).

Corresponding to the finding that reserpine produces excitement in animals pretreated with imipramine, Poldinger has reported dramatic clinical improvement after reserpine was added to the therapeutic regimen of a small number of depressed patients who had failed to respond to imipramine alone (74). Further study, however, will be required to document this potentially important finding.

Since electroconvulsive therapy (ECT) has been well established as an effective treatment for some depressed patients, ECT has been studied by several investigators in an effort to determine whether the clinical effects were associated with an alteration in amine metabolism (14, 44, 47, 106). Increases in plasma and urinary norepinephrine and epinephrine have been reported in unmodified ECT but these changes are markedly diminished when barbiturates or muscle relaxants are employed. In animals, increased permeability of the blood-cerebrospinal fluid barrier to norepinephrine has been suggested to occur after ECT (81).

Conclusion

There is good evidence to support the thesis that the antidepressant effects of both the monoamine oxidase inhibitors and the imipramine-like drugs are mediated through the catecholamines, and that, by different biochemical mechanisms of action, both of these classes of drugs increase the active catecholamines at adrenergic receptor sites. Moreover, the available evidence suggests that catecholamine depletion is associated with reserpine-induced sedation in animals, although other amines, particularly sero-

tonin, are probably also of importance in this phenomenon.

It is not possible, however, either to confirm definitively or to reject the catecholamine hypothesis of affective disorders on the basis of data currently available. Although there does appear to be a fairly consistent relationship between the effects of pharmacological agents on norepinephrine metabolism and on affective states, a rigorous extrapolation to pathophysiology from pharmacological studies alone clearly cannot be made. At best, drug-induced affective disturbances can only be considered models of the natural disorders, while it remains to be demonstrated that the behavioral changes produced by these drugs have any relation to naturally occurring biochemical abnormalities which might be associated with the illness.

In interpreting studies of drugs effective in the treatment of psychiatric disorders, it cannot be assumed without verification that their mode of action involves correction of the underlying abnormality. Such drugs could, indeed, produce unrelated changes which compensate for the naturally occurring abnormality, and there are many examples of such successful symptomatic treatments in medicine. Thus, pathophysiological hypotheses, such as the catecholamine hypothesis, derived from studies of the mechanism of action of drugs which induce mood disorders or drugs effective in their treatment are primarily of heuristic value in suggesting directions for further research. Confirmation of such hypotheses must ultimately depend upon the direct demonstration of the biochemical abnormality in the naturally occurring illness.

It has not been the aim of this paper to consider the important roles of personality, environmental or genetic factors in the affective disorders. Many clinicians, including the author, have observed, however, the significant effects which social and interpersonal factors have on the clinical response to antidepressant drugs. An effect of genetic factors on the response to antidepressant medication has also been reported recently (72). While our systematic knowledge in these areas is currently limited, their importance must be stressed and the need for further study emphasized.

Recent physiological and pharmacological studies have supported the long-standing observation, based on clinical phenomenology, that depression does not represent a single homogeneous entity (7, 40, 41, 54, 78, 80, 89, 109).

Although the endogenous-neurotic dichotomy has recently been the primary focus of attention, especially among the British investigators, it is unlikely that any simple dichotomous subdivision will be adequate to classify the depressions into biologically or clinically homogeneous subgroups. Thus, it is possible that the catecholamine hypothesis of affective disorders may ultimately be confirmed for certain subgroups, but not necessarily for all depressions.

Moreover, the relative or absolute decrease in norepinephrine available at brain receptor sites, which is hypothesized to be associated with depression, could result from several different biochemical mechanisms. These would include decrease in norepinephrine biosynthesis, impairment of norepinephrine binding and storage, increased intracellular release and deamination of norepinephrine, or decrease in receptor sensitivity to norepinephrine. The possible relationship of these discrete biochemical mechanisms to the clinical phenomenology and subgroups of depression is currently under investigation. Such hypothetical changes in catecholamine metabolism may be conceptualized to be a part of the pathophysiology of depression, although not necessarily of primary etiological significance. Since the importance of psychological factors in the etiology of at least some depressions is well established, investigation of the possible effects of psy-

chological factors on catecholamine metabolism seems a most promising area for future research.

Thus, although lacking direct experimental confirmation, the catecholamine hypothesis currently seems to be the strongest and most useful pathophysiological hypothesis of affective disorders. It must be stressed, however, that this hypothesis is undoubtedly, at best, a reductionistic oversimplification of a very complex biological state and that the simultaneous effects of the indoleamines, other biogenic amines, hormones and ionic changes will ultimately have to be included in any comprehensive formulation of the biochemistry of the affective disorders. In our present state of knowledge, however, the catecholamine hypothesis is of considerable heuristic value, providing the investigator and the clinician with a frame of reference integrating much of our experience with those psychopharmacological agents which produce alterations in human affective states.

Summary

The "catecholamine hypothesis of affective disorders" proposes that some, if not all, depressions are associated with an absolute or relative decrease in catecholamines, particularly norepinephrine, available at central adrenergic receptor sites. Elation, conversely, may be associated with an excess of such amines. Evidence supporting this hypothesis was reviewed.

Data from pharmacological studies, mainly in animals, suggest that the actions of both major classes of antidepressant drugs are mediated through the catecholamines. The monoamine oxidase inhibitors increase brain concentrations of norepinephrine while imipramine-like agents potentiate the physiological effects of norepinephrine. Reserpine, a drug which can cause clinical depression, depletes catecholamines, but other amines may also be involved in its mechanism of action. A vigorous extrapolation from pharmacological studies to pathophysiology clearly cannot be made. Clinical studies relevant to the catecholamine hypothesis are limited and the findings are inconclusive.

It is not possible, therefore, to confirm definitively or to reject the catecholamine hypothesis on the basis of data currently available. In our present state of knowledge, however, the catecholamine hypothesis is of considerable heuristic value, providing the investigator and the clinician with a frame of reference integrating much of our experience with those pharmacological agents which produce alterations in human affective states.

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L-DOPA, Catecholamines, and Behavior: A Clinical and Biochemical Study in Depressed Patients

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L-DOPA was administered in large oral doses to 16 depressed patients under double-blind conditions to evaluate the possible effects of this catecholamine precursor on mood and behavior. The dosages used (5 to 20 times those used in previous studies of L-DOPA in depression) were equivalent to those which produce behavioral effects and brain amine changes in animals, as well as being equal to those recently found to be therapeutic in Parkinson's disease. Changes in cerebrospinal fluid and urinary catecholamine and indoleamine metabolites, and in cortical evoked potential measurements provide suggestive evidence that L-DOPA altered catecholamines both in brain and the periphery. An antidepressant therapeutic response was observed in only 4 of the 16 patients. All of the patients who responded had retarded depressions; none of the five patients with an agitated depression syndrome improved. Placebo substitution was associated with relapses of depression in three of the four responders, confirming the significance of the initial response and suggesting that a subgroup of retarded depressed patients may be sensitive to L-DOPA. The production of anger in all patients who received 4 g of L-DOPA and did not show an antidepressant response may reflect activation of a central dopaminergic or noradrenergic pathway. The relevance of this clinical finding to aggressive phenomena produced in animals by L-DOPA administration is discussed. The clear lack of therapeutic effectiveness in 75% of the patients offers some evidence against the importance of the hypothesized deficit in brain catecholamines, particularly dopamine, in the majority of patients with clinical depression. Since norepinephrine in brain may not be increased by L-DOPA, this evidence remains inconclusive. However, it can be fairly concluded that amine depletion as defined by the reserpine model (reversable by L-DOPA) is not a sufficient explanation of the pathophysiology of depression in the majority of our patients. The consistent induction of hypomania or mania in all five of the depressed patients who had prior histories of mania suggests that catecholamines, especially dopamine, may be directly involved in the genesis, or triggering, of manic behavior in susceptible individuals. In addition, this combination of an activation of hypomania in the absence of a reversal of depression suggests that depression and mania are not opposite poles of the same entity.

Introduction

The purpose of this paper is to present the results of a clinical and biological study of the use of sustained high doses of L-DOPA, a catecholamine precursor, in patients with affective illness. These results will be considered in the light of theories implicating the biogenic amines in altered emotional states, in particular, the possible relationships between brain dopamine and behavior. The biogenic amine hypothesis of affective illness states that depression is associated with a functional deficit of brain neurotransmitter amines at specific central synapses, and that, conversely, mania is associated with a functional excess of these amines.

This hypothesis originated out of observations concerning the biochemical actions of certain drugs on central and peripheral adrenergic systems in animals. This extensive area has been reviewed in detail (Bunney and Davis, 1965; Shildkraut, 1965) and can be summarized as follows: drugs which act as effective antidepressants have been found to elevate brain amine levels (monoamine oxidase inhibitors) or to potentiate the amine released at the neuronal junction by inhibiting its reuptake into the presynaptic nerve ending (tricyclic compounds). Conversely, reserpine, a compound which depletes brain amines, is associated with a small but consistent incidence of depression in patients treated with high doses over many months. One difficulty in the interpretation of these data is the relative nonspecificity of these drugs in relation to their biochemical effects; for example, the elevation of brain amines following monoamine oxidase (MAO) inhibition does not distinguish norepinephrine (NE), dopamine (DA), or serotonin (5-HT), since all three are elevated with this treatment. Also, these compounds have other biochemical effects not directly related to amine functions, such as effects on energy metabolism, ion transport, and cholinergic function (Ban, 1969). Furthermore, the majority of evidence relating drug effects to the more complex processes such as transmitter release and reuptake has been obtained from *peripheral* systems.

The so-called "precursor-load strategy" has been proposed as one more direct way to evaluate the presumed functional significance of a given compound, and it has been quite usefully applied to the study of certain metabolic diseases (Mandell and Spooner, 1969).

In relation to the amine hypothesis the rationale for this strategy is quite simple; if depression involves a deficiency of a specific amine in the brain, then the most direct way to correct that deficiency would be to administer the amines in large doses —a form of replacement therapy. Since the amines in question (NE and DA) do not pass the blood-brain barrier, it is necessary to administer the amino acid precursor dihydroxy-phenylalanine (DOPA), which can enter the brain after oral or parenteral administration, to be converted to DA and NE (*see* Fig. 1). One refinement in the use of a precursor for this purpose involves administering, in addition, a compound which selectively inhibits the metabolism of the precursor in peripheral tissues but not in brain. Inhibitors of aromatic L-amino acid decarboxylase which do not penetrate the blood-brain barrier (at doses sufficient to inhibit decarboxylase in the periphery) are available, and have been shown to potentiate the behavioral and biochemical effects of peripherally administered L-DOPA in animals (Bartholini, 1967; Udenfriend *et al.*, 1956). One of these, α-methyl-DOPA-hydrazine (MK-485) has been used in combination with

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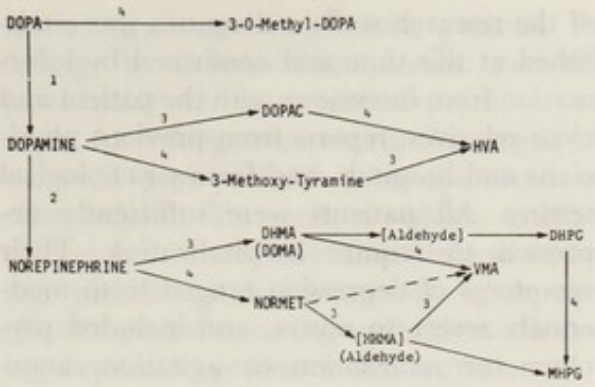

Figure 1. Major metabolites of DOPA, dopamine, and norepinephrine. Enzymes: 1, DOPA decarboxylase; 2, dopamine-β-hydroxylase; 3, monoamine oxidase (MAO); 4, catechol-o-methyltransferase (COMT). Metabolites: DOPAC, 3,4 dihydroxyphenylacetic acid; HVA, homovanilic acid; DHMA (DOMA), dihydroxymandelic acid; VMA, 3-methoxy-4-hydroxy-mandelic acid; NORMET, normetanephrine; NHMA, 3-methoxy-4-hydroxy-mandelic aldehyde; MHPG, 3-methoxy-4-hydroxy-phenyl-glycol; DHPG, 3,4-dihydroxyphenylglycol. From Kopin (1966).

L-DOPA in seven of our patients.

The behavioral effects of large doses of L-DOPA in animals have been studied in a variety of species under different conditions. These studies, and their relevance to the results reported here, will be discussed.

Previous Studies in Depression

In the first report of the use of DOPA in depression (Pare and Sandler, 1959), small doses of DL-DOPA (equivalent to 125 mg of L-DOPA) were given over a 48-hr period to three depressed patients with no improvement observed. However, three subsequent studies not done under double-blind conditions did report varying degrees of activation in some patients. Turner and Merlis (1969) studied 13 patients (11 of whom were diagnosed as schizophrenic) who received 50–150 mg of DOPA per day in combination with an MAO inhibitor from eight days to nine weeks. Three patients became less depressed and two became more assertive; in general, these patients were described as showing increased motor activity, being overtalkative, and having difficulty sleeping. Ingvarsson (1965) treated two patients with long-standing refractory retarded depression with 50 mg L-DOPA iv and described a rather rapid but brief improvement in the depressive mood. Matussek *et al.* (1966) noted activation in eight of ten patients with retarded depression during an iv infusion of 25–50 mg L-DOPA. This was characterized by a change in facial expression, increased mobility, and increased verbalization.

In the first double-blind study of DOPA in depression Klerman *et al.* (1963) reported negative findings with up to 1 g of DL-DOPA (equivalent to 500 mg L-DOPA) orally in 12 patients for periods up to five weeks, with and without an MAO inhibitor. In another double-blind study from our group (Davis *et al.*, 1966), agitated and retarded depressed patients were treated with 50–350 mg of L-DOPA iv from one to five days. The dose was increased in most patients to the point of nausea and vomiting. Although clear activation of movement and speech occurred in three of the patients, the majority showed no change in symptoms of depression.

In an interesting study of 22 patients under treatment with reserpine, Degkwitz (1960) reported that over half described feeling better with less fatigue and a decreased feeling of heaviness in their limbs following L-DOPA (350 mg).

Thus, the major conclusion from these previous studies, in particular from the two double-blind studies, was that L-DOPA in relatively small doses did not possess significant antidepressant properties; however, the earlier impressions that some retarded depressed patients did respond with activa-

tion is interesting, particularly in light of our current findings with large doses of L-DOPA under double-blind conditions.

Behavioral Effects of L-Dopa in Parkinsonian Patients

In addition to these earlier studies in psychiatric patients, the recent widespread and successful use of L-DOPA in Parkinson's disease (Cotzias *et al.*, 1967; 1969; Yahr *et al.*, 1969; McDowell *et al.*, 1970; Klawans and Garvin, 1970) has provided some information on the behavioral and mood effects of L-DOPA, although to date no systematic controlled evaluation of these effects in Parkinsonian patients has been reported. A collation of side-effect data recently attempted, from 700 Parkinson patients treated in 13 different medical centers indicates that "psychic changes" are noted in approximately 15–25% of the patients, depending on the criteria used. The most frequently reported changes are agitation, hyperactivity, delusions, "toxic psychosis," depression, somnolence, delirium, and confusion; however, the wide variability in the reports of different groups, and the lack of standard terminology makes any general conclusion unwarranted at this time. For example, there are two reports of depression as a psychiatric complication (McDowell *et al.*, 1970; Wagshul and Daroff, 1969), while other reports do not mention depression at all but rather stress the occurrence of hyperactivity and even hypomania (Calne *et al.*, 1969; Godwin-Austen *et al.*, 1969).

Methods

The patients were studied on two 12-bed metabolic research units, at the National Institute of Mental Health, specifically designed for the collection of behavioral and biochemical data on a longitudinal basis. Prior to admission, patients were evaluated in a psychiatric interview by two members of the research staff; a diagnosis was established at this time and confirmed by information from interviews with the patient and close relatives, reports from previous physicians and hospitals, and from psychological testing. All patients were sufficiently depressed to require hospitalization. Their symptoms of depression ranged from moderately severe to severe, and included psychomotor retardation or agitation, anorexia, weight loss, sleep disturbance, and depressive thought content often of psychotic proportions, dominated by feelings of hopelessness, worthlessness, preoccupation with guilt, and suicidal ideation.

All but one of the patients included in this study were classified as either manic-depressive or psychotic depressive, based on the above symptoms and the presence or absence of a prior history of manic episodes; one patient was considered schizo-affective with marked depressive symptoms. They were further classified as either predominantly retarded or predominantly agitated, based on their levels of anxiety, physical activity, and speech. Thus, the agitated patients tended to show anxiety, pacing, hand wringing and the like, while the retarded patients evidenced slow speech (at times virtual muteness), slowed movement, and social withdrawal. For the statistical analyses, Student's *t*-test was used for most data; for the response-nonresponse comparisons, Chi-square analysis was used. The patients' clinical state was independently assessed by a trained nursing research team who rated the patients twice daily on a 15-point multi-item scale designed to evaluate depression, mania, anger, psychosis, anxiety, and physical activity (Bunney and Hamburg, 1963). This scale, in use on this project over the last seven years, has consistently shown high inter-rater reliability for these items.

L-DOPA and placebo were administered double-blind in a nonrandom design so that periods of drug and placebo were available

for comparison within each patient. In timing the double-blind placebo periods, particularly in the manic-depressive patients, knowledge concerning the length of the individual patient's prior episodes was often helpful. Obviously, the ability to infer efficacy from the occurrence of relapses during placebo periods depends upon the placebo period's coming while the underlying depressive process is still active.

Seven patients were treated with MK-485 prior to and during L-DOPA administration; in evaluating our overall results in depression, we have included these patients. However, the systematic analysis of other behavioral parameters such as anger and mania has been completed only for the 11 patients who were treated with L-DOPA alone.

L-DOPA dosage was started at 0.5 g and built up slowly (0.25–1.0 g/day) until either clinical improvement was achieved, unacceptable "peripheral" side effects were encountered, or neurological side effects were observed. (Tables I and II indicate the maximum dose for each patient and the side effects.) The maximum dose averaged 7.2 for the group, equivalent to approximately 100 mg/kg, with a range of 55–148 mg/kg.

For the patients on MK-485, the L-DOPA dose required was approximately one-sixth to one-tenth of that without the inhibitor. MK-485 dosage ranged from 750–1500 mg/day with the majority of patients receiving 750 mg/day; it was started four to seven days prior to L-DOPA. With MK-485 pretreatment, it was possible to build the L-DOPA dose up to its optimum more rapidly.

Recumbent and standing blood pressures and pulse were measured four times per day. Patients were examined by a neurologist on a regular basis. A comprehensive battery of hematological and chemical tests was run on all patients before and during the course of drug treatment; CBC, platelet count, ESR, serum bilirubin, cholesterol, SGOT, SGPT, LDH, alkaline phosphatase, serum electrophoresis, serum electrolytes, calcium, iron, copper, manganese, glucose, PBI, BUN, complete urinalysis, and 24-hr urinary protein were all obtained at least biweekly. Twenty-four-hour urine pools were collected daily and aliquots were frozen for the determination of DOPA,

Table I. Individual patient data

Patient	Age	Sex	Weight, lb	Diagnosis	Maximum dose	
					mg/kg	g
L.R.	43	M	185	Manic-depressive	148	12.5
G.A.	73	M	125	Psychotic depressive	142	8.1
W.L.	52	F	140	Psychotic depressive	110	7.0 (0.3[a])
Q.M.	24	F	140	Psychotic depressive	110	7.0
A.C.	55	F	145	Manic-depressive	106	7.0
C.J.	47	F	150	Psychotic depressive	100	8.0
R.B.	42	F	175	Manic-depressive	84	5.0
J.L.	42	M	180	Manic-depressive	73	6.0
T.E.	57	F	100	Psychotic depressive	66	3.0
K.S.	46	F	160	Psychotic depressive	55	4.0 (0.3[a])
T.J.	47	M	185	Manic-depressive	47	4.0
W.T.	29	M	175	Schizo-affective	19	1.5[a]
D.D.	66	M	145	Psychotic depressive	12	0.8[a]
L.F.	62	M	160	Psychotic depressive	11	0.8[a]
K.F.	44	M	165	Psychotic depressive	7	0.5[a]
H.M.	54	F	145	Psychotic depressive	6	0.4[a]

[a] MK-485 plus L-DOPA.

Table II. Nonpsychiatric side effects of L-DOPA

	DOPA (11 patients)	DOPA–MK–485 (7 patients)
Nausea	6	1
Vomiting	4	0
Belching	3	0
Total gastro-intestinal	9	1
Hypotension	2	1
Arrhythmia	1	0
Total cardiovascular	3	1
Akathesia	2	1
Choreiform movements	1	1
Slurred speech	1	0
Total neurological	2	2

DA, homovanilic acid (HVA), 3-methoxy-4-hydroxy phenylglycol (MHPG), 3-methoxy-4-hydroxy mandelic acid (VMA), and 5-hydroxy-indole-acetic acid (5-HIAA) (Sourkes and Murphy, 1961; Sato, 1965; Wilk *et al.*, 1967, 1965; Udenfriend *et al.*, 1955). Whenever possible, cerebrospinal fluid (CSF) was obtained before and during DOPA administration and analyzed for HVA and 5-HIAA (Ashcroft and Sharman, 1962; Gerbode and Bowers, 1960.)

Clinical Results

Effects of L-DOPA on Depression

The overall results in the 16 depressed patients are summarized in Table III. In evaluating the question of antidepressant response, we have combined the 11 patients who received L-DOPA alone with the seven who were treated with the combination of L-DOPA and MK-485 (Goodwin *et al.*, 1970). (Two patients received both L-DOPA alone and the combination in separate treatment periods.) Only 25% of the total group (four patients, seven trial periods) showed a consistent improvement in depression on L-DOPA (Bunney *et al.*, 1970*b*). In addition, in five of the seven trials in the "responders," a relapse following placebo substitution was observed. Table IV summarizes the rating data for the seven treatment periods in the four patients classified as responders.

The criterion for designation of the responders involved a comparison of the mean depression ratings for separate five-day periods. Thus, if the mean rating for the five days just prior to placebo substitution (period of maximum dose) was at least three points lower than the pre-DOPA mean, the patient was designated as a responder.[1] The fact that in five of the six trials the depression ratings went back up after placebo substitution indicates that the improvement was probably related to the medication in these patients.

In light of the clear-cut lack of antidepressant effect in the majority of the patients, it would seem important to describe the clinical course of the four apparent responders in some detail. As a group, the responders represented patients with moderately severe depressions including both psychotic depressive diagnoses and manic-

Table III. Clinical results in depression[a]

	Response	Nonresponse	Totals
Overall group	4	12	16
Retarded	4	7	11
Agitated	0	5	5

[a] See text for description.

[1] A 3-point rating change represents a substantial degree of clinical change, since in practice the upper and lower ranges of the 15-point scale are rarely used.

Table IV. Responder group: Change in depression rating for individual patients

Patients	Drug	Maximum dose of L-DOPA	Double-blind depression ratings (mean of five-day periods)		
			Prior to L-DOPA administration	Period of maximum dose prior to placebo substitution	Placebo period
W.L. (1st treatment period)	L-DOPA	6 g	10	7	8
W.L. (2nd treatment period)	L-DOPA	7 g	8	4	8.5
G.A.	L-DOPA	8.1 g	9	6	7.5
W.L. (3rd treatment period)	MK-485 plus L-DOPA	300 mg	10	4	[b]
L.F.[a] (1st treatment period)	MK-485 plus L-DOPA	500 mg	9.5	6.0	7.5
L.F. (2nd treatment period)	MK-485 plus L-DOPA	500 mg	7.5	5	[b]
K.F.	MK-485 plus L-DOPA	750 mg	7	3.5	3.5

[a] Ratings represent psychiatrist double-blind ratings based on interviews. [b] Discharged on MK-485 plus L-DOPA.

depressive diagnoses (*see* Table I for diagnoses of the individual patients). In three of the four patients, the degree of improvement was essentially complete, that is, the patients were well enough to be discharged at the end of the treatment period. One patient (G.A.) improved only moderately on L-DOPA and subsequently showed a complete response to imipramine.

It is of considerable interest that none of the clinical responses to L-DOPA occurred among the agitated patients. This difference between the agitated and retarded groups in regard to L-DOPA response is statistically significant ($p < 0.05$). Thus, it appears that the patients most likely to show some clinical response to L-DOPA would be predominantly retarded without prominent features of agitation.

Figure 2 illustrates one of the patients classified as a responder (W.L.), a 65-year-old woman with a past history of periodic depressive episodes, without definite history of mania, who had experienced moderate to severe retarded depression (which included a suicide attempt) for four months prior to hospitalization. During the pre-DOPA period, she was given depression ratings in the moderately severe range by both the nursing rating team and a psychiatrist rater, all of whom were blind to the medication. Figure 2 shows mean depression ratings for three periods when it was above 3 g. The patient's behavior during the initial 33 days on placebo or low doses of DOPA was characterized by retardation, confusion, stereotyped slow speech, an inability to cry, sad facial expression, decreased appetite, and feelings of hopelessness and worthlessness. During the last 13 days of this period (on L-DOPA

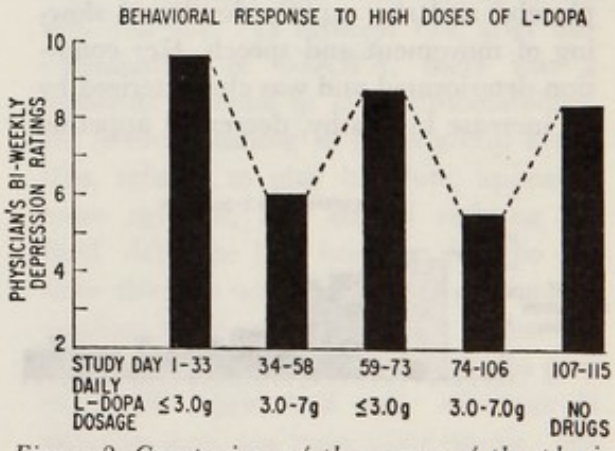

Figure 2. Comparison of the means of the physician's double-blind depression ratings for periods above and below 3 g L-DOPA per day. Three grams was chosen as the "cut-off" point for this analysis because this is the level where therapeutic effects begin to occur in the treatment of Parkinson's disease.

but below 3 g) there was a moderate but progressive decrease in these symptoms. From day 34 to day 58, the dose of L-DOPA was increased from 3 to 7 g/day and the patient showed a marked remission of symptoms. At first, there was an increase in activation with return of her ability to cry. Later, her depressed feelings decreased and she expressed a desire to leave the hospital. Increased speed of speech and movement were noted, along with a thawing of her previously "frozen" appearance.

On day 59, a placebo was again substituted for L-DOPA and she developed an exacerbation of depressive symptoms to the point where she was apathetic, withdrawn, disheveled, and hopeless; she could not laugh or cry, and secluded herself in her room. She was restarted on L-DOPA during the last nine days of this period but did not begin to improve until she reached the 3-g level of day 74, after which she continued to improve to a point where her speech assumed a normal speed and her therapist, who was blind to the medication, wrote: "she has shown a remarkable change in assertiveness and mood." On day 106 the patient was again placed on placebo and she rapidly developed slowing of movement and speech. Her condition deteriorated and was characterized by an increase in apathy, decreased appetite,

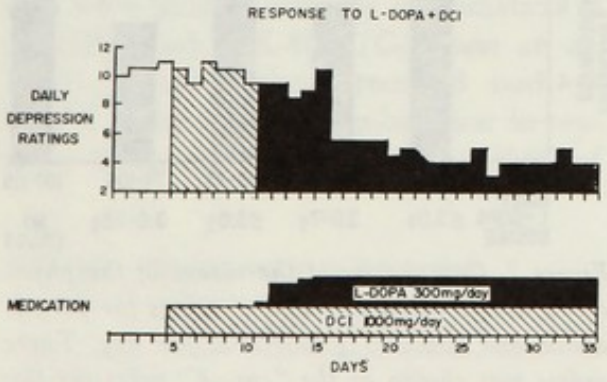

Figure 3. Clinical response to L-DOPA in combination with MK-485 (DCI—decarboylase inhibitor).

feelings of being very hopeless, and extreme passivity.

Following this she was started on L-DOPA for the third time, this time in combination with MK-485. Figure 3 illustrates the rapid and dramatic remission on this combination. This patient was discharged on MK-485 and L-DOPA and maintained on them as an outpatient for nine months, generally doing well but with occasional recurrences of depressive feelings. At this point she was readmitted and taken off the drugs, since data on possible toxicity with chronic use of MK-485 were not available. Again, following the placebo substitution, she became quite depressed, a change which was documented by the nurses' double-blind ratings. She later showed a therapeutic response to imipramine.

Second responder (G.A.), a 67-year-old male, was admitted with severe psychotic depression of one month's duration. He had experienced one previous episode of depression during the five years prior to this hospitalization. As illustrated in Fig. 4, there was a gradual and moderate decrease in depression ratings from 9 to 7 following L-DOPA administration and a slight increase when placebo was substituted. The psychosis rating (bottom bars) showed a more pronounced decrease from 6 to 1 and again a mild increase when L-DOPA was discontinued.

Prior to L-DOPA administration this patient showed a stable course of severe retarded depression, during which he was essentially mute and quite withdrawn most of the time, occasionally interspersed with periods of agitation characterized by increased anxiety, pacing, moaning, groaning, and an idiosyncratic snorting. During this time, he expressed a number of depressive and psychotic thoughts, including ideas that he was unable to swallow. He insisted that he had no pulse or blood pressure, asked to be cut open to see

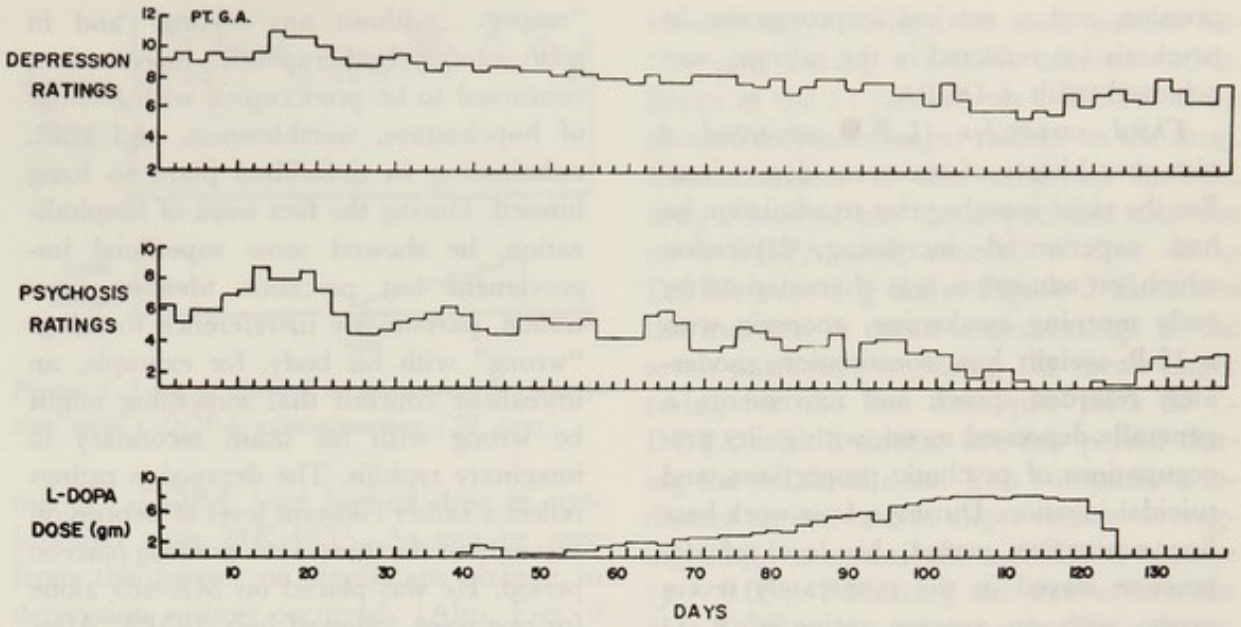

Figure 4. Change in depression and psychosis ratings on L-DOPA.

"what's stopping me up." During the week prior to the administration of L-DOPA, he said, "nothing is going to help me" and expressed other thoughts of hopelessness and worthlessness. He required continual urging to take fluids and to feed himself, and was paranoid and negativistic about the food.

L-DOPA was started on day 40, and was slowly increased to 3 g by day 70. At this point, the patient was described as somewhat more verbal with an increase in expression of anger. He continued to be psychotic, depressed, and periodically agitated, and showed no active participation in any group activities. Two weeks later, on day 83, when the patient reached the 5-g range, he spontaneously initiated conversation for the first time. There was a decrease in his resistiveness to eating, and a few days later he was described as more talkative and able to carry on a conversation. He was able to play his flute and dance. However, he remained somewhat paranoid and periodically appeared quite depressed.

During the period from day 90 to day 95, the patient continued to show some improvement, seemed much more relaxed, ate fairly well, and showed little evidence of psychotic thinking. He started to read magazines and did some painting. On day 103, he reached an 8-g dose and from that point on until the medication was discontinued on day 123, the patient continued to improve. There was no evidence of psychosis, he became more spontaneous conversationally, and was eating fairly well. On days 122 through 134, after discontinuation of L-DOPA, there was a moderate increase in his symptomatology. He needed pushing to go to group activities, refused to play his flute, appeared more agitated, and started resisting his food. After he had been on placebo for three days, he was described as pacing and needing more push; therapist notes "he appears apprehensive and anxious in general." He again had some elements of paranoia and was more preoccupied. The patient was subsequently treated with imipramine and over the course of four weeks showed a complete remission of symptoms, reaching a level of improvement greater than he had with L-DOPA. Thus, in this patient a moderate improvement in de-

pression and a marked improvement in psychosis (as reflected in the ratings) was achieved with L-DOPA.

Third responder (L.F.) presented a nine-year history of recurrent depressions. For the eight months prior to admission he had experienced increasing depression which, on admission, was characterized by early morning awakening, anorexia with a 15-lb weight loss, constipation, moderately retarded speech and movements, a generally depressed mood, with guilty preoccupations of psychotic proportions, and suicidal ideation. During a four-week base line evaluation period, his level of depression stayed in the moderately severe range, with an average rating of 9. L-DOPA was started after 12 days of pretreatment with MK-485. He showed slight improvement in depression during the 12 days on the peripheral decarboxylase inhibitor alone and, after one week on L-DOPA, he was noticeably improved (average rating 6), saying, "I have my energy and ambition back." Two days after placebo substitution, he was described as "angry and depressed," "showing hopelessness" — "I'll never get out of this . . .", and showed increased preoccupation with physical symptoms. The L-DOPA, MK-485 combination was restarted after ten days, and again there was a decrease in depressive symptomatology reflected in a rating drop from 7.5 to 5; the patient was subsequently discharged on lithium.

Fourth responder (K.F.) experienced the onset of depression abruptly four months prior to admission, when he awoke with unexplained feelings of anxiety and "extreme guilt." From that point on, his functioning deteriorated. He became socially withdrawn, and was unable to continue working, explaining that this was precluded by the "foul odor" of his body. He evidenced periods of psychomotor retardation, interspersed with bursts of increased anxiety and agitation. He felt "empty . . . without any feeling" and in spite of psychotherapeutic intervention, continued to be preoccupied with feelings of hopelessness, worthlessness, and guilt, culminating in unfulfilled plans to hang himself. During the first week of hospitalization, he showed some superficial improvement but psychotic ideation continued, particularly in reference to things "wrong" with his body, for example, an unrealistic concern that something might be wrong with his brain secondary to imaginary syphilis. The depression ratings reflect a rather constant level of depression throughout the three-week predrug placebo period. He was placed on MK-485 alone for one week followed by L-DOPA. After seven days on L-DOPA (when the dose had reached 250 mg) his depression ratings began to drop, and over the next six days he showed a steady decrease in depression, reaching a rating level of 3, reflecting a virtual absence of depressive symptoms. Four days later, placebo was substituted and the patient evidenced a mild recurrence of somatic preoccupations and feelings of depression, as noted by his physician.[2] However, after another few days off the drug, his mood again improved, and he maintained this improvement until discharge. Thus, although the depression in this patient clearly remitted while on L-DOPA and MK-485, the absence of relapse in the postdrug period makes the result equivocal.

Figures 5 and 6 illustrate treatment courses typical of the majority of patients, that is, lack of antidepressant response. At doses of 8 g, Q.M. (Fig. 5) showed no change in ratings of depression as compared with placebo or low drug periods. Patient W. T. (Fig. 6) received up to 1500

[2] However, the presumed change was slight and subtle and was not recorded in the double-blind nursing ratings.

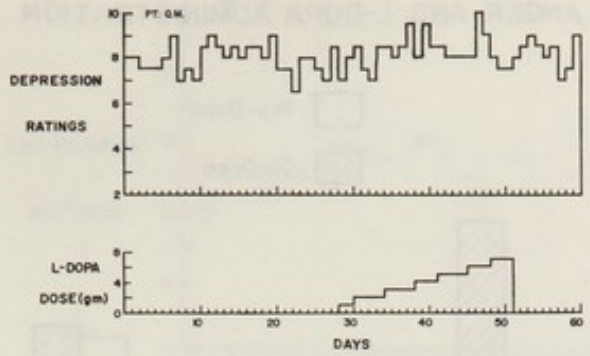

Figure 5. Lack of clinical improvement in depression with L-DOPA administration (23 days).

mg of L-DOPA (our highest dose in conjunction with MK-485). As can be seen from the figure, no significant change in depression ratings occurred. (Also, Figs. 9 and 10 illustrate the lack of improvement in depression ratings in two other patients on L-DOPA.)

Occurrence of Anger in Relation to L-DOPA Administration

Clinical impressions suggested that there may be a relationship between L-DOPA administration and the production of angry feelings and behavior. Therefore, we reviewed anger ratings for each patient before and during L-DOPA administration. Seven of the 11 patients on L-DOPA alone showed increased anger ratings on the drug. Characteristics of this subgroup include, first, a lack of any antidepressant response on L-DOPA and, second, a dose of L-DOPA over 4 g daily. Figure 7 illustrates the increase in mean anger ratings in the seven patients, comparing the mean anger rating for the five days just prior to L-DOPA with a similar five-day period during the maximal dose. This comparison indicates an increase in anger ratings averaging 35%, a statistically significant change ($p < 0.05$). Following the discontinuation of L-DOPA, the mean anger ratings decreased by 22%.

The global rating of anger is divided into three major components; verbal expression of anger, angry facial expression, and physical aggression to others. An analysis of these three subclassifications did not indicate an increase in physical aggressiveness towards others, but rather an increase in both verbal and facial expressions of anger. Figure 8 illustrates longitudinally

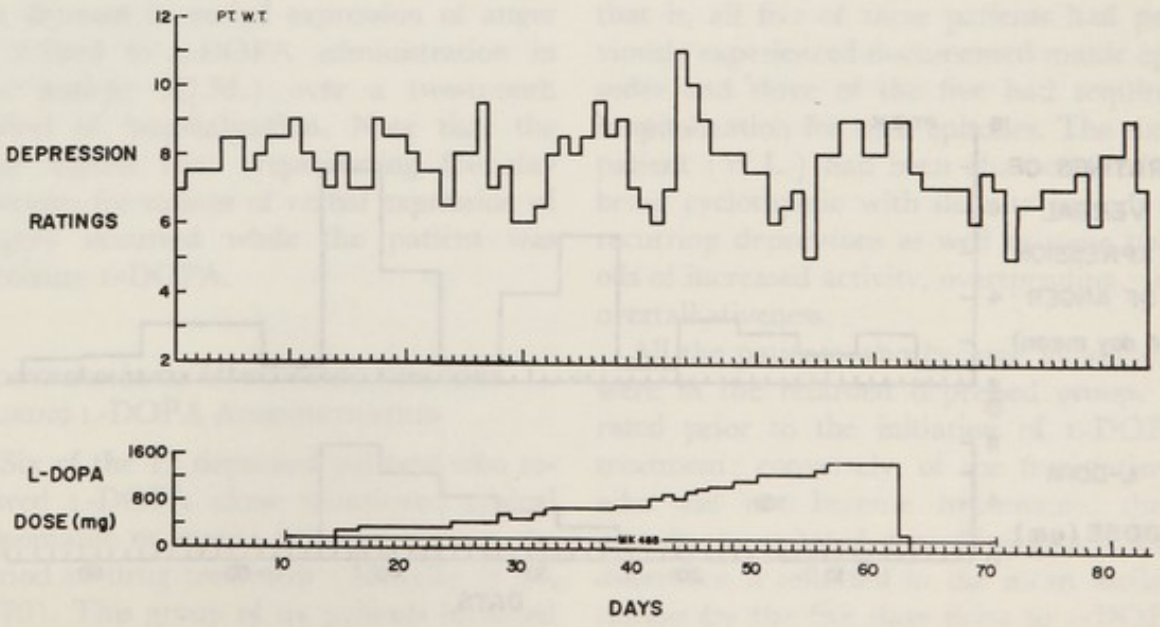

Figure 6. Lack of clinical improvement in depression with L-DOPA plus MK-485 administration (50 days).

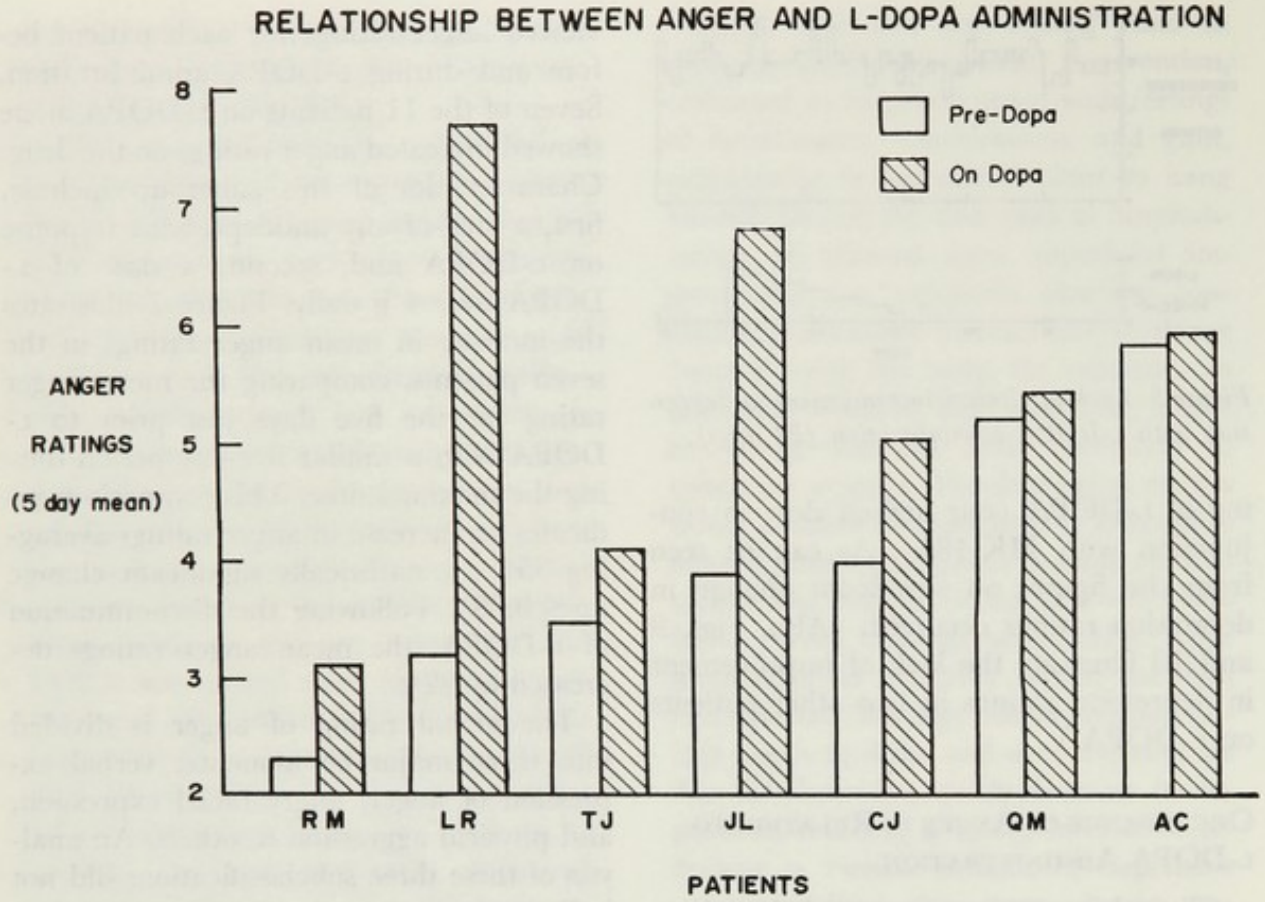

Figure 7. The open bars represent the mean of the anger ratings for the five-day period just prior to L-*DOPA; the cross-hatched bars represent the mean anger ratings for five consecutive days on the highest dose of* L-*DOPA.*

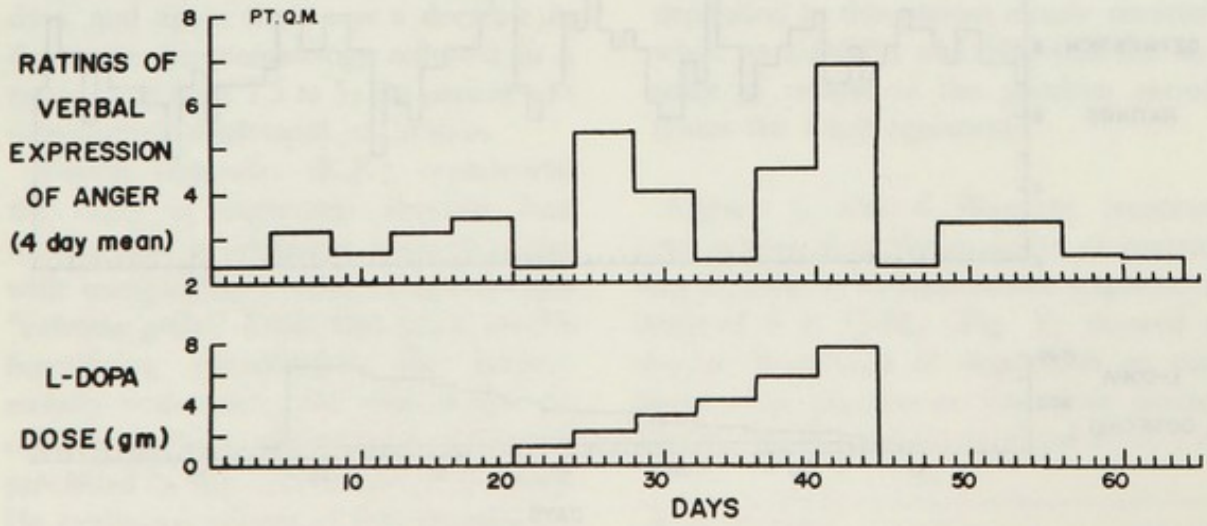

Figure 8. The top bars represent the mean of the ratings of verbal expression of anger for consecutive four day periods throughout the course of hospitalization in one patient.

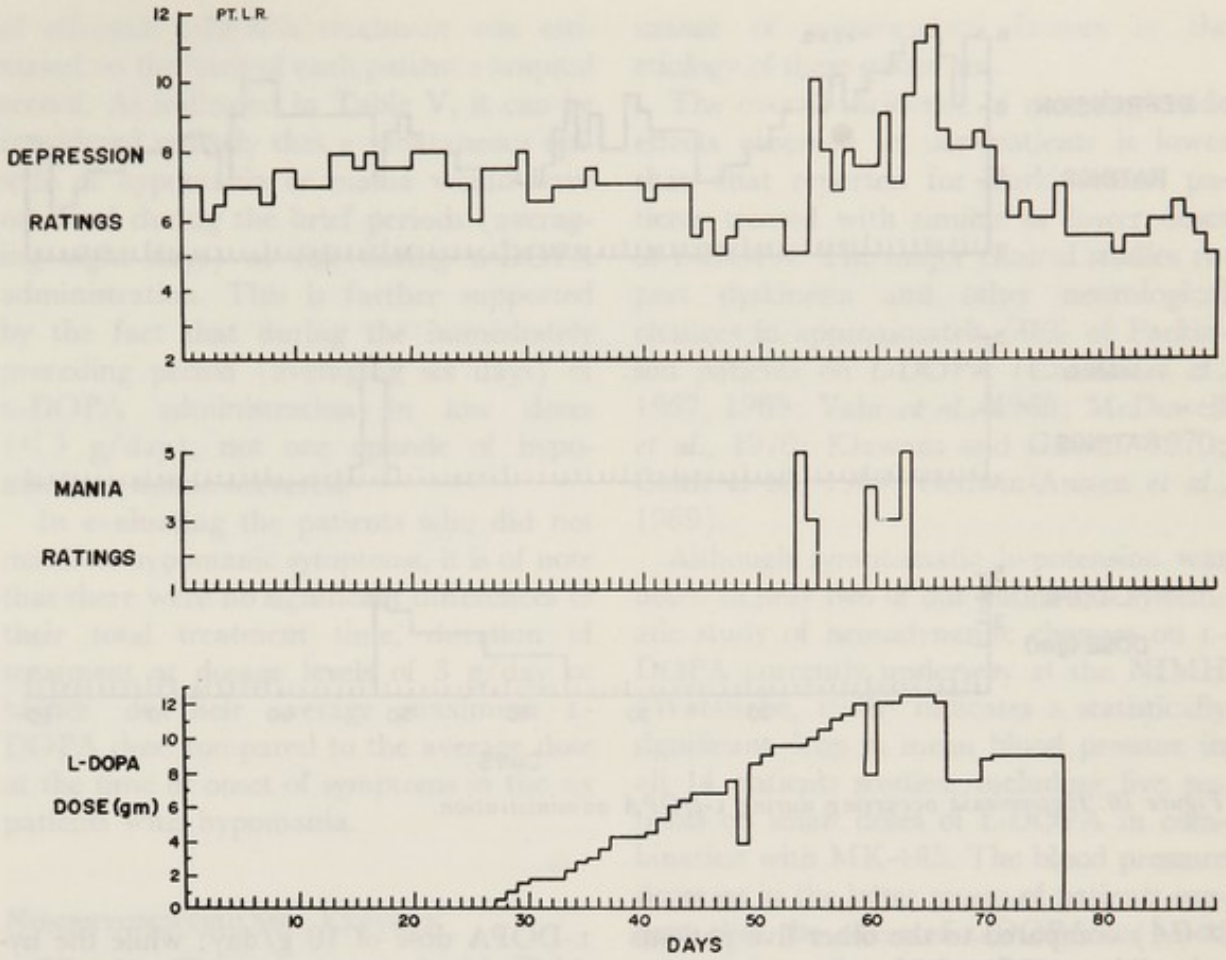

Figure 9. Hypomania occurring during L-*DOPA administration.*

the increase in verbal expression of anger as related to L-DOPA administration in one patient (Q.M.) over a two-month period of hospitalization. Note that the four highest bars (representing four-day averages for ratings of verbal expression of anger) occurred while the patient was receiving L-DOPA.

Occurrence of Hypomanic Episodes During L-DOPA Administration

Six of the 11 depressed patients who received L-DOPA alone manifested typical hypomanic or manic behavior during the period of drug treatment (Murphy *et al.*, 1970). This group of six patients included all five of the DOPA-treated patients who were diagnosed as being manic-depressive; that is, all five of these patients had previously experienced documented manic episodes and three of the five had required hospitalization for such episodes. The sixth patient (W.L.) had been characterized as being cyclothymic with definite periods of recurring depressions as well as some periods of increased activity, overspending, and overtalkativeness.

All the patients who became hypomanic were in the retarded depressed group, as rated prior to the initiation of L-DOPA treatment; conversely, of the five patients who did not become hypomanic, three were in the agitated depression group. This difference is reflected in the mean anxiety ratings for the five days prior to L-DOPA being significantly lower ($p < 0.05$) in the six patients who became hypomanic (6.8

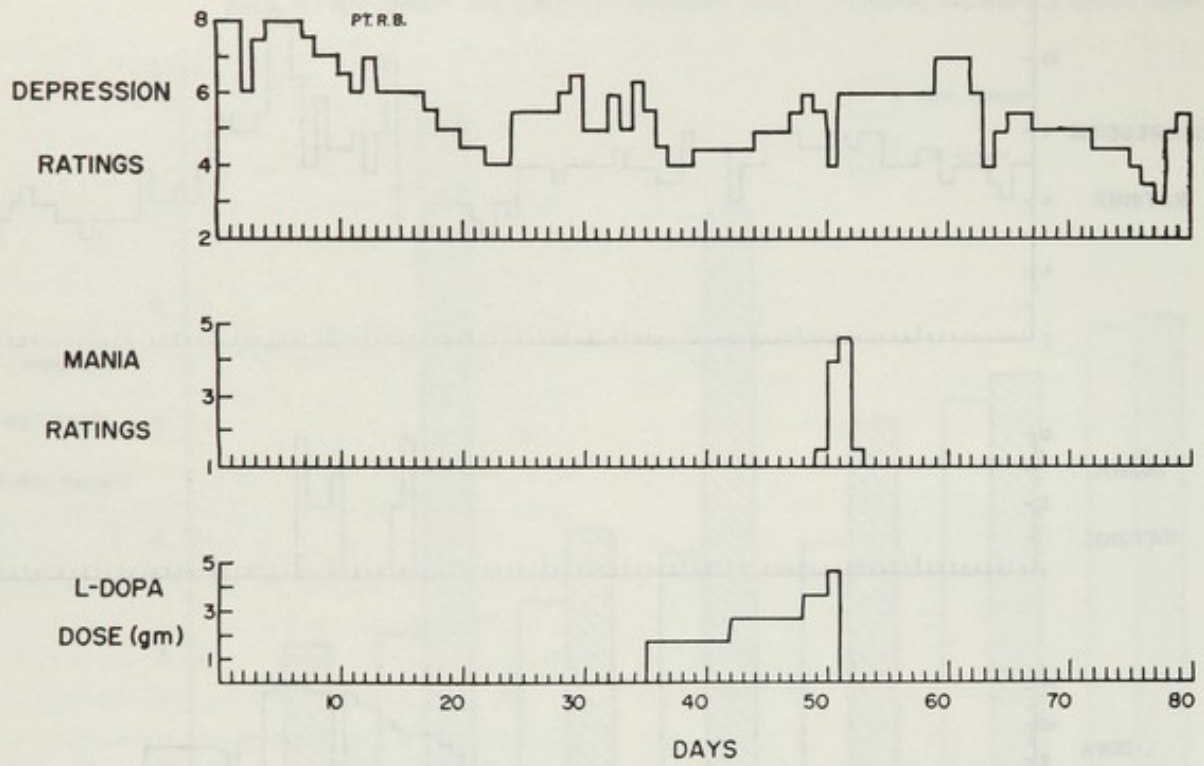

Figure 10. Hypomania occurring during L-DOPA administration.

± 0.4) compared to the other five patients who did not (8.9 ± 0.7).

The periods of hypomanic behavior were of several days duration and typically included increased motor and verbal activity with pressured speech, increased social involvement, intrusiveness, some increase in expressed anger, grandiosity, sleeplessness, some agitated behavior but minimal euphoria (present clearly only in the patient (W.L.) who became less depressed on L-DOPA). It is of considerable interest that during the periods of hypomania the patients generally were *not* less depressed in mood and no significant change in depression ratings was found for the group at this time.

In two of the patients the hypomanic episode was self-limited and administration of the drug was continued at the same dosage level without further manic symptoms. In one patient (L.R., illustrated in Fig. 9), mild hypomania occurred at an L-DOPA dose of 10 g/day; while the hypomania appeared self-limited, similar symptoms recurred when the dose was increased, disappearing again just before the L-DOPA dose was reduced. In two patients (one of whom is illustrated in Fig. 10), the onset of hypomanic symptoms at relatively low doses (4 g/day) led to discontinuance of the drug followed by disappearance of the hypomanic symptoms within 48 hr in both patients. One patient (J.L.) became frankly manic while receiving L-DOPA. This patient had experienced several similar episodes at approximately monthly intervals prior to beginning L-DOPA during a period of apparently stabilized depression. Discontinuation of L-DOPA was not followed by any immediate change; his manic symptoms persisted until eight days after cessation of DOPA treatment.

The probability of a spontaneous hypomanic episode occurring during the period

of effective L-DOPA treatment was estimated on the basis of each patient's hospital record. As indicated in Table V, it can be considered unlikely that a spontaneous episode of hypomania or mania would have occurred during the brief periods (averaging eight days) at risk during L-DOPA administration. This is further supported by the fact that during the immediately preceding period (averaging six days) of L-DOPA administration in low doses (< 3 g/day), not one episode of hypomania or mania occurred.

In evaluating the patients who did not manifest hypomanic symptoms, it is of note that there were no significant differences in their total treatment time, duration of treatment at dosage levels of 3 g/day or higher, or their average maximum L-DOPA dose compared to the average dose at the time of onset of symptoms in the six patients with hypomania.

Nonpsychiatric Side Effects

The side effects are summarized in Table II. Ten of the 11 patients receiving L-DOPA alone experienced some side effects; nausea, the most common side effect, was experienced by six patients, four of whom also had episodes of vomiting.

It is of note that the combined administration of L-DOPA with the peripheral decarboxylase inhibitor appeared to decrease substantially the incidence of gastrointestinal side effects, suggesting a predominance of extracerebral factors in the etiology of these symptoms.

The overall incidence of neurologic side effects observed in our patients is lower than that reported for Parkinsonian patients treated with similar or lower doses of L-DOPA. The major clinical studies report dyskinesia and other neurological changes in approximately 50% of Parkinson patients on L-DOPA (Cotzias *et al.*, 1967, 1969; Yahr *et al.*, 1969; McDowell *et al.*, 1970; Klawans and Garvin, 1970; Calne *et al.*, 1969; Godwin-Austen *et al.*, 1969).

Although symptomatic hypotension was noted in only two of our patients, a systematic study of hemodynamic changes on L-DOPA currently underway at the NIMH (Watanabe, 1970) indicates a statistically significant drop in mean blood pressure in all 14 patients studied, including five patients on small doses of L-DOPA in combination with MK-485. The blood pressure decrease in the latter group of patients suggests that the effect of L-DOPA on blood pressure is mediated centrally.

A cardiac arrhythmia characterized by bursts to premature ventricular contractions was encountered in one patient. Anorexia, a common side effect of L-DOPA in Parkinson patients, was, of course, difficult to evaluate in our population of depressed patients, since many of them experience this symptom as part of their depression. No hematologic, renal, or hepatic dysfunctions were noted.

Table V. Patients with hypomanic or manic episodes during L-DOPA treatment

Patient	Sex	Age	Diagnosis[a]	Mania attack frequency[b]	Days on L-DOPA, 3+ g/day, prior to hypomania	L-DOPA dose at time of hypomania onset (g/day)	Probability of hypomania occurring with L-DOPA, 3+ g/day
A.C.	F	55	M.D.	3/203	1	3.0	1/68 0.02
R.B.	F	42	M.D.	2/156	7	4.0	7/78 0.09
J.L.	M	42	M.D.	4/76	6	6.0	6/19 0.32
T.J.	M	47	M.D.	0/113	2	4.0	— < 0.01
L.R.	M	43	M.D.	0/101	18	10.0	— < 0.01
W.L.	F	52	P.D.	0/217	13	7.0	— < 0.01

[a] M.D., manic-depressive illness; P.D., psychotic depression. [b] Episodes of mania per nonmanic days in hospital.

Table VI. CSF metabolites and L-DOPA administration

DOPA dose	Number of determinations	HVA ng/ml	5-HIAA ng/ml
Pretreatment	10	30 ± 7	25 ± 6
DOPA (8–9 g)	10	425 ± 92[a]	20 ± 3
MK-485 plus DOPA (Avg. dose 650 mg)	7	120 ± 20[b]	19 ± 3
Post-DOPA (12–15 days)	2	7 ± 2	19 ± 3

[a] Statistically significant ($p < 0.001$) when compared with the pretreatment values. [b] Statistically significant ($p < 0.01$) when compared with the pretreatment values.

Biological Results

Changes in Amine Metabolites in CSF

Table VI shows the CSF levels of 5-HIAA and HVA in relation to L-DOPA administration. Levels of HVA, the principal metabolite of dopamine in the central nervous system, increased over tenfold in two patients receiving 8–9 g L-DOPA daily. In patients who received a combination of L-DOPA with MK-485 the HVA levels were moderately increased over pretreatment levels. There is no significant change in 5-HIAA levels with high doses of L-DOPA or with L-DOPA in combination with MK-485.

Measurement of amine turnover is of more functional significance than levels alone. Work is currently underway in our laboratory on a method for the determination of amine turnover in brain in patients which uses probenecid to block exit of the acid metabolites from CSF; this technique allows estimation of turnover as reflected in the rate of accumulation of indoleamine and catecholamine metabolites in CSF. Preliminary results (in two patients) indicate an increase in brain dopamine turnover and a decrease in serotonin turnover following the administration of L-DOPA plus MK-485 (Tamarkin *et al.*, 1970).

Changes in Urinary Amine Metabolites on L-DOPA

Twenty-four-hour urinary excretion of DOPA, DA, and HVA was determined in four patients for the pre-DOPA period and at four different dose levels. Very large increases in all three compounds were observed. In Table VII typical results from one patient are presented; note that the increases were approximately linear with increasing dose.

The question whether L-DOPA treatment results in increases in NE is of considerable interest; we therefore examined 24-hr urinary excretion of VMA and MHPG, both metabolites of NE. Preliminary data from two patients are available. In one patient (Fig. 11) both VMA and MHPG were approximately doubled at high doses of L-DOPA (8 g) but showed no change at lower doses (2 g). The second patient (Fig. 12) also showed a

Table VII. Urinary excretion of DOPA, dopamine, and HVA as related to L-DOPA administration in one patient (C.J.)

L-DOPA dose, g/24 hr	Urinary excretion (mg/24 hr) DOPA	Dopamine	HVA
0	0.074 ± 0.04	0.98 ± 0.07	5.5 ± 1.1
2	1.77	21.6	742
4	7.4 ± 2.7	61.1 ± 3.1	1290 ± 13
6	33.4 ± 0.97	206.2 ± 2.5	2400 ± 20
8	27.3	206.2	2800

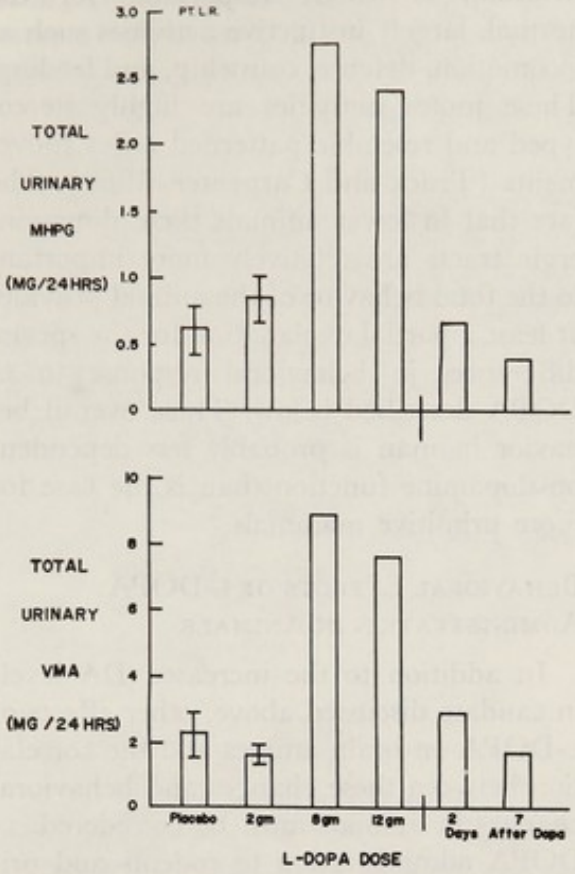

Figure 11. Changes in urinary MHPG and VMA in relation to L-*DOPA administration in one patient.*

doubling of VMA and MHPG on L-DOPA (4 g); in addition, very large increases in MHPG, but not VMA, were observed in this patient during a brief episode of hypomania. Cautious interpretation of these data is necessary in the light of the small number of determinations; nevertheless this large increase in MHPG (without a change in VMA) during the manic period is interesting in light of the evidence of Maas and Landis (1968) suggesting that changes in urinary MHPG may reflect NE metabolism in brain.

Cortical-Evoked Potential Changes and Sleep Changes During L-DOPA Treatment

Serial determinations of cortical-evoked potentials following visual stimuli were obtained in 12 patients during the course of L-DOPA treatment (Buchsbaum *et al.*, 1970). In almost all of the patients an increase in the average evoked response amplitude-intensity slope was produced by L-DOPA. These changes signify an augmentation or apparent amplification of sensory input, and are in the opposite direction from those produced by α-methyl-*p*-tyrosine which inhibits catecholamine synthesis (Spector *et al.*, 1965).

A preliminary analysis of longitudinal sleep recordings made prior to and during L-DOPA treatment in five patients indicates a definite reduction in rapid eye movement (REM) sleep duration during the period of drug administration (Fram, 1970). This change is also in the opposite direction from the increase in REM sleep accompanying the initial period of α-methyl-*p*-tyrosine administration in man (Wyatt, 1970). These evoked response and sleep results supplement the CSF neurochemical changes in confirming that central effects were achieved during L-DOPA treatment in these patients.

Discussion

The administration of large amounts of L-DOPA undoubtedly produces a variety of biochemical effects in brain, particularly on the biogenic amine neurotransmitters,

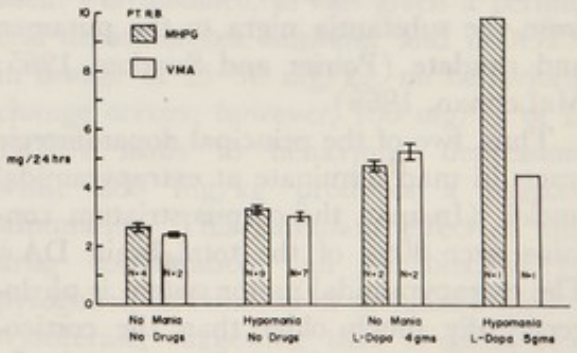

Figure 12. Changes in urinary MHPG and VMA in relation to L-*DOPA administration and hypomania in one patient.*

dopamine, norepinephrine, and serotonin.

Of these, dopamine deserves our primary focus since the changes in this amine following L-DOPA administration have been more extensively studied and the results appear to be more consistent and straightforward than is the case with either NE or DA. For example, it is well documented (Pletscher and Bartholini, 1969) that L-DOPA administration to animals in doses comparable to those used in our patients results in an increase in the DA content of the caudate nucleus, an area rich in dopaminergic neurons. (However, no information is yet available on L-DOPA effects on DA turnover.)

Dopamine Function in Brain

Hornykiewicz (1966) has reviewed the evidence that dopamine is a physiologically active substance in brain, involved in the function of some extrapyramidal centers, specifically the neostriatum. Under conditions of direct iontophoretic application to neuronal membranes, dopamine has been shown to suppress synaptic discharge in some brain areas (Bloom, 1965) while exciting it in others (York, 1968). There is good evidence in primates that dopamine is involved as a synaptic transmitter in the caudate, specifically in a pathway leading from the medial thalamus (McLennan, 1967). Evidence has also accumulated for the involvement of dopamine in a pathway from the substantia nigra to the putamen and caudate (Poirier and Sourkes, 1965; McLennan, 1965).

Thus, two of the principal dopaminergic tracts in man terminate at extrapyramidal nuclei. (In man the corpus striatum contains over 80% of the total brain DA.) The extrapyramidal motor system is phylogenetically much older than the corticospinal system found only in mammals. In more primitive animal species the extrapyramidal system, particularly the corpus striatum, is wholly responsible for the normal, largely instinctive activities such as locomotion, defense, courtship, and feeding. These motor activities are highly stereotyped and resemble patterned reflex movements (Truex and Carpenter, 1969). The fact that in lower animals these dopaminergic tracts are relatively more important to the total behavior of the animal provides at least a partial explanation for the species differences in behavioral response to L-DOPA described below. Thus, overall behavior in man is probably less dependent on dopamine function than is the case for more primitive mammals.

Behavioral Effects of L-DOPA Administration in Animals

In addition to the increased DA levels in caudate discussed above, other effects of L-DOPA on brain amines and the correlation between these changes and behavioral changes in animals must be considered. L-DOPA administration to rodents and primates can produce a variety of effects on activity and behavior which appear dose-dependent and species-related. Behavioral changes after L-DOPA have most often been studied following pretreatment with other drugs, including reserpine, monoamine oxidase inhibitors, decarboxylase inhibitors, or inhibitors of catecholamine synthesis.

L-DOPA administered alone may either depress or activate motor activity and conditioned avoidance behavior, with lower doses generally inhibiting, and higher doses stimulating, behavior. Doses of L-DOPA below 50 mg/kg generally produce no effect (Butcher and Engel, 1969; Scheckel *et al.*, 1969).

In somewhat higher doses (100–500 mg/kg), L-DOPA decreases spontaneous motor activity, conditioned avoidance responses, schedule-controlled operant behavior, and produces a sedated appearance in rats (Butcher and Engel, 1969; Scheckel

et al., 1969; Boff and Heise, 1963). However, a "slight increase" in motor activity in mice was observed ½ hr after L-DOPA, 200 mg/kg, in one study (Everett and Wiegand, 1962).

At L-DOPA doses of 500–1000 mg/kg, excitement, hyperactivity, and irritability have been observed, particularly in mice, and less often in rats (Scheckel *et al.*, 1969; Everett and Wiegand, 1962). The increased activity seen in rats 90 min after 800 mg/kg was followed by death at 4 hr (Lotti and Porter, 1970). Perhaps of greater relevance to our clinical data are the findings of Scheckel *et al.* (1969) indicating stimulation of motor activity in monkeys at lower doses (100 mg/kg) than in mice, rats, or rabbits.

Reserpine Plus L-DOPA

The ability of L-DOPA in doses approximating those used in our patients to reverse reserpine-induced sedation and decreased activity in animals has been well documented; thus in reserpinized animals L-DOPA leads to marked increases in motor activity, conditioned avoidance-response behavior, aggressiveness, and excitation. The "awakening effect" is immediate, with excited motor activity persisting for 2–3 hr and then gradually decreasing, until the animals return to the reserpinized state in 4–8 hr (Everett and Wiegand, 1962; Carlsson, 1959; Blaschko, 1959). These changes have been related to increases in brain dopamine; this interpretation is supported by the evidence that in reserpinized animals dihydroxyphenylserine, which restores brain norepinephrine but does not restore dopamine levels, also does not restore activity (Creveling *et al.*, 1968). Similarly, tryptophan administration, which returns brain serotonin levels to prereserpine levels also does not reverse the depressed behavioral state (Carlsson, 1965).

MAO Inhibitors and Decarboxylase Inhibitors Plus L-DOPA

Monoamine oxidase inhibitors and L-DOPA produce an "alerting effect" in the rabbit and monkey, while rats given an MAO inhibitor plus L-DOPA in amounts as high as 500–1000 mg/kg exhibit no behavioral changes (Scheckel *et al.*, 1969).

The selective inhibition of DOPA decarboxylase in the periphery by several different compounds in combination with L-DOPA leads to much higher brain dopamine levels and unusual forms of behavioral activation. Hyperkinesia and stereotyped head and forepaw movements have been observed (Butcher and Engel, 1969). Motor excitation plus a bizarre form of social behavior in response to stimulation by noise (male rats stand in pairs face to face) follows a dose of 62 mg/kg of L-DOPA plus the inhibitor. Under these conditions female rats exhibit behavior suggesting sexual arousal with masculinelike mounting behavior. These responses are blocked by chlorpromazine and haloperidol (Randrup and Munkvad, 1969; Lammers and Van Rossum, 1968).

Rats, mice, monkeys, and dogs all exhibit some behavioral excitation following a peripheral decarboxylase inhibitor plus L-DOPA in lower dosage than amounts which will produce behavioral effects by itself. For instance, in rats given a peripheral decarboxylase inhibitor and L-DOPA in dosage of 25–50 mg/kg, no behavioral change occurs; however, 100 mg/kg of L-DOPA leads to behavioral depression, while 200 mg/kg produces a marked stimulation. This stimulant effect of this drug combination can be blocked by pyrogallol, an inhibitor of catechol-*o*-methyl transferase, suggesting that a methylated product of DOPA or DA may be involved in the behavioral change (Scheckel *et al.*, 1969; Jonas and Scheel-Kruger, 1969;

Ernst, 1965). In relation to this Bartholini *et al.* (1969) have demonstrated substantial increases in brain *o*-methyl-DOPA following L-DOPA plus a peripheral decarboxylase inhibitor.

The decrease in conditioned avoidance responses produced by the inhibition of catecholamine synthesis by α-methyl-*p*-tyrosine is restored by L-DOPA, 100 mg/kg.

Brain Amine Changes in Animals

L-DOPA produces large increases in brain DA (Everett and Wiegand, 1962) a substantial portion of which may remain in the wall of the small brain capillaries (see below). Although the level of NE in the brain is not elevated by large doses of L-DOPA (Iversen, 1967; Butcher and Engel, 1969; Everett and Borcherding, 1970), we have recently demonstrated a significant increase in the *turnover* of NE following the oral administration of L-DOPA (200 mg/kg) to rats (Gershon *et al.*, 1970).

Pretreatment with an inhibitor of monoamine oxidase is reported to potentiate the DOPA-induced rise in both DA and NE, but the percent elevation in DA is greater than in NE (Everett and Wiegand, 1962). In the reserpinized animal the evidence that L-DOPA administration increases brain NE is more consistent (Seiden and Peterson, 1968), but in this situation the amine is being increased from approximately 5% to only 15% of normal. Variations from study to study in regard to L-DOPA dose, pretreatment with other drugs, species, assay method, and brain area examined make generalization difficult, particularly when one attempts to correlate behavioral change with changes in any one amine. However, it is clear that under all conditions reported the *ratio* of DA to NE in brain is increased by L-DOPA administration.

It is also of importance to consider the effects of L-DOPA on brain 5-HT metabolism and function. Substantial decreases in endogenous levels of brain 5-HT have been reported following large doses of L-DOPA alone (Butcher and Engel, 1969; Scheckel *et al.*, 1969; Everett and Borcherding, 1970), or in combination with a peripheral decarboxylase inhibitor (Butcher and Engel, 1969; Scheckel *et al.*, 1969; Bartholini *et al.*, 1968). L-DOPA has been shown to compete with 5-hydroxytryptophan (5-HTP), the precursor of 5-HT, for uptake into brain (Bartholini *et al.*, 1968); also L-DOPA competitively inhibits the decarboxylation of 5-HTP in brain tissue (Bartholini *et al.*, 1968; Yuwiler *et al.*, 1959). Pretreatment with parachlorphenylalanine, an inhibitor of 5-HT synthesis, prevented the behavioral stimulation associated with L-DOPA plus a peripheral decarboxylase inhibitor; these data along with data on increases in 5-HIAA with L-DOPA administration suggest that at least a part of the mechanism of behavioral stimulation of L-DOPA involves 5-HT release (Scheckel *et al.*, 1969).

Clinical Results in Depression

What implications, if any, can be drawn from the evidence presented here that L-DOPA clearly was not an antidepressant in the majority of our patients? It could be argued that the dose or duration of treatment may not have been sufficient; this argument is a difficult one since it is clear that we were producing both biochemical changes (reflected in CSF) and physiological changes (alterations in cortical-evoked potentials, production of centrally mediated side effects). Furthermore the doses used were equal to or greater than those shown to produce clear-cut improvement in Parkinsonism patients.

L-DOPA in doses comparable to those reported here consistently reverses reserpine-induced sedation in animals (Hornykiewicz, 1966) and in man (Degwitz *et al.*, 1960),

but clearly does not reverse the majority of clinical depressions. From this it seems reasonable to conclude that amine depletion (as defined by the reserpine model) is not a sufficient explanation of the pathophysiology of depression in the majority of our patients.

The interpretation of the increased brain DA in animals on L-DOPA, as well as the increased HVA in the CSF of patients on the drug, must be made cautiously. It has been shown by fluorescent histochemical techniques (Bertler *et al.*, 1966) that at doses below about 50 mg/kg, L-DOPA does not penetrate into the brain parenchyma, but rather gets "trapped" within the capillary wall where it is decarboxylated to DA; this trapping mechanism is not overcome until doses over 50 mg/kg are achieved. Thus, a substantial portion of increases in brain DA following L-DOPA administration represents capillary wall DA. It is quite possible that the very large levels of HVA in the CSF seen after L-DOPA administration are the result of metabolism of DA within the vascular wall to HVA with subsequent passage into the subarachnoid space and then into the CSF. Furthermore, Taylor and Laverty (1969) have recently presented evidence that brain HVA levels reflect predominantly the extraneuronal metabolism of DA. Peripheral decarboxylase inhibitors have been shown to prevent the decarboxylation of DOPA in the capillary walls of brain, resulting in the appearance of DA (as seen by fluorescence techniques) throughout the parenchyma (Bertler *et al.*, 1966). In light of this, it is of interest that the HVA level in the CSF of patients on MK-485 plus DOPA is significantly lower than in patients on L-DOPA alone—in spite of similarity in therapeutic response (Parkinson patients: Cotzias *et al.*, 1969; Siegfried, 1969) or centrally mediated side effects (our patients). Thus the difference between the HVA in the two groups of patients may represent "spillover" of DA that never reached neurons but was metabolized in the capillary wall.

The questions of why a small subgroup of these patients (4 out of 16) showed an apparent antidepressant response to L-DOPA is of course quite interesting. The one feature which tended to differentiate them from the nonresponders was the presence of psychomotor retardation (although there were some retarded patients who did not respond). Some of the animal data suggest that dopamine function might be more involved in the level of psychomotor activation than in mood, and L-DOPA did produce some form of "activation" in virtually all our patients. Perhaps the responders reacted to this activation as indicating impending improvement, and this alone may have been sufficient to mobilize them out of their depression. The relapse after placebo substitution could also follow from a withdrawal of this activation.

An additional hypothesis relevant to the interpretation of our clinical data suggests that functional abnormalities in different amines might characterize separate subgroups of depressed patients. Monoamine oxidase inhibitors or imipramine are effective in the majority of depressions since they each potentiate both catecholamines and indoleamines, whereas DOPA or tryptophan would be useful only in patients with a functional deficiency in catecholamine or indoleamine respectively. Thus, the use of these precursors might serve to separate out "indoleamine depressions" from "catecholamine depressions."

Increased Anger During L-DOPA Administration

L-DOPA administration has been associated with increased biting behavior in mice (Vanderweade, 1962) and fighting (Everett and Borcherding, 1970). Randrup and Munkvad (1969) have shown an increase in biting behavior in rats fed L-

DOPA, a behavior they classify as stereotyped in nature, and which is attributed to elevated striatal dopamine concentrations. Similar behavior has been elicited via the activation of dopaminergic receptors in striatum by microinjections of dopamine and apomorphine (Ernst, 1966).

The administration of L-DOPA plus a monoamine oxidase inhibitor to rats produces an aggressive response characterized by increased biting and active fighting (Randrup and Munkvad, 1969). These authors hypothesize that dopamine formation is responsible for that part of the aggressive behavior which can be labeled stereotyped, such as biting, and that norepinephrine synthesis is responsible for such components of aggression as attacking. If this distinction can be made, then L-DOPA administration to humans might be accompanied by one or both of these elements of aggression.

We have evaluated our ratings of physical aggression in the patients receiving L-DOPA and can find no evidence of an increase in this form of aggressive activity, neither did we observe any apparent stereotyped behavior. However, anger ratings did increase in all patients receiving high doses of L-DOPA (4g) who showed no antidepressant response. This increase in verbal and facial expression of anger might represent a less primitive form of aggressive behavior in man and could be associated with increased catecholamine synthesis from the administration of L-DOPA.

Occurrence of Hypomania During L-DOPA Administration

Although hyperactivity and agitation are reported among the frequently encountered psychological side effects in L-DOPA treatment of Parkinson's disease, hypomania, or mania is apparently much less common. Several large studies, including one of over 100 patients, do not even mention hypomania as a side effect; in these studies hyperactivity and agitation occurred in approximately 5% of the patients (Cotzias *et al.*, 1967, 1969; Yahr *et al.*, 1969; McDowell *et al.*, 1970; Klawans and Garvin, 1970). In the present study, the very high incidence of hypomania in this psychiatric patient group is directly attributable to the inclusion of manic-depressive patients, since all of these patients manifested hypomanic or manic behavior during treatment with L-DOPA alone. This strongly suggests that this effect of L-DOPA can be considered an activation of the hypomanic syndrome in an affect-labile individual.

Only one of the patients who became hypomanic was considered to have become clearly less depressed while receiving L-DOPA. In most patients, the several day period of hypomania was associated with minimal or transient changes in depression ratings. In the patient illustrated in Fig. 9, the two hypomanic episodes occurred during the patient's most severely depressed period. A similar coexistence of depression during spontaneous manic periods has been observed previously in many manic-depressive patients studied on our units, and appears to be more common than any pattern of clear-cut alteration between these two states (Goodwin *et al.*, 1969).

The induction of hypomania by L-DOPA is of special interest in the light of the hypothesis implicating an excess of brain catecholamines in mania (Bunney and Davis, 1965; Schildkraut, 1965). The contrast between the consistent activation of hypomania in the manic-depressive subgroup and the absence of a consistent change in depression suggests several possibilities: (i) the catecholamine hypothesis for mania as originally stated may only apply strictly to persons with a preexisting abnormally labile affect state; (ii) the catecholamine hypothesis for depression seems an oversimplification in that doses of L-DOPA large enough to produce hypomania are not capable of reversing depression; and (iii)

depression and mania may prove to be separable entities (albeit often occurring together) and thus may not be simply the clinical reflections of opposite poles of a single biochemical continuum.

In recent studies with manic-depressive patients, the sequence of changes in the "switch process" from depression to mania has been examined in relation to catecholamines (Bunney *et al.*, 1970*a*). Increased excretion of urinary catecholamines as well as a decrease in REM sleep, which is thought related to brain amines, occur just prior to and at the onset of spontaneous switches into mania in depressed patients. The administration of imipramine, which is thought to act by increasing effective biogenic amine concentrations at synapses by inhibiting amine reuptake (Iversen, 1967), can also lead to manic episodes with similar changes in sleep patterns, particularly in manic-depressive patients. The similar capability of L-DOPA administration to reduce REM sleep and to induce hypomania thus provides further direct support implicating brain catecholamine changes in the switch process from depression to mania.

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Catecholamines and Affective Disorders Revised: A Critical Assessment

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It is the object of this paper to look again at the catecholamine theory of affective disorders, one of the biochemical postulates underlying this group of emotional illnesses that has perhaps had the greatest impact on psychobiological research. Nearly a decade has passed since the introduction of this hypothesis, and, although the literature has been extensive, there has been little attempt to appraise this theory with a discriminating critical eye. The review that follows is not impartial, however comprehensive; it brings together and focuses on, perhaps for the first time, bodies of negative or controversial data which fail to confirm this theory. Included here are several clinical-biochemical studies collaboratively undertaken by our departments. Although it does appear that changes in the metabolism of norepinephrine can occur concomitantly with clinical change in affective state, the etiological significance of these changes remains obscure, however, and awaits clarification. The available clinical-biochemical evidence offered in this paper cannot readily support any theory of disturbed norepinephrine metabolism as specific or pathognomonic, for either manic or depressive illness.

The era of neuropsychopharmacology has had the greatest impact on psychiatric theory and practice since Freud. The formulation of the catecholamine hypothesis of affective disorders stands as the hallmark of progress in this behaviorally oriented biological science. The intuitively brilliant theory, however reductionistic or simplistic in retrospect, has nevertheless provided a unique heuristic stratagem for exploring the group of affective illnesses. A greater appreciation of nosological and phenomenological aspects of manic and depressive illness has emerged, as well as potential genetic penetration into these disorders. Extending far beyond the bounds of affective illness or even of psychiatry, histochemical and neurochemical insights into the metabolism of brain amines (which were only dimly suspected a decade ago) have been advanced in pursuit of these theories.

Although, when devised, the available experimental data were consistent with the "catecholamine theory," the portrait fashioned from contemporary investigational evidence makes this hypothesis less tenable at this point. This does not rule out the possibility that affective disorders involve a disturbance in norepinephrine or other catecholamines.

Implications are, however, that, if we are to advance our knowledge in this area of psychobiological research, then newer, equally inventive, and more sensitive approaches need to be designed to elucidate the role of the adrenergic system as well as of other neuronal systems in these psychiatric disorders. Although the experimental approaches and systems to be explored will by necessity differ, it is anticipated that the resulting insights will eventually converge with previous data to elaborate the mechanisms underlying the affective illness entities.

Blood and Urine

If attempts at uncovering an abnormality in the metabolism of norepinephrine (NE) in patients with affective disorders have not produced convincing evidence to support the existing hypothesis, the studies focusing on the analysis of NE or its metabolites in blood or urine may contribute least to any existing hypotheses. Epinephrine and NE are continuously synthesized, released, and metabolized in the body. Small amounts of both amines are always present in arterial blood, and exposure to a variety of both physical and mental stimuli can induce changes in secretion. Almost all of the circulating epinephrine originates from the adrenal medulla, although small amounts may be produced by chromaffin cells in other organs. The greater part of circulating NE is released as a neurotransmitter by the sympathetic nerve endings, while a minor portion is produced by the adrenal medulla. Blood levels are difficult to interpret quantitatively (60) and the methodology used at the time of early studies was neither sensitive nor specific enough to measure adequately plasma cathecholamines reliably (107). Although epinephrine excretion may provide a satisfactory quantitative measure of the rate at which this hormone is secreted by the adrenal medulla, urinary NE probably gives a less reliable estimate of sympathetic activity, since a large part of the NE released is reabsorbed by the nerve endings and does not enter the blood stream or urine. Only a small portion of the epinephrine and NE released into the blood is excreted as the free amine, the major part being metabolized or rebound before excretion. The catecholamine metabolite 3-methoxy-4-hydroxymandelic acid (vanillylmandelic acid, VMA) occurs in urine in considerably larger amounts than the free amines. However, this metabolite is formed by both epinephrine and NE, and VMA estimates, therefore, do not give any information about the relative secretion of the two amines under different conditions (41).

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Blood

Catecholamine Concentrations

With regard to studies dealing with plasma catecholamine concentrations, and contrary to the suggested catecholamine hypothesis, Wyatt *et al.* (109) measured the total resting catecholamine concentration from 13 drug-free depressed patients and found concentrations to be significantly elevated over concentrations from 47 normal controls. Differential determinations of epinephrine and NE reveal that both catecholamine components were elevated in the patients. Not only were plasma NE concentrations elevated in the depressed patients but, in two subjects who responded to psychotherapy as sole treatment, plasma catecholamine concentrations decreased with amelioration of the depression and anxiety.

Seven other patients treated with a monoamine oxidase inhibitor and two treated with a tricyclic compound also had improvement associated with change from initially elevated plasma catecholamine concentration toward normal levels. Plasma catecholamine concentrations in other studies (69, 84) have failed to differentiate between depressed patients and normal subjects.

Dopamine-β-Hydroxylase (DβH) Activity

DβH catalyzes the last step in NE biosynthesis; it is the enzyme which converts dopamine to NE (59). The more recent development of a sensitive assay system (14, 73) has permitted the detection of this enzyme in serum of both man and rat (103). Although the source of circulating DβH has not been clearly defined, it has been suggested that it is a reflection of peripheral sympathetic activity involving the release of catecholamines (6). In animals (103) and man (6), stress has been shown to elevate serum DβH, which suggests that the serum enzyme activity rises in a situation known to cause an increased release of catecholamines. Since the affective illnesses constitute a psychiatric entity, in which NE or its release is believed to play an important role, our group (95) measured DβH in the serum of such psychiatric patients. The psychiatric population included bipolar subjects, neurotic depressives, endogenous depressives (bipolar and unipolar), schizophrenics, and character disorders.

Serum DβH activity in the psychiatric subjects investigated failed to differentiate the various diagnostic groups; the emotionally ill population did not show blood levels varying from normal controls with the same age range (Figure 1).

Although some patients in all psychiatric diagnostic groups showed DβH levels below the normal range, they did not have clinical or biochemical correlates that differed from other patients having the same diagnosis; nor did these individuals differ by age, sex, severity/duration of episode, or extent of motor activity. Abnormal DβH activity in these relatively few patients would thus appear related to secondary factors other than psychiatric illness. Serum DβH activity is said to reflect peripheral sympathetic function; preliminary work by Freedman, Shopsin, and Goldstein with guanethidine supports this conclusion in humans. Measurement of this enzyme (like the measure of NE/NE metabolites in blood or urine) appears, therefore, relevant to any overall assessment of studies exploring peripheral NE metabolism in the affective disorders. Based on our findings with DβH, support for linking abnormal peripheral NE metabolism to the affective psychiatric entities is not forthcoming.

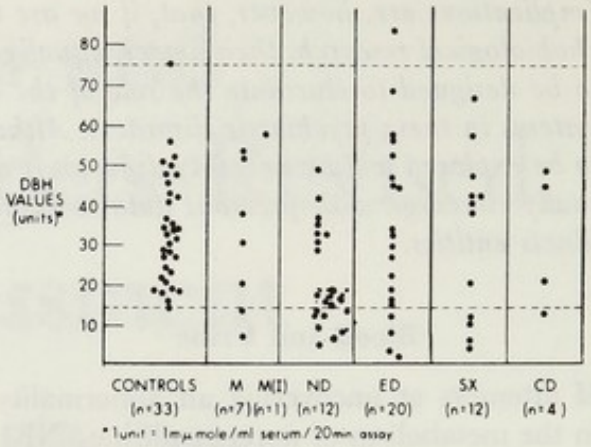

Figure 1. Serum DβH activity in psychiatric patients. M = cyclic (bipolar) manic-depressive in manic phase; M(I) = manic in interphase-asymptomatic; ND = neurotic depressives; ED = unipolar (endogenous) depressives; SX = schizophrenics; CD = character disorders.

Tyrosine Levels

Blood plasma levels of tyrosine, the amino acid precursor of catecholamines, have also been examined; the findings vary

across the different studies. In one investigation manic-depressive individuals showed no difference in fasting levels of plasma tyrosine compared to normal controls (100); in another study, depressed patients showed significantly lower 8 a.m. levels of plasma tyrosine compared to normals (11); in yet another study (10), there were no differences in 8 a.m. tyrosine levels in endogenous depressives when compared to normal controls, neurotic depressives, or schizophrenics, but the 11 a.m. levels in endogenous depressives were significantly lower than these other control groups. The apparent discrepancies await clarification.

Urine

Factors Effecting Catecholamine Excretion Rates

Catecholamine excretion rates vary widely depending upon a host of variables. Physical stress and muscular work can lead to pronounced increases in excretion rates, even under moderate conditions (36–38, 58, 64). Normetanephrine (NM) and nephrine excretion increases in association with agitated and unstable behavior (74). Urinary 3-methoxy-4-hydroxyphenylglycol (MHPG) has been shown to increase in response to various forms of stress (66, 86) and may also vary in response to postural changes or motor activity. Catecholamine excretion displays a marked diurnal variation (80). Body weight is also a factor of importance, and it appears that differences reported in catecholamine excretion rates between age groups, and between males and females can generally be accounted for by differences in body weight. However, sex differences have been found at some age levels (25). Cardon and Guggenheim (25) have indicated that diet can affect urinary excretion of catecholamines. Beckett *et al.* (8) have reported that the level of amine metabolites excreted increases as the urine pH becomes alkaline. Dawson and Bone (32), in a review of data concerning excretion of NE related to mania, indicate that the elevated NE excretion corresponds to urine volume. The relationship between urine volume and catecholamine excretion in man is elsewhere discussed (34). Various centrally acting drugs are capable of influencing catecholamine output. A series of investigations by Frankenhaeuser (41) indicates that whereas meprobamate decreases the excretion of NE, even moderate quantities of nicotine and alcohol can significantly increase catecholamine output. The latter finding with alcohol is of significance in that more recent evidence suggests that there is an increase in the urinary excretion of the major cerebral NE metabolite (MHPG) in subjects ingesting alcohol; the excretion of this metabolite is directly related to the rise of circulating blood alcohol level (75). The ingestion of coffee, even in moderate amounts, results in a significant increase in urinary catecholamine excretion (9).

The foregoing data are of critical significance inasmuch as few studies, if any, have attempted to control the significant array of variables that can influence the output of NE and its metabolites. The influence of various drugs is perhaps of major importance in that most of the earlier studies did not take this variable into account or allow for adequate washout periods. Even in the more contemporary studies, the long washout periods in manic-depressive patients often require the use of such drugs as chloral hydrate and/or paraldehyde for behavioral control or sedation. The use of these drugs in light of existing evidence concerning the influence of alcohol on catecholamine output is telling.

Specific Studies

There are various psychobiological studies which report specific changes in NE ex-

cretion which indeed run counter to the "catecholamine hypothesis." Curtis *et al.* (30) found an increase in urinary NE in a group of depressed patients but not in anxious subjects. Bunney *et al.* (22) reported elevated urinary NE in endogenously depressed patients, but not in those with neurotic depression. Reflecting the consistent disparity that one finds from one study to another in this area of research, Perez-Reyes (81) found NE output to be high in neurotic depressives but not in endogenous depressives. A number of different investigations have indicated that NE in the brain of various mammals is metabolized predominantly to the alcohol 3-methoxy-4-hydroxyphenylethylene glycol or MHPG (65, 70, 87, 89). Studies by Maas *et al.* (68), Greenspan *et al.* (50), and Bond *et al.* (13) have revealed a lowering of MHPG in the urine of depressed subjects; the two latter investigations (13, 50) have also revealed elevated MHPG excretion in manic patients. On the other hand, a more recent publication by Fawcett and Maas (40) reported that of 12 depressed patients studied with regard to MHPG output, only half showed lowered MHPG excretion; the other half showed either normal or increased excretion of MHPG. MHPG excretion did not correlate with the unipolar bipolar nature of the depressive illness and the degree of motor activity was not assessed. This same group of investigators has suggested a possible relationship between low mean baseline levels of MHPG in depressed patients and eventual response to dextroamphetamine sulfate as well as tricyclic antidepressant drug treatment (40, 67). Clinical improvement was generally associated with enhanced *excretion* of MHPG. These latter findings stand in stark contrast, however, to two previous reports by Schildkraut (90, 92) where favorable response to treatment with amitryptyline was observed in patients with high urinary MHPG excretion (as well as NM and VMA) but not in patients excreting lower levels of MHPG (and other metabolites). Other reports contribute to the inconsistency in findings (83).

Significance of Urinary Studies

The most serious criticism of studies measuring NE/NE metabolites in the blood and urine of psychiatric patients is based on the fact that such an assessment appears to reflect total body change of which the central nervous system (CNS) contribution is likely minimal. In fact, measurement of NE and NM reflects only peripheral sympathetic activity since these amines do not pass unchanged out of the brain (43). Maas and Landis (65) simultaneously injected ^{3}H-NE into the cisterna magna and ^{14}C-NE into the jugular vein of dogs; urine was collected every 12 hours. Through this double isotope technique, they concluded that 22 to 27 per cent of urinary MHPG in the dog represents central NE metabolism and that 0.7 to 1.0 per cent of urinary VMA originates from the brain. These investigators estimated, on the basis of these calculations, that 50 to 60 per cent of brain MHPG was eventually excreted in the urine. However, whereas the VMA to MHPG ratio in the dog is in the order of 15 to 1, in humans this ratio has been reported between 1.5 to 1 and 2.6 to 1 (104) *i.e.*, of the total deaminated metabolite, a much greater fraction can be ascribed to MHPG. Therefore, the percentage of MHPG in urine derived from the brain may be quite small. If this were indeed the case, changes in urinary MHPG would largely reflect changes in peripheral sympathetic activity, and small changes in cerebral NE metabolism would be obscured. Consequently, human studies utilizing urinary MHPG as a measure of central events should be regarded with some reservation.

Cerebrospinal Fluid (CSF)

NE

Studies of amines and their metabolites in CSF likely represent the most direct available means for evaluating amine metabolism in the human subject (72). That the CSF is a reservoir for NE metabolites has been clearly exhibited by Glowinski and Axelrod (42) in the rat. Furthermore, there is considerable evidence that very small amounts of NE metabolic products pass from the systemic circulation to the CNS. NE concentrations have been measured in the CSF of psychiatric patients by Denker *et al.* (33), who found that the levels of depressed subjects were greater than three times that of nondepressed patients. In two other studies, normal concentrations of NE have been reported in brains of patients who recently committed suicide (15, 79).

MHPG

The occurrence of MHPG in CSF has been documented (88, 89). It was our belief, based on the interpretation of the above-cited data, that measuring CSF MHPG in man would yield critical information on the relationship between catecholamines and affective disorders. With several modifications (105) of the gas-liquid chromatographic technique developed for measuring MHPG in urine (106), we set out to test the catecholamine hypothesis by measurement of CSF MHPG levels in carefully selected patient groups before and after drug therapy (96, 107, 108). Our studies collectively indicate that the vast majority of psychiatric patients thus far investigated, regardless of diagnosis, show CSF MHPG levels falling within the range of values seen in normal control subjects (Figure 2). All depressed patients, whether they be endogenous or reactive, bipolar or unipolar, and irrespective of the degree of psychomotor agitation or retardation, show normal MHPG levels in CSF. In the study presented at the 10th ACNP (96), we reported that some manic and schizophrenic patients showed CSF MHPG levels elevated beyond the range of our normal controls; for the manic and schizophrenic groups taken as a whole, statistical significance was attained for each group, with greatest significance in the manics ($p < .001$). There was no statistically significant difference between the manic and schizophrenic groups. Those patients in each group showing abnormal values do not show clinical or chemical characteristics distinguishing them from other patients having the same diagnosis nor do they differ with regard to age, sex, severity of acute episode, illness chronicity, or the degree of motor activity.

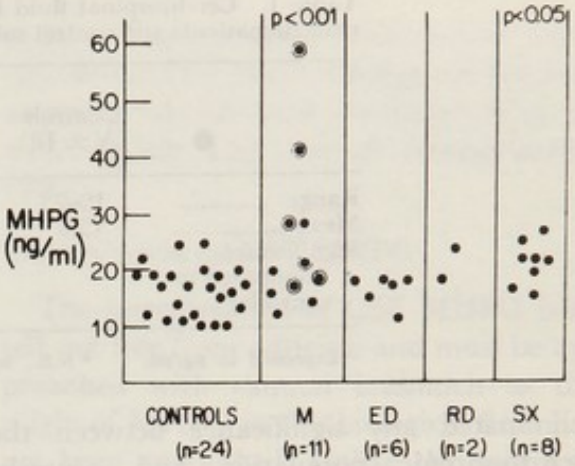

Figure 2. Cerebrospinal fluid MHPG data comparison in hospitalized psychiatric patients (27) and controls (24). M = manics; = fem. manics; ED = endogenous depressives; RD = reactive depressives; SX = schizophrenics.

With the addition of more patients, we currently have 13 manic individuals, 8 endogenous depressives, 2 reactive depressives, and 19 schizophrenics who have been explored with regard to CSF MHPG values (Table 1). The greater N has reduced the significance between the manic population and control group to $p < .005$ and has

Table 1. Cerebrospinal fluid levels of MHPG[a] in hospitalized psychiatric patients and control subjects

	Controls ($N = 18$)	Manics ($N = 13$)	Depressives ($N = 8$)	Schizophrenics ($N = 19$)
Range	10–23	10–57	11–20	7–29
Mean	15.9	23	15.8	17.2
Significance (compared to controls)		$p < .05$	N.S.[b]	N.S.

[a] Expressed in ng/ml. [b] N.S., not significant.

eliminated any significance between the schizophrenic population and controls. Again, the two additional endogenously depressed patients showed normal values of CSF MHPG and for the depressed population as a whole there is no statistical difference compared to the mean of the control group.

Coppen (29) has recently found that MHPG in the CSF of his endogenously depressed individuals is within the normal range; the NIMH group finds CSF MHPG lower in some depressed individuals (46). The available data collectively suggest that brain NE may not be lowered in depression. Because there are no apparent clinically discernible features in those patients with high values from others within the same diagnostic category showing normal CSF MHPG levels, implications are that the elevated values seen in some manic, schizophrenic, and depressed patients across different studies may be related to secondary factors. It is less likely that these elevations represent a primary biochemical defect common to these illnesses.

The data, therefore, do not readily support the notion of specificity with regard to the involvement of NE in the affective, psychiatric disorders.

It is noteworthy to mention, however, that clinical change in some of our bipolar manic-depressives was clearly associated with a marked shift in MHPG levels corresponding to the direction of mood swing (96) (Figures 3 and 4). Although this cannot be duplicated in all bipolar subjects, it may well be that using each patient as his own control and relating the time of spinal tap to symptom onset would best reveal the hypothesized changes in NE levels in manic and depressed individuals. This would be consistent with previous data by the NIMH group suggesting that catecholamines may only be involved in the "switch process" rather than the steady state, *i.e.*, that only the onset and cessation of the manic state may be associated with abnormal catecholamine metabolism (48).

Monoamine Metabolites in CSF of Patients with Neurological Disease

Perhaps the greatest single argument against any notion of specificity with regard to findings with any catecholamine in the CSF of psychiatric patients is forthcoming from studies measuring these same metabolites in the CSF of patients with neurological disorders having known biochemical abnormalities. A number of studies have demonstrated decreased values for CSF homovanillic acid (HVA), both with and without probenecid treatment in parkinsonism (56, 77, 102). Direct brain measurements in parkinsonism have confirmed the fact that dopamine (DA) is decreased (35). In reviewing the data concerning catecholamine metabolites in the CSF of such neurological patients, however, one finds an inconsistency in findings

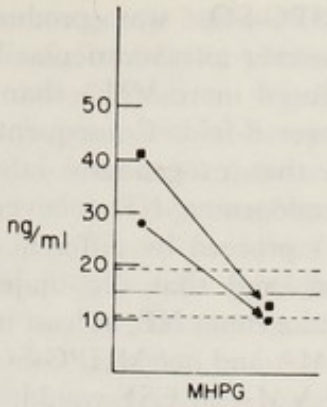

Figure 3. CSF-MHPG change in two manic patients during treatment with lithium carbonate. —— = mean for normals; – – – = S.D. for normals.

across different studies and there are unresolved questions that await clarification. The levels of HVA in the CSF of Parkinson patients do not correlate with severity or duration of illness (28, 102) nor with the therapeutic response to L-dopa treatment (28). Animal studies indicate that L-dopa raises brain DA levels but that NE levels are raised only slightly, or not at all (7, 23, 39). Curiously, however, patients studied by Goodwin *et al.* (48) responded to L-dopa with unequivocal elevations in the urinary excretion of the NE metabolites VMA and MHPG. Similar changes in VMA and MHPG excretion were seen in parkinsonian patients treated with high doses of L-dopa (24). Others, however, found decreased urinary NE metabolites (VMA and NM) after L-dopa in normal and parkinsonian patients (76).

Of perhaps greater significance, are the data indicating lowered HVA levels in the lumbar CSF of patients with neurological disorders unrelated to diseases of the basal ganglia. Amyotrophic lateral sclerosis (17), seizure disorders, inflammation of the CNS and Creutzfeldt-Jakob disease (19) have all been associated with reductions, sometimes significant, of CSF HVA.

Drugs such as phenothiazines (51, 82) and the butyrophenone, haloperidol (16), can elevate CSF HVA. Changes in this CSF amine metabolite have also been associated with aspirin and steroid administration (31).

Significance of CSF MHPG

The interpretation of CSF MHPG is itself not free from criticism and must be approached with caution inasmuch as the origin of MHPG in this biological fluid has not been established. Unlike the acid metabolites, the alcohols, when not in the conjugated form, can cross the blood-brain barrier (44). The contribution of peripheral MHPG to CSF levels is unknown; one may speculate that the peripheral contribution is negligible. MHPG in urine is excreted almost totally in the conjugated form. The CSF level of MHPG in a patient with phenochromocytoma having high circulating levels of MHPG was normal (Gitlow and Wilk, unpublished observations). The contribution of MHPG from spinal cord NE to the total CSF MHPG level is also an unknown variable. Levels of MHPG in ventricular and lumbar CSF have been reported to be approximately

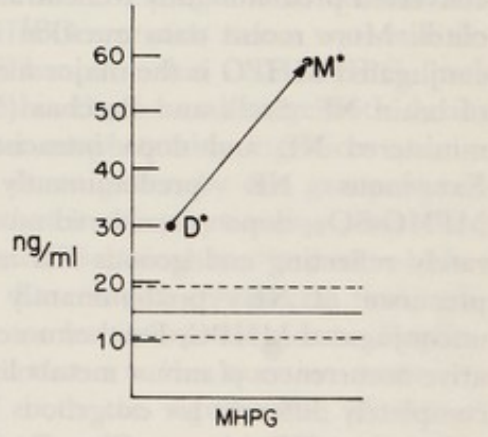

Figure 4. CSF-MHPG change in a cyclic manic-depressive during shifts in clinical state. —— = mean for normals; – – – = S.D. for normals; → = 4-week period on placebo; D = depressive phase; M* = manic phase.*

equal (49). Thus, complications in interpretation of lumbar CSF levels of acid metabolites due to a concentration gradient may be absent for MHPG. Although the weight of experimental evidence favors MHPG as the major brain NE metabolite, there has been some work to indicate that VMA rather than MHPG is the major brain NE metabolite (27). However, endogenous MHPG is found in measurable quantities in the brain whereas the existence of endogenous VMA in the brain has not been documented. Even if one assumes that MHPG in CSF is derived from the metabolism of cerebral NE, it is still possible that levels of this metabolite do not reflect functional noradrenergic activity. The dynamics of cerebral NE metabolism and the relative contributions to CSF MHPG from physiologically active and storage sites await elucidation.

The impression of the data so far reviewed indicates that MHPG is the major CNS metabolite of NE; however, this may prove not to be the case. Chase *et al.* (27) concluded that in the brain, phenylethylamine derivatives were converted to acidic metabolites, whereas the hydroxylated derivatives (NE, NM, and octopamine) were converted predominantly to neutral metabolites. More recent data question whether conjugated MHPG is the major metabolite of brain NE. Stolk and Barchas (97) administered NE and dopa intracisternally. Exogenous NE predominantly gave MPHG-SO_4; dopa (considered more accurately reflecting endogenous NE as it is a precursor of NE) predominantly yielded unconjugated MHPG. Furthermore the relative occurrences of minor metabolites were completely different for exogenous NE and endogenous NE (dopa). Chase *et al.* (27) measured the urinary excretion of labeled NE metabolites in dogs after injection intravenously or intraventricularly with either ^{3}H-NE or ^{14}C dopamine. It was seen that when NE was administered by either route more MHPG-SO_4 was produced than VMA. However intraventricular ^{14}C dopamine produced more VMA than MHPG-SO_4, by over 8-fold. Consequently it was concluded that exogenously administered NE and endogenous NE (converted from dopamine) proceed by different routes of metabolism, and that the major metabolites of endogenous NE, at least in the dog, may be VMA and not MHPG-SO_4. Quantitation of VMA in CSF would, therefore, represent an important test of the catecholamine hypothesis if this were indeed the case in man. Attempts to isolate VMA from brain tissue have been routinely unsuccessful, however (3, 63), and at the present time there is no reported assay for VMA in human CSF that yields nanogram sensitivity.

Urine and CSF

Schildkraut *et al.* (93) have suggested that there is support for the catecholamine hypothesis by correlating mood and MHPG excretion in individuals given amphetamines. Patients who had ingested amphetamine chronically and were not suffering from an affective disorder showed urinary MHPG elevation when amphetamine was taken and a fall in the output of this amine after the drug was withdrawn. This MHPG excretion pattern was found to correlate with the patient's mood which was hypomanic while the patient was on amphetamine and which became depressed after the drug was stopped.

Although intuitively, lumbar CSF is likely to represent a more accurate index of central neurochemical activity than urine, and the legitimate criticisms leveled against any interpretation of data from urinary studies notwithstanding, a dispute has nevertheless arisen concerning the relative merits of each. Persuaded to resolve this problem for those who still seek to explore urine as the index of amine metabolism in

the brain, our group has carefully studied four physically healthy amphetamine abusers who volunteered to ingest amphetamine in large doses, to co-operate with behavioral assessments and urine collections, and to undergo lumbar punctures (5). This experiment would not only serve to verify the findings by Schildkraut *et al.* (93) that mood changes associated with amphetamine ingestion in man are associated with corresponding changes in urinary MHPG, but would also serve to compare the data with MHPG in CSF and urine. Our findings failed to indicate any significant effects on urine levels of VMA or HVA as a result of amphetamine administration, and the urinary levels of these metabolites remained well within the normal range throughout the study. Urinary MHPG excretion was variable, showing no consistent change during or after amphetamine. Likewise there were no consistent changes in CSF MHPG levels; change in CSF MHPG, when apparent, could not be correlated with mood alteration or change in urinary MHPG excretion. CSF HVA showed wide variation and it is not possible to assess the findings. There was no apparent correspondence between urine CSF amine metabolite changes for any of the metabolites explored. Jönsson *et al.* (57) previously studied urinary concentrations of NE and epinephrine, and CSF concentrations of HVA during amphetamine-induced psychoses and after recovery. Although these investigators noted that urinary NE and epinephrine were both increased over normal levels during amphetamine administration, there were no significant changes in CSF HVA concentrations. The interpretation of findings coming from the studies by our group and those of Jönsson *et al.* and Schildkraut *et al.* is indeed difficult because the studies are not replications of each other; different experimental circumstances prevailed in each study. However, it becomes apparent in reviewing these studies that amphetamine ingestion, even in large doses, produces no consistent or predictive changes in CSF HVA or MHPG; likewise, there are no consistently meaningful changes in urinary excretion of MHPG or VMA. The findings of Jönsson *et al.* of an increase in urinary NE and epinephrine with amphetamine use, taken together with our findings of no change in CSF MHPG indicate that the findings with respect to urinary excretion of MHPG suggested by others are probably the result of peripheral release of NE and particularly epinephrine by amphetamine and therefore, are not a reliable index of central neurochemical events. Moreover, even within the same studies, there were no correlations between findings in CSF and urine nor could behavioral mood change be correlated with the amine levels measured in the CSF or urine. Although one of our patients was observed to have increased excretion of MHPG while taking amphetamine, he was not at all consistently euphoric and overactive during the days that elevated values were obtained. In fact, this patient became progressively withdrawn and depressed while the amphetamine was given, and during the period that this mood change occurred, the urinary MHPG excretion values were still elevated. Then, too, his CSF MHPG levels were within the normal range both during and after amphetamine ingestion.

This investigation by our group is critical in that it compares amine metabolites in the two biological media over which a dispute has ensued concerning their relative merits for interpreting data. Implications are that a serious question arises concerning both the significance of urinary MHPG excretion as an index of central noradrenergic activity in amphetamine-induced states, and the conclusion that its correlation with mood constitutes support of the catecholamine hypothesis of affective disorders. Perhaps more than any other

single study, our finding of such discrepancies between values in urine and CSF raises the question of the ultimate value of using urine as an index of central neurochemical events.

Comments

The evidence for a causal relationship between abnormalities in NE metabolism and the affective disorders stems largely from considerations of the mechanism of action of mood-altering drugs (20, 91). Thus, a depletion of NE effected by reserpine is related to its behaviorally depressant properties, whereas an elevation in brain amine levels by monoamine oxidase inhibitors is associated with the antidepressant effects of these drugs. Similarly, the antidepressant effect of the tricyclic drugs is ascribed to a potentiation of the response to physiologically released transmitter by inactivation of neuronal reuptake mechanisms.

On the other hand, although reserpine-induced depression in animals is reversed by L-dopa, this drug appears ineffective in most cases of clinical depression. The reserpine model may, therefore, not be relevant to human depression (48). Reserpine has been reported to have central cholinomimetic properties (45, 99); the depressant effects of reserpine are remarkably similar to those of cholinesterase inhibitors. It is not clear how inhibition of monoamine oxidase leads to increased levels of functionally active amines. In fact, the antidepressant effects of these drugs may be better correlated with their ability to block amine reuptake (52). Endogenously depressed patients are largely unresponsive to the amphetamines. The ability of the tricyclic drugs to block amine uptake rapidly does not correlate with the long delay in appearance of antidepressant effects after treatment (94). Recent observations suggest that the antidepressant effects of iprindole are not likely due to inhibition of the neuronal uptake of noradrenaline, dopamine (or 5-HT) (85). The chemical look-alike structure of imipramine and iprindole throws serious doubt on the validity of existing hypotheses that the therapeutic action of tricyclic antidepressants is due to an inhibition of the neuronal reuptake of these amines (26, 42, 53). Then too, the tricyclics have been used successfully in the treatment of acute mania as well as against recurrences of both mania and depression in bipolar subjects (1, 2, 4, 62, 98, 101). The antimanic properties of lithium are not readily explained by effects on NE metabolism (12, 54). Also, there is a delay of 8 to 10 days for normalization of the manic states, and the drug has been used successfully in treating acute depressive episodes in some bipolar (47) and unipolar (71) patients and can stave off both depressive and manic recurrences in bipolar patients. Finally, based on the hypothesized biochemical construct of affective disorders, investigational drugs with a defined pharmacological action have been introduced as therapy for manic and depressive illness. Attempts to introduce a rational therapy for depression by precursor loading, however, [tyrosine (29), L-dopa (18, 21, 48, 61, 78)], or for mania, by synthesis inhibition alphamethyl-P-tyrosine (α-MPT) have been largely unrewarding. Of perhaps greater importance here is the failure to correlate urine-CSF amine metabolite levels with any mood change concomitant with the administration of these drugs. L-Dopa administration is accompanied by a significant increase in CSF HVA and both urinary VMA and MHPG (48) without producing any consistent mood change in depressed subjects. α-MPT lowers these amine metabolites but does not alter the mood behavior of manic individuals (21). The failure of L-dopa to raise brain NE has been attributed to peripheral decarboxylation (18). However, evidence by

Wilk and Mones (104) shows that L-dopa with decarboxylase inhibitors does not increase brain NE as measured by CSF MHPG in parkinsonism (104).

There are now data (55) to suggest that an adrenergic-cholinergic balance may underlie the affective disorders. Physostigmine, a centrally active cholinesterase inhibitor, has been shown to exhibit an acute, rapid and dramatic antimanic effect, associated with anergic symptoms in manic individuals. Depression ensued in the majority of subjects tested; placebo or neostigmine could not induce these mood behavior changes. The effects of physostigmine were likely due to increased central acetylcholine levels.

A decade ago the available experimental data were consistent with the theory involving NE in the affective disorders. However, since that time, new experimental evidence indicates that mental depression or mania may not be explained solely by this hypothesis. Therefore, we feel that other studies need to be designed and initiated in an effort to elucidate the role of the adrenergic system as well as other neuronal systems in the affective states. Although the experimental approaches and systems to be explored will by necessity differ, it is hoped that the resulting data will eventually converge with previous information to elaborate the mechanisms underlying the affective illness entities.

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Indoleamines and Affective Disorders

Alec Coppen, MD, DPM

There is now a considerable amount of evidence which suggests that the biogenic amines are involved in the aetiology of the affective disorders. This evidence consists of a growing number of investigations of the biogenic amines in patients suffering from depression and mania and also from observations of the effect on mood of manipulating brain amines in patients and in normal subjects. What I propose to do in this paper is to examine some of the direct evidence for a disturbance in biogenic amines in patients suffering from affective disorders, to examine the aetiological implications of these findings and also to consider what the implications of these findings are for treatment. I shall be dealing with the indoleamines—5-hydroxy-tryptamine (5-HT) and tryptamine whose biosynthesis and metabolism are illustrated in Fig. 1. I do this, not because I naively think that only 5-HT is important in these conditions but because most of my own research interests have been centred in this area; later, Dr. Schildkraut [1] will be describing catecholamine metabolism in affective disorders. Moreover, I should like to stress from the outset my view that the clinical pathology of the affective disorders is probably very complex—involving not only the biogenic amines but probably also other abnormalities.

Investigation of the chemical pathology of depression and mania is hard to carry out because of the difficulty of obtaining data from the organ that is presumably most involved in the process—that is the brain. No one approach can give anything but a limited amount of information but by pooling the information available I think some sort of consistent picture is emerging. Direct studies on the central nervous system of these patients must rely on investigations on the cerebrospinal fluid (C.S.F.) of patients or on post-mortem studies on the brains of depressive patients who have committed suicide. There are no studies available on the brains of manic patients as suicide is relatively rare in these patients.

C.S.F. Studies

Although the amines which have been mostly studied in the affective disorders—the catecholamines and 5-hydroxytryptamine (5-HT)—are not detectable in the C.S.F., the acid metabolites of these amines —5-hydroxyindoleacetic acid (5-HIAA)

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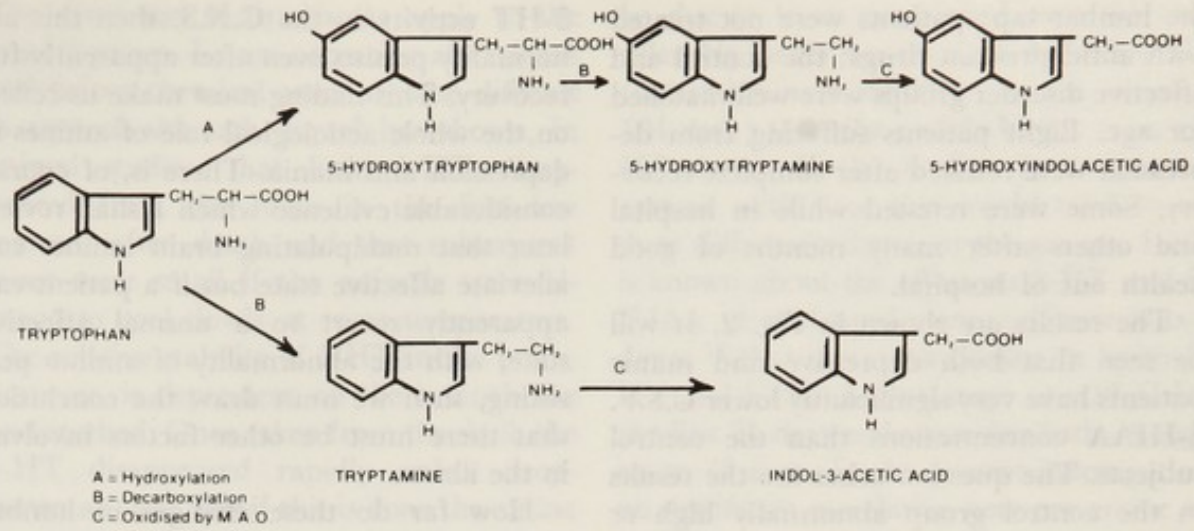

Figure 1. Biosynthesis and metabolism of indoleamines.

and homovanillic acid (HVA)—are measurable in the lumbar C.S.F. of man. It must be emphasized that one must interpret any differences one finds in lumbar C.S.F. concentrations with caution. Many factors are known to influence the C.S.F. concentrations of 5-HIAA and HVA—some of which can be controlled by the experimental design and some not. For example, C.S.F. concentration of 5-HIAA varies with age; ventricular and cisternal fluid have higher concentrations than lumbar fluid so that the test must be standardised and the same amount of fluid taken off by the lumbar tap. Again 5-HIAA is transported out of the C.S.F. by an active process and so any change of concentration of lumbar 5-HIAA concentrations may reflect changes in the transport of 5-HIAA out of the C.S.F. rather than any change in its turnover in the central nervous system. However, if these and other limitations are borne in mind and if the investigation is properly controlled for age of subject, amount of fluid removed, time of day the test is performed, I believe that abnormal levels of 5-HIAA in C.S.F. are strongly indicative of some change of 5-HT activity in the central nervous system. Early reports on the C.S.F. concentration of 5-HIAA showed a satisfying agreement.[2,3] Both groups reported a decreased concentration of 5-HIAA in depressive patients. However, these reports were contradictory as far as mania was concerned. Ashcroft's group reported normal lumbar C.S.F. levels but Dencker's reported decreased levels in manic patients. Subsequent reports have shown further conflicts. Bowers *et al.*[4] did not find significantly lower levels in depressive patients and the Swedish group could not confirm their earlier findings[5] but Van Praag *et al.*[6] reported significantly decreased levels in depressives. We therefore decided to investigate the matter further[7] and we were particularly concerned with the following questions:

1. Is there an abnormality in C.S.F. 5-HIAA (a) in depression and (b) mania?
2. If so, does this abnormality revert to normal after clinical recovery?

We obtained lumbar C.S.F. from 31 patients suffering from depression, from 18 patients suffering from mania and from 20 patients who were investigated in a neurological unit and who were shown to have no conspicuous psychiatric or neurological morbidity. The test was standardised as far as possible; estimations of 5-HIAA were carried out on the first 11 ml of C.S.F. from

the lumbar tap; patients were not treated with antidepressant drugs; the control and affective disorder groups were well matched for age. Eight patients suffering from depression were retested after complete recovery. Some were retested while in hospital and others after many months of good health out of hospital.

The results are shown in Fig. 2. It will be seen that both depressive and manic patients have very significantly lower C.S.F. 5-HIAA concentrations than the control subjects. The question arises are the results in the control group abnormally high or are they abnormally low in the group of affective disorders? As described above, age, sex, time of day of lumbar puncture were controlled and in any case were not found to show any significant correlation with C.S.F. 5-HIAA levels. The control patients were a group of subjects investigated for a heterogeneous variety of symptoms and who were not found, subsequently, to have any significant neurological or psychiatric morbidity. The question of the influence of stress on the results is difficult to assess. Certainly, the depressed patients were far more emotionally disturbed on the occasion of the first test, when they had been admitted to hospital with a depressive illness than on the follow-up test when they had recovered, yet there was no significant difference between the results on the two occasions.

Depressive and manic patients show the same deviation from controls and the situation with indoleamines is analogous to our investigations into sodium metabolism in affective disorders where we found increased residual sodium both in mania and depression.[8] One of the most significant findings in this investigation are the values obtained after clinical recovery. Most of these samples were obtained from the patients after discharge from hospital, when they had been drug free and clinically well for many months. If these low levels of C.S.F. 5-HIAA are an index of abnormal 5-HT activity in the C.N.S. then this abnormality persists even after apparently full recovery. This finding must make us reflect on the whole aetiological role of amines in depression and mania. There is, of course, considerable evidence which I shall review later that manipulating brain amines can alleviate affective state but if a patient can apparently revert to a normal affective state, with the abnormality of amines persisting, then we must draw the conclusion that there must be other factors involved in the illness.

How far do these changes in lumbar C.S.F. reflect changes in the brain? There are now three investigations published on post-mortem examination of the brains of depressive subjects who committed suicide. There are all sorts of factors which must make one interpret these results with caution. It is difficult to obtain reliable diagnostic data on these subjects; their nutritional state is uncertain; often it is difficult to be sure of the drugs they had been taking; the time of day when they committed suicide is often difficult to obtain and so on.

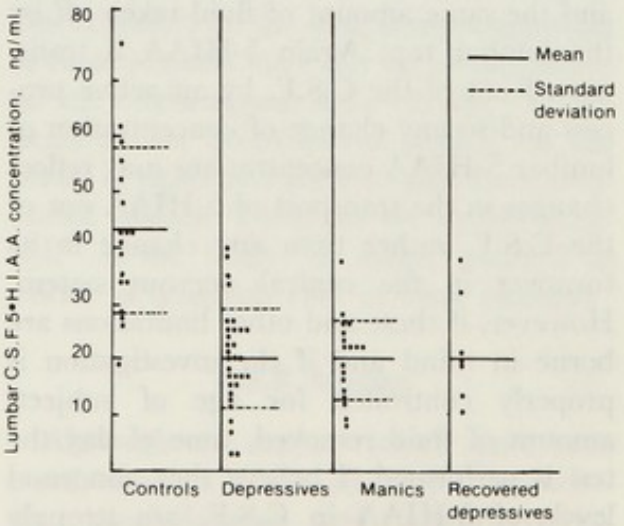

Figure 2. Lumbar CSF, 5-HIAA in control patients, depressive patients, manic patients and depressed patients following recovery.

The same sort of drawbacks apply to the control group. Losses, occurring after death and before chemical assay are also difficult to control although Joyce[9] has shown, in animal studies, that little 5-HT disappeared from the brain in the first few minutes after death and that subsequent losses were small if the animals were allowed to cool slowly at room temperature. The relative stability of 5-HT in the brain, however, is dependent on the brain being undisturbed. Once taken from the skull, the 5-HT disappeared rapidly unless deep-frozen at once, but if this is done the amine was preserved at least for a few days.

In a report from our laboratory, Shaw, Camps and Eccleston[10] reported significantly lower hindbrain concentration of 5-HT in depressive suicides than in a control group of subjects who died from other means—250 ng/g compared to 307 ng/g in the control group.

The second investigation we carried out was in collaboration with the National Institute of Health, Bethesda, U.S.A.[11] We obtained post-mortem material from a London coroner. The hindbrains were then deep-frozen and flown to Bethesda for the hindbrain concentration of 5-HT, noradrenaline and 5-HIAA to be estimated. The time between collection and assay was considerably longer than in the first investigation—174 days.

The results are shown in Table 1. It was found that the values of 5-HT concentration are considerably lower than those found by Shaw *et al.* and we think that this may be due to losses occasioned over the considerably longer storage time. Moreover, the control brains were stored longer (average 184 days) than the suicide brains (average 159 days). If the decline in amines increased with time this would tend to reduce differences between the groups. Little is known about the effect on 5-HT and 5-HIAA of prolonged storage. There is evidence [12] that there is a decline in brain 5-HT and 5-HIAA on storage at −17°C for the first 25 days and thereafter little change up to 75 days. In the present investigation no significant correlation between amine or 5-HIAA concentration was found for the subjects as a whole or any subgroup except the subgroup of coronary controls who showed a significant correlation between storage time and 5-HIAA concentration (0.63; $P < 0.02$). The positive correlation in this subgroup is opposite to the experimental findings just cited and is not shown by the other subgroups and is probably a chance finding.

The material was examined in two ways. Firstly, mean values for all suicides were compared with the mean values for all non-suicides. There was no significant difference in noradrenaline or 5-HT between the two groups: 5-HIAA was significantly reduced in the suicides. From this material two more homogeneous groups were selected: (a) a control group, consisting of 15 patients who died suddenly from a coronary infarction but who were not known to have any other medical or psychiatric condition; (b) a depressive group who

Table 1. Mean noradrenaline, 5-hydroxytryptamine and 5-hydroxyindoleacetic acid levels in hindbrain of suicides and control subjects.

	All controls (ng/g)	*n*	All suicides (ng/g)	*n*	Coronary controls (ng/g)	*n*	Depressed subjects (ng/g)	*n*
Noradrenaline	439	27	444	21	388	15	444	15
5-hydroxytryptamine	234	25	213	23	218	13	211	16
5-hydroxyindoleacetic acid	1826*	28	1315*	23	1698*	15	1271*	16

* $P < 0.025$.

were diagnosed as having suffered from a depressive illness by a retrospective study of the information available at the Coroner's Court and who were not alcoholic. These more homogeneous groups showed the same patterns; mean noradrenaline concentrations were slightly increased and mean 5-HT concentrations slightly decreased, but not significantly so, in the depressive group. If the concentration of 5-HIAA in the coronary control group is corrected for storage time to that of the depressed suicides the level of significance between the two groups was reduced to $p < 0.10$. A recent publication by Pare *et al.*[13] is in line with these findings. In a similar examination on the brains of depressed patients, 5-HT was found to be significantly lower than in the control group. They only examined 5-HIAA in a small number of cases but this tended to be lower in the depressives than in the controls. There was no significant difference in brain noradrenaline or dopamine.

Urinary Studies

I should like now to turn to an investigation into tryptamine in depression that suggests, contrary to the C.S.F. data, that there is some change with clinical recovery. In our laboratory we have examined the urinary excretion of tryptamine and its metabolite indoleacetic acid in 13 patients before and after recovery from a depressive illness. In this investigation diet and fluid intake were rigorously controlled. The tests were carried out on two occasions: the first, a few days after admission. The patients were then treated with E.C.T. and the tests repeated after recovery. During each period of testing two 24-hr specimens of urine were collected, and on the third day each patient was given an L-tryptophan load (50 mg/kg bodyweight) and urine was collected for the following 6 hours. It was found that the average urinary excretion of tryptamine during the period of depression was approximately half that of the normal average and of the levels found in patients after recovery (Table 2). We concluded that as far as the kidney is concerned that there is some change in tryptamine metabolism during depression, although one cannot, from this experiment decide whether these changes are paralleled by similar changes in the central nervous system.

Taking all these findings together, I feel that they support the notion that there is a lowering of both 5-HT and 5-HIAA in the brains of depressed suicides and that the C.S.F. findings are consistent with the view that this occurs in depressed patients both before and after clinical recovery. It would seem, therefore, that either there is some deficiency in the synthesis of 5-HT in these patients because of some deficiency of tryptophan hydroxylase or some lowering of serotonergic function in the C.N.S. of depressive patients.

What is the causal relationship between this abnormality and the depressive illness? There is considerable evidence that reser-

Table 2. Urinary excretion of tryptamine and IAA before and after recovery from a depressive illness (13 patients).

Clinical state	Age (years)	pH	Tryptamine (μg)		IAA (mg)	
			24 hr*	Load†	24 hr*	Load†
Depressed	56·8	6·1	39·2	53·8	3·7	4·0
Recovered		6·0	66·6	118·3	3·2	3·8
p		NS	0·001	0·05	NS	NS

* Average values of two 24-hr collections of urine.
† 6-hour collections of urine after taking 50 mg L-tryptophan/kg of body weight.

pine, a drug that depletes the brain of biogenic amines can produce depression in a significant number of patients given the drug for hypertension.[14] There is also evidence that *para*-chlorophenylalanine (PCP), which inhibits tryptophan hydroxylase and lowers the brain concentration of 5-HT, can also produce symptoms mainly of an affective nature in subjects without a previous psychiatric history.[15] It is also of relevance to consider the activity of methysergide in affective disorders. This compound is a specific antagonist of 5-HT and initial reports that this drug was a specific treatment of mania were of obvious great theoretical importance.[16] However, a carefully controlled trial showed that not only was methysergide ineffective against mania but that it was significantly less effective than placebo. That is, methysergide had a deleterious effect on the course of a manic illness.[17] This is in keeping with the observation that manic patients have a similar deficiency of lumbar 5-HIAA to depressive patients.

The action of the antidepressant drugs are to increase the amount of free amines present, either by decreasing the metabolism of the amines (the monoamine oxidase inhibitors), or by increasing the proportion of free amine present by interfering with cellular binding (the tricyclic drugs). These two groups of drugs, however, influence both the catecholamines and 5-HT. In order to get some idea of what amine is involved we attempted to increase the level of brain amines selectively by administering a monoamine oxidase inhibitor together with large quantities of the amino acid precursor of the amine.

We have now performed two double-blind trials on the therapeutic effect of (1) a MAOI alone compared with a MAOI together with tryptophan,[18] (2) tryptophan compared with imipramine.[19] The results are summarised in Fig. 3 where the re-

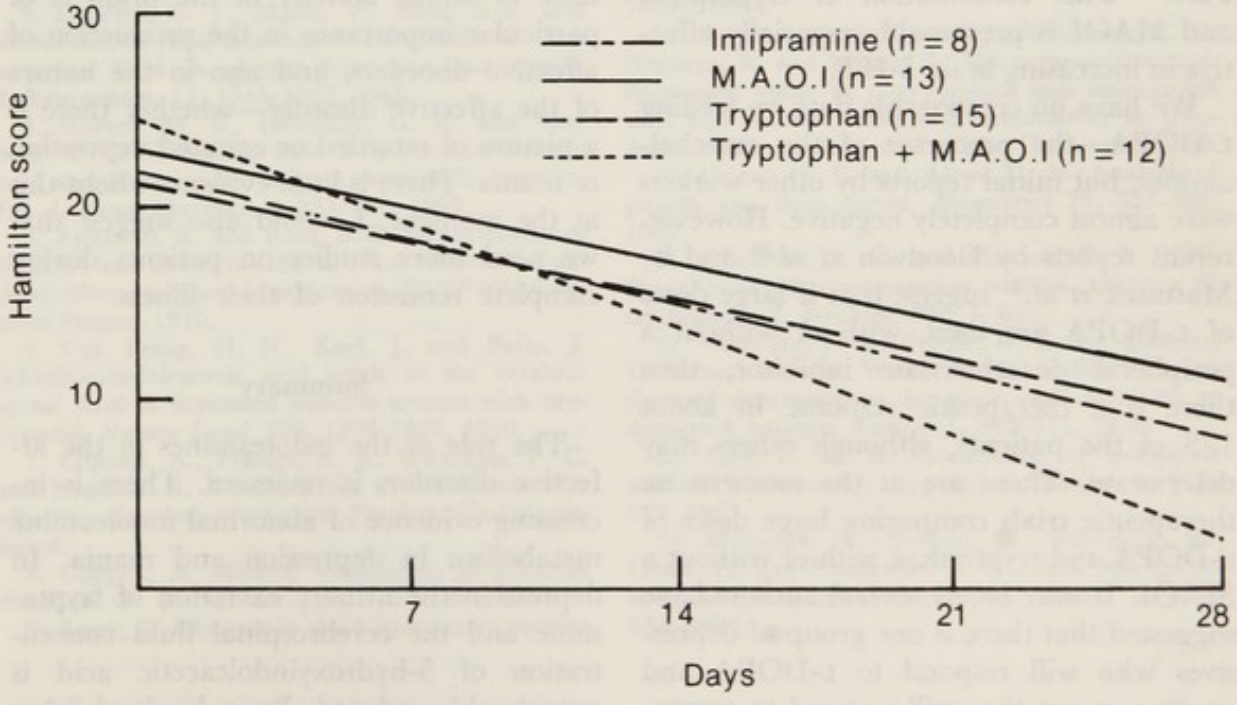

Figure 3. Regression lines of Hamilton Rating Scores over time in groups of depressed patients treated with (a) tryptophan; (b) monoamine oxidase inhibitor; (c) imipramine; (d) tryptophan and monoamine oxidase inhibitor.

sponse is shown in the form of linear regression lines although the statistical method employed was the analyses of covariance described by Grizzle and Allen.[20] Details of the trials will be found in the references. It was found that MAOI and tryptophan was significantly better than MAOI alone ($p < 0.001$) but that there was no significant difference between tryptophan and imipramine. The two trials were carried out at different times but in the same unit with a similar selection of patients using the Hamilton Rating Scale and so a further analysis of the four groups was performed. As these were two separate trials, the results must be interpreted with caution but it was found that MAOI alone, imipramine and tryptophan alone gave very similar response curves but that the combination of tryptophan and MAOI was superior to all three.

The superiority of tryptophan and MAOI to MAOI alone has also been reported by Glassman and Platman[21] and by Pare.[22] This combination of tryptophan and MAOI is presumably especially effective in increasing brain 5-HT.

We have no comparable data on feeding L-DOPA—the precursor of the catecholamines, but initial reports by other workers were almost completely negative. However, recent reports by Goodwin *et al.*[23] and by Matussek *et al.*[24] suggest that if large doses of L-DOPA are used, with or without a peripheral decarboxylase inhibitor, then there is a therapeutic response in about 1/3 of the patients, although others may deteriorate. There are at the moment no therapeutic trials comparing large doses of L-DOPA and tryptophan with or without a MAOI. It may be, as several authors have suggested that there is one group of depressives who will respond to L-DOPA and another group that will respond to tryptophan. However, this has to be demonstrated and in our limited experience patients that do not respond to tryptophan do not seem to respond to L-DOPA. The possibility of combining L-DOPA and tryptophan also remains an intriguing possibility.

To summarise, it seems to me that there is good evidence for an abnormality in 5-HT in both mania and depression but it seems that clinical recovery is not accompanied by any change in this abnormality. This seems to indicate that these changes in 5-HT and possibly other amines are only part of the chemical pathology and may be a necessary predisposition that requires another factor—perhaps endocrinological—to produce the clinical picture of depression and mania. However, in spite of this, the manipulation of amines seems to be a useful area for therapeutic intervention. It seems from our data that increasing amines, especially 5-HT by administering large doses of tryptophan and a MAOI is a very effective antidepressant treatment and it may be that certain cases respond favorably to L-DOPA. It may be that the balance of amine activity in the brain is of particular importance in the production of affective disorders, and also in the nature of the affective disorder—whether there is a picture of retarded or agitated depression or mania. There is little evidence about this at the moment. I would also suggest that we need more studies on patients during complete remission of their illness.

Summary

The role of the indoleamines in the affective disorders is reviewed. There is increasing evidence of abnormal indoleamine metabolism in depression and mania. In depression the urinary excretion of tryptamine and the cerebrospinal fluid concentration of 5-hydroxyindoleacetic acid is considerably reduced. Brain levels of 5-hydroxytryptamine and 5-hydroxyindoleacetic acid are lower in the brains of suicides than in those of subjects who died by other

means. In mania, C.S.F. levels of 5-HIAA were also found to be low. In neither mania nor depression did the lumbar C.S.F. 5-HIAA levels change after clinical recovery. These changes in indoleamine metabolism may play a role in the aetiology of depression, since tryptophan, the amino acid precursor of the indoleamines, administered with or without a monoamine-oxidase inhibitor has a therapeutic action in depressed patients.

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A Cholinergic-Adrenergic Hypothesis of Mania and Depression

David S. Janowsky, MD; M. Khaled El-Yousef, MD; John M. Davis, MD; and H. Joseph Sekerke, PhD

Summary. *Central cholinergic factors may play a role in the ætiology of affective disorders. Specifically, a given affective state may represent a balance between central cholinergic and adrenergic neurotransmitter activity in those areas of the brain which regulate affect, with depression being a disease of cholinergic dominance and mania being the converse. Support for this hypothesis comes from animal experiments demonstrating antagonistic cholinergic and adrenergic central behavioural effects. Furthermore, reserpine, a drug which causes depression, has central cholinomimetic properties. Conversely, tricyclic antidepressants have central anticholinergic properties. In man, physostigmine and other centrally acting cholinomimetic agents which increase central acetylcholine levels counteract mania and may cause depression in some individuals. Considering manic-depressive disorders and related phenomena from the viewpoint of cholinergic-adrenergic balance, or conceptualising behaviour as having both adrenergic and cholinergic components, provides a framework for understanding the affective disorders. Possibly, manic-depressive illness represents compensatory overreaction of certain parts of the central autonomic nervous system. A natural tendency toward homœostasis, associated with compensatory adrenergic activation, could explain why most depressions are self-limiting. To further confirm or deny the cholinergic-adrenergic balance hypothesis, more direct evidence is needed on the changes which occur in both systems during various affective states. Nevertheless, it seems that biological influences are involved in the ætiology of affective disorders, and possibly they include cholinergic and adrenergic factors.*

Introduction

Although the specific biochemical disturbances in mania and depression have not been definitely established, there is considerable evidence to suggest that brain monoamines, including noradrenaline, dopamine, and serotonin are significant determinants of mood and behaviour.[1–7] In most investigations and reviews, a single-monoamine hypothesis of affect has been proposed. We postulate that the cholinergic nervous system is also involved in the regulation of affect. Specifically, affective disorders may be determined by a complex

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balance between adrenergic and cholinergic factors, with a relative imbalance between central adrenergic and cholinergic neurotransmitter activity existing in those areas of the brain which regulate affect. Thus, depression may be a disease of central cholinergic predominance and mania a disease of central adrenergic (or serotonergic) predominance in the "affect system."

Animal Behavioural Studies Demonstrating Adrenergic-Cholinergic Balance

A balance between cholinergic and adrenergic neurotransmitter activity determines the direction and extent of bodily functions such as heart-rate, gastric mortility and tone, and pupillary size.[8] Carlton[9] has reviewed data which indicate that the extent of arousal (behavioural activation) in an animal is the result of a similar balance between adrenergic arousing factors and cholinergic inhibiting factors. Carlton and other workers[9-25] have reported data which indicate that central cholinergic activation causes depressant inhibitory effects, while anticholinergic agents or adrenergic stimulation cause behavioural activation and arousal. Centrally active cholinomimetic agents cause decreased self-stimulation[12-15] and locomotor activity,[19,20] and these effects are opposite to those which occur when centrally active sympathomimetics are administered.[21-23] Significantly, increased locomotor activity and self-stimulation have been deemed to be animal models of mania.[25,26] Furthermore, methylphenidate-induced increases in locomotor activity have been reported to be antagonised by physostigmine, a centrally active acetylcholinesterase inhibitor, but not by neostigmine, which does not easily cross the blood-brain barrier.[19] Centrally acting anticholinergic agents which pass the blood-brain barrier block these inhibitory cholinomimetic effects,[12,13,16,17] and have themselves been reported to increase locomotion,[22] self-stimulation,[23] and other forms of behavioural activation.[9] There is evidence that central adrenergic stimulation causes compensatory increases in cholinergic phenomena and vice versa. Fibiger et al.[19,20] have shown that administration of cholinomimetic agents may cause a late-onset increase in locomotor activity, presumably mediated by compensatory activation of the adrenergic nervous system. Amphetamine and anticholinergic agents, given together, exhibit synergistic effects on locomotor activity in mice,[9,24] possibly because anticholinergic agents block compensatory increases in cholinergic activity.[9] Conversely, Mandell and Knapp[27] have shown that brain choline acetylase, the rate-limiting enzyme in the production of acetylcholine, is increased after amphetamine administration; and Ho et al. have shown a similar increase in choline acetylase activity after intraventricular administration of noradrenaline.[28] Possibly, the tachyphylaxis occurring in man during chronic administration of high doses of amphetamine represents a compensatory increase in central acetylcholine activity. The depressed mood which follows amphetamine withdrawal may represent unantagonised compensatorily increased central acetylcholine.

In man, methylphenidate, an amphetamine-like psychostimulant, has been used to shift central adrenergic-cholinergic balance toward an adrenergic predominance, presumably by releasing dopamine and noradrenaline from neuronal stores.[29] Since methylphenidate ('Ritalin') causes a statistically significant increase in interactions, thoughts, and talkativeness,[29] its effects may be judged to be a pharmacological model of central activation in man and possibly a model of mania. Physostigmine, administered to methylphenidate-stimulated human subjects of various diagnostic types, causes a dramatic decrease in methylphenidate-induced activation, presumably by increasing central acetylcholine levels, so as

to balance the increase in central adrenergic activity. Also, a physostigmine-induced anergic syndrome, consisting of depression, lethargy, apathy, drained feelings, and motor retardation, can be rapidly reversed by methylphenidate.[30] Thus, there is evidence in man and in animals that central adrenergic and cholinergic influences are antagonistic, with adrenergic influences causing behavioural activation and cholinergic influences causing behavioural inhibition.

Reserpine

The depletion of central noradrenaline is postulated to be the mechanism by which depression occurs in some patients receiving reserpine.[1–3,8] However, reserpine causes effects in animals which parallel those of the cholinomimetic agents. Like cholinomimetic agents, reserpine causes miosis, lacrimation, salivation, diarrhoea, akinesia, tremor, sedation, decreased locomotor activity,[1,2,8] decreased self-stimulation,[3] decreased conditioned responses,[9,16] and antagonism of methylphenidate-induced increased stereotyped gnawing behaviour.[31] Thus, in addition to depleting monoamines, reserpine causes a generalised increase in central cholinergic activity.[32]

Reserpine also exhibits significant cholinomimetic-like effects in man.[8] These include increased salivation, increased gastric secretions, vomiting, nausea, precipitation of asthmatic attacks and bronchospasm, biliary colic, nasal congestion, and diarrhoea.[33,34] Furthermore, the psychological side-effects of reserpine are remarkably similar to those occurring after exposure to centrally acting cholinomimetic agents[4,33–36] and include apathy, lassitude, slowed-down thinking, psychomotor retardation, lack of interest in usual activities, fatigue, impaired concentration, lethargy, drowsiness, fatigue, some paranoid ideas, nightmares, and depression.[1,3,8,33,34] Thus, the behavioural effects of reserpine may be explained on the basis of reserpine's central cholinomimetic effects. Reserpine would thus be expected to shift the adrenergic-cholinergic balance to a cholinergic predominance, since cholinergic activity would be increased and adrenergic neurotransmitters decreased after its administration. α-methyl-paratyrosine, which specifically blocks catecholamine synthesis without being reported to alter central acetylcholine, has not been reported to produce depression in hypertensive patients.

Tricyclic Antidepressants

The tricyclic antidepressants' ability to elevate mood in depressed patients and to occasionally induce mania has been attributed to their ability to increase monoamine availability by blocking uptake and/or increasing turnover. This is consistent with an adrenergic hypothesis of affective disorders.[1–4] However, iprindole, an effective tricyclic antidepressant, apparently neither blocks re-uptake nor does it increase noradrenaline turnover.[37] Imipramine blocks the increase in central cholinergic activity occurring with reserpine administration,[38] and, in contrast to methamphetamine, antagonises physostigmine-induced suppression of operant behaviour in pigeons.[17]

In man, imipramine also has prominent central anticholinergic effects, causing a toxic confusional state, reversed by physostigmine, which consists of disorientation, agitation, short-term memory loss, and hallucinations. This state is similar to that seen with atropine or scopolamine poisoning.[39] Thus, tricyclic antidepressants block central cholinergic activity, as well as increasing functionally available adrenergic neurotransmitters. This would shift the adrenergic-cholinergic balance towards an adrenergic predominance.

Atropine and Scopolamine

Anticholinergic drugs such as atropine and scopolamine cause behavioural activation and potentiate the effects of amphetamine-like stimulants in animals. In man, uncontrolled studies indicate that anticholinergic drugs have antidepressant effects.[40–43] Evaluation of these antidepressant effects are limited by the behavioural toxicity of centrally acting anticholinergic agents, which includes visual and auditory hallucinations, short-term memory loss, and disorientation, and by the uncontrolled nature of reported studies. Anticholinergic drugs do induce euphoria, talkativeness, and flight of ideas,[44] symptoms common also to mania.

Levodopa and the Extrapyramidal System

Parkinsonian symptoms are generally thought to represent a disruption of the functioning of the corpus striatum. The striatum is rich in acetylcholine and dopamine, neurotransmitters which have opposing actions in this structure. Parkinsonian symptoms are thought to be due to a depletion of dopamine or a blockade of dopamine receptors, leading to a functional overactivity of cholinergic mechanisms.[45] The treatment of parkinsonian symptoms has generally focused on increasing dopamine activity and/or decreasing cholinergic activity.[45] In many parkinsonian patients, levodopa, a dopamine precursor, alleviates the psychological and neurological symptoms of Parkinson's disease, presumably by increasing dopamine levels.[45] In certain parkinsonian patients, an increase in parkinsonian symptoms caused by physostigmine can be antagonised by levodopa. Furthermore, this antagonism seems to predict the therapeutic efficacy of levodopa in a given parkinsonian patient.[46] Possibly, the reason that the antagonism of physostigmine-induced increased extrapyramidal symptoms by levodopa predicts the effectiveness of levodopa therapy is that this pharmacological interaction challenges the potential for dopaminergic predominance over cholinergic factors.

Although such a balance is not necessarily present in all neural systems involving acetylcholine, a balance between adrenergic and cholinergic factors may similarly exist in those centres which regulate affect, as has been shown to exist in the regulation of extrapyramidal motor activity. In support of this possibility, monoamine oxidase (M.A.O.) inhibitors, tricyclic antidepressants, levodopa, amphetamines, and anticholinergic agents are all believed to be efficacious in treating Parkinson's disease and have all been judged to be antidepressants.[1–7,40–43] Also, depression is a frequent concomitant of Parkinson's disease. Levodopa may not be effective against all depressions [7] because, as in Parkinson's disease, it cannot always completely antagonise cholinergic activity. Depressed patients who do improve with levodopa[4] may have a relative increase in central adrenergic activity, with little compensatory increase in cholinergic activity.

Cholinomimetic Drugs

The most convincing direct evidence that central cholinergic activity plays a significant role in the regulation of human affect comes from studies of the psychological effects of centrally active cholinomimetic agents in man. Several studies in normal individuals have shown that the cholinesterase inhibitor insecticides and nerve gases increase depression, jitteriness, fatigue, tension, listlessness, mental and physical slowing, fading away of thoughts, confusion, withdrawal, grogginess, irritability, and motor retardation.[35,36,47–49] They also reduce friendliness and the ability to think clearly.[47–49]

Gershon has reported several cases of in-

dividuals poisoned with organophosphorous cholinesterase-inhibitor insecticides who had severe depressive reactions (7 of 16 cases) in addition to peripheral toxicity.[36] He found that the incidence of depression may be higher in people who cultivate orchards. These case-reports are supported by the uncontrolled work of Rowntree et al.,[35] who chronically administered the irreversible cholinesterase inhibitor, di-isopropyl fluorophosphate (D.F.P.), to 10 normal controls and 9 manic-depressive patients. All normal subjects developed a characteristic syndrome consisting of irritability, lassitude, depression, apathy, slowness and poverty of thought which preceded the onset of cholinomimetic physical symptoms. 2 manic-depressive patients tested while in remission had mental changes similar to those seen in the normal group. 2 hypomanic patients improved on D.F.P. and continued to be euthymic after its withdrawal. 1 hypomanic patient became less manic and became slightly depressed during each of two courses of D.F.P., but relapsed upon D.F.P. withdrawal. 1 hypomanic patient nearly in remission became floridly manic upon D.F.P. withdrawal, and 1 depressed patient had a considerable increase in depression during D.F.P. administration.

Janowsky et al. studied the effects of the reversible cholinesterase inhibitor, physostigmine, on patients with symptoms of hypomania (6 manic-depressives, 2 bipolar manics with schizoaffective features).[30,50] In a double-blind study, acute administration of intravenous physostigmine caused a rapid and dramatic decrease in manic symptoms[50] in the 8 patients. 5 of the 8 patients also demonstrated physostigmine-induced depressive mood, in addition to alleviation of manic symptoms. In addition, a total of 22 subjects (manics, acute schizophrenics, normal subjects, and remitted patients) had drained feelings, decreased thoughts, apathy, psychomotor retardation and, in some cases, depression and irritability after acute administration of physostigmine.[30] Neostigmine, a cholinesterase inhibitor which does not effectively cross the blood-brain barrier, caused no significant psychological effects in these patients.

Acute administration of physostigmine has also been found to induce severe depression in marijuana-intoxicated patients. In 2 cases, physostigmine, administered on a double-blind basis, caused a clinically severe, profound depressive reaction which was reversible with atropine.[20,51] Thus, in direct studies, central cholinergic activation seems to cause depression and to antagonise euphoria and related manic symptoms and to have effects opposite to those occurring in situations where adrenergic activation occurs.

Adrenergic-Cholinergic Balance and Schizophrenia

Although we have postulated that a balance between the central adrenergic and cholinergic systems may play a part in the aetiology of manic-depressive disease, it would be premature to identify a single neurotransmitter or the balance between two neurotransmitters as unique to a single mental disease. For example, adrenergic-cholinergic balance may play a role in altering schizophrenic symptoms. Adrenergic agents such as levodopa, amphetamine, methylphenidate, tricyclic antidepressants, and M.A.O. inhibitors intensify and precipitate schizophrenic symptoms in susceptible individuals.[1–3,5,29,52]

Anticholinergic agents also seem to activate schizophrenic symptoms. N-ethyl-3-piperidyl phenylcyclopentylglycolate ('Ditran'), a potent anticholinergic agent, has been noted to acutely activate underlying psychotic symptoms in schizophrenics, in

addition to causing a "central anticholinergic syndrome" consisting of memory loss, disorientation, and hallucination.[53] Pfeiffer and Jenney[16] and Von Andel [34,55] have noted that the acute administration of cholinomimetics, including arecoline and physostigmine, causes temporary lucid intervals in catatonics and other schizophrenics. Other workers have found that chronic administration of cholinesterase inhibitors intensifies schizophrenic symptoms.[35,36] Furthermore, methylphenidate or amphetamine-induced stereotyped gnawing behaviour in rats, judged by some to be an animal model of schizophrenia, is augmented by anticholinergic drugs and counteracted by cholinomimetic agents[18,56–58] administered on an acute basis.

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4. Neurosis

The neuroses constitute a class of emotional disorders in which considerable subjective distress and impaired social functioning may occur. Unlike psychoses, in neuroses there is usually no gross personality disorganization or misinterpretation of external reality.[19,60] Anxiety appears to play a central role in neuroses, and in fact, the different symptom patterns seen in the neuroses may result from the various mechanisms by which individuals attempt to reduce anxiety.[61,62]

Classification

Anxiety Neurosis. Anxiety neurosis is characterized by a general feeling of anxiety and panic associated with a variety of somatic signs and symptoms that commonly affect the cardiovascular and respiratory systems.[63] These include palpitations, rapid heart rate, transient elevations in blood pressure, chest pain, a pounding sensation in the large vessels of the neck, a sense of suffocation, and rapid breathing. The rapid breathing sometimes leads to a hyperventilation syndrome, characterized by sensations of numbness and tingling and muscular spasms around the mouth and extremities. The muscular spasms result from metabolic changes caused by the increased respiration. Gastrointestinal symptoms such as epigastric pain, "butterflies in the stomach," and diarrhea are seen in about 40% of patients suffering from anxiety neurosis. Other symptoms include headache, faintness, muscular tension, excessive perspiration, and dry mouth. These attacks may come on suddenly, often without obvious immediate external provocation.

Phobic Neurosis. Unlike the "free-floating" anxiety of anxiety neurosis, in the phobic neurosis there is a circumscribed irrational fear focused at a specific object or situation. Common phobias include fear of flying and fear of heights. According to psychoanalytic theory, such fear has special symbolic significance usually in an area of emotional conflict. Learning theorists suggest that a phobia represents a conditioned fear to a stimulus that was initially associated with a noxious event.

Hysterical Neurosis. Hysterical neurosis is subdivided into conversion hysteria and dissociative hysteria. In conversion hysteria there is typically a discrete loss of motor or sensory function that cannot be explained on the basis of any physical defect. Psycho-

genic blindness, deafness, loss of smell, paralysis, muscle weakness, or loss of sensation in a part of the body are common manifestations of conversion hysteria. The loss of function may provide some escape from an inner conflict and may result in the patient being relieved of some unpleasant responsibilities. It should be noted that conversion reactions can be seen in psychiatric conditions other than hysteria.

Dissociative hysteria is characterized by an altered state of consciousness, often manifested as amnesia and occasionally as multiple personalities. The amnesic patient responds to conflict with an inability to recall the traumatic event. Such amnesia is frequently seen in combat neuroses. In the individual with multiple personalities each personality may act out a different aspect of a conflict. For example, a patient in the dissociated state may act upon sexual impulses unacceptable to the normal self.

Obsessive-Compulsive Neurosis. Obsessivė-compulsive neurosis is characterized by the repetitious intrusions into consciousness of unwanted thoughts, and by urges to action which the individual is unable to control. Although the compulsive behavior that usually accompanies these obsessional thoughts is recognized by the patient as irrational, failure to perform the actions results in intense anxiety. Obsessional thoughts may be simple words, phrases, or sentences, while compulsions may range from simple acts to elaborate rituals.

Depressive Neurosis. This form of neurosis is characterized by persistent feelings and thoughts in reaction to a personally significant environmental change, such as change in marital status, death of a loved one, or alteration in socioeconomic status; the identification of such an external precipitating event is critical to the diagnosis of depressive neurosis. Somatic processes such as appetite, sleep, and sex drive are usually disturbed, but less so than in psychotic affective disorders. Although experiential factors are generally considered to be of primary importance in the etiology and pathogenesis of depressive neurosis, the possible role of biological factors is of considerable interest, especially since there is some overlap between the classifications of unipolar depression and depressive neurosis (see pages 136–139 for additional discussion).

Hypochondrical Neurosis. A disorder characterized by excessive preoccupation with bodily sensations and the status of one's physical health.

Depersonalization Neurosis. Depersonalization neurosis is generally a chronic condition marked by episodes of estrangement from self and external reality. These individuals feel as if they were observers of their emotions, thoughts, and actions and usually also sense that activities in their environment are unreal or dreamlike. Depersonalization may be a symptom in other psychiatric illnesses and it may occasionally occur as a normal experience.

Treatment

Various types of psychotherapy as well as somatic therapies are used in the treatment of neuroses.[64] Although it has been difficult to demonstrate meaningful differences in the effectiveness among the psychotherapies, some studies indicate that behavior therapy is more successful than other types in the alleviation of certain neurotic problems, particularly the phobias and compulsions.[65]

Minor tranquilizers such as the benzodiazepines chlordiazepoxide and diazepam (Librium® and Valium®) are widely used in the treatment of patients with neurotic disorders. The major clinical effect of these drugs is to decrease anxiety, and perhaps as a con-

sequence other neurotic symptoms may diminish as well. Benzodiazepines have been shown to be more effective than placebo in double-blind studies and carry less risk of addiction or overdose than barbiturate sedatives, which have also been used in the treatment of anxiety.[66]

Beta-adrenergic blocking agents such as propranolol (Indural®), widely used in the treatment of cardiovascular problems, have also been used with variable success for anxiety neurosis.[67] These drugs reduce palpitations and other somatic symptoms of anxiety attacks and are thought to act by interrupting the positive feedback between somatic symptoms and the subjective experience of anxiety. Their use for the treatment of anxiety is not generally recommended. Tricyclic antidepressants and monoamine oxidase inhibitors have been used successfully in the treatment of some patients with resistant phobias and phobic anxiety.[68,69]

Finally, the synergistic effects of drugs and psychotherapy, a field that has been termed "psycholopharmacology," is just beginning to be researched.[65] Other somatic therapies such as psychosurgery and electroconvulsive therapy are infrequently employed in the United States.

Reading Selections

Although neurosis is most often thought to result from adverse parent-child interactions or environmental circumstances, there is evidence that genetic factors are operative in at least some neuroses, particularly anxiety neurosis. This evidence is based primarily on family studies, as discussed in Miner's article entitled *The Evidence for Genetic Components in the Neuroses.* Other research techniques such as crossfostering, which involve the examination of individuals adopted in infancy, may at some point be used in the study of the neuroses and prove useful in validating these initial findings.

There is some evidence that biochemical mechanisms may be involved in the etiology of anxiety neurosis. As discussed by Miner, many of the bodily changes associated with anxiety neurosis are similar to those produced by strenuous physical exercise. In fact, individuals with a history of this disorder often report a worsening of neurotic symptoms with exercise. Several investigators have reported that, although blood lactate levels increase in all individuals during exercise, this increase is significantly greater in anxiety neurotics (lactate is a normal by-product of sugar metabolism in the body).

This observation led Pitts and McClure[70] to hypothesize that excess lactate might induce anxiety attacks. To examine this possibility, they injected solutions of either lactate or glucose (as a placebo control) into patients with anxiety neurosis and control subjects. The results of their experiment were dramatic. The administration of lactate alone produced an anxiety attack in almost every anxiety neurotic. Glucose produced only minimal effects. The same relative effects of the two solutions were produced in individuals who had no obvious psychiatric disorders; however, lactate administration in those individuals resulted in fewer and less severe neurotic symptoms.

Pitts and McClure concluded from their findings that excess lactate might produce the symptoms of anxiety neurosis by binding with calcium and thus interfering with normal neural transmission. Neurotic patients would be more responsive than controls if the injected lactate was added to the chronic overproduction of lactate in such individuals.

These conclusions have, however, been subject to some criticism.[71] High lactate levels in the blood and the induction of anxiety symptoms do not always correlate. In fact,

Pitts and McClure found that a substantial increase in blood lactate was not sufficient by itself to produce anxiety attacks in control individuals who had no previous history of psychopathology. Therefore, elevated lactate levels may be necessary, but other factors presumably play an important role in the production of anxiety symptoms.

Henderson[72] and Eldridge[73] have criticized Pitts and McClure's study on other grounds. They point out that both the D and L forms of lactate were injected, whereas only the L form is produced naturally in the body. They suggest the the D isomer, a foreign substance, may be responsible for the induction of anxiety. It would have been more significant in terms of the etiology of naturally occurring anxiety neurosis if the L form alone were shown to be responsible for the behavioral findings in Pitts and McClure's study.

Finally, the triggering of an anxiety episode by lactate infusion does not necessarily indicate that lactate is involved in the etiology and pathogenesis of anxiety neurosis. Ackerman and Sachar[74] suggest that lactate could produce such peripheral effects as palpitations and difficulty in breathing which, if previously associated with anxiety attacks, could be responsible for initiating such an attack by means of a conditioned response to the peripheral symptoms. If these somatic symptoms were not previously associated with severe anxiety, then increases in blood lactate would not be expected to elicit an anxiety attack. This may partially explain the failure of Pitts and McClure to produce anxiety attacks in individuals who had no previous history of the disorder. It is apparent that further research is necessary to determine the mechanism by which lactate produces anxiety attacks in individuals diagnosed as anxiety neurotics.

In his article entitled *Modern Biochemical Concepts of Anxiety,* Warburton hypothesizes that certain serotonergic systems in the brain, which are activated by adrenal corticosteroids, mediate anxiety. There is some evidence that excess corticosteroids are associated with the production of anxiety in humans: patients with adrenal corticosteroid overproduction (Cushing's disease) have a number of psychiatric symptoms, including anxiety; administration of steroids results in symptoms of anxiety or proneness to react with anxiety to emotionally charged situations; in psychotics steroid production and anxiety are closely correlated[75]; and some evidence also indicates that corticosteroids produce "equivalent" changes in animal behavior.

The possible role of various biogenic amine systems in the pathogenesis of anxiety has been examined with the use of the pharmacological bridge research strategy.[32] In experimental animals steroids have been reported to facilitate central adrenergic and serotonergic functioning, and the most effective class of antianxiety agents, the benzodiazepines, appear to suppress the activity of these biogenic amine systems.[76] Some evidence indicates that the drug-induced decrease in serotonergic activity may be more closely related than the decrease in catecholaminergic activity to the antianxiety effects of the benzodiazepines. Therefore, Warburton suggests that corticosteroid-induced serotonergic hyperactivity is an important factor in producing anxiety.

The postulated role for steroids in the pathophysiology of anxiety needs to be interpreted with some caution. As discussed by Ackerman and Sachar,[74] when a chemical introduced into the body produces somatic changes that have been associated with the anxiety syndrome, an anxiety attack could conceivably be triggered. Thus, if administered steroids are capable of producing such changes in susceptible individuals, then these hormones could conceivably initiate an anxiety response without necessarily being involved in the pathogenesis of anxiety neurosis.

The Evidence for Genetic Components in the Neuroses

A Review

Gary D. Miner, PhD

Evidence from studies of families and twins presented by several investigators suggests that some neuroses, such as anxiety neurosis, have an important genetic component whereas others, such as hysterical neurosis, may have none or a relatively unimportant genetic component. The heritability takes the form of a genetic predisposition that culminates in clinical neurotic symptoms only when the person is subjected to the proper set of environmental stresses. Psychological test studies show significant heritabilities of various personality traits, including "neurotic tendencies," and animal studies show that rats can be selected for "emotionality" or "nonemotionality." Evidence suggests the hypothesis that the genetic basis is a complex polygenic system in which some genetic loci are additive while other loci function via various genetic mechanisms.

Man has looked at mental illness from many different viewpoints; early in the history of the study of neurosis and other mental illness, genetic factors were thought to be causal or at least contributing. With the advent of Freudian theory, little attention was paid to genetic factors by most disciples of psychiatry. Eliot Slater was an exception. From the beginning of his work in the late 1930's, he was concerned with the genetic basis of mental illness. Slater studied information from 2,000 neurotic soldiers of World War II and published his early papers concerning neurosis in 1943 and 1944.[1,2] He showed that 50% to 55% of the patients who were diagnosed as neurotic had a positive family history, meaning that their first-degree relatives (parents, siblings or children) had suffered from some form of psychopathology. From this study he developed the hypothesis that generalized predispositions for neurosis were largely responsible for the development of neurotic symptoms when stress occurs for a person. He suggested that this "constitutional" tendency toward neurosis was at least partially the result of genetic factors.

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Studies

Family. Brown looked at the hereditary component in three forms of psychoneuroses: anxiety states, hysteria, and ob-

sessional states.[3] He investigated the quantity of these and other psychiatric problems in both first- and second-degree relatives of 104 randomly selected probands having one of those three types of neurosis. Among the 104 probands, 63 were classified as having anxiety neurosis, 21 as hysteric, and 20 as obsessional. Control subjects were selected randomly from persons about the same age as the patients with neuroses. Brown's study was done prior to World War II, so that environmental stresses affecting the subjects were of the usual types that occur in the family, sexual relationships, and work, rather than the unusual stresses of war as in Slater's study.

Brown's data showed significantly more neurotic states among first-degree relatives (parents and siblings) of the various types of neurotic probands than in the relatives of the control population. Among the first-degree relatives of hysteric probands, there was a significant excess of hysteria; among the first-degree relatives of persons who were obsessional there was a significant excess of obsessional neurosis. His data showed that these neurotic conditions tend to "breed true" about 15% of the time in anxiety neurosis, and about 7% of the time in obsessional and hysterical states. He found no significant differences in the frequency of neurosis between the mothers and fathers of probands. The frequency of neurotic abnormalities in second-degree relatives is small and, with the exception of abnormal personality and depression, did not differ significantly from the controls.

Table 1 shows the percentages of anxiety neurotics among relatives of anxiety neurotic probands as given in three studies, including Brown's. The percentage of relatives with the same neurosis remains constant in all three studies, about 15%

Animal. There may be parallels from lower-animal studies to bolster a genetic hypothesis about anxiety in man. The data from studies by Broadhurst, later published by Slater and Shields, are given in Figure 1. Two lines of rats, called reactive and nonreactive, were developed by starting with a group of rats having a large amount of genetic variability (hybrid or "outbred") and then selecting those that defecated at a high rate from those with a low rate during a two-minute trial period in an open field environment.[4,7] After 12 to 15 generations these rats still appeared to be diverging, suggesting that probably a large number of genes are associated with this trait. A high defecation rate in the open field was equated with anxiety by Broadhurst. It is difficult to extend the results of animal studies to humans, but, if Broadhurst's study is a fair measure of anxiety, then his evidence clearly indicates that a polygenic component is involved and that this component is a limiting factor on the behavior of the animal. Other studies have also demonstrated selection for "anxiety" or "emotionality." [8–10]

Table 1. Anxiety neurosis in relatives of anxiety neurotic probands (modified by the author from data in Slater and Shields, 1969[4])

Investigation	No. Probands	Parents and Siblings of Probands			Relatives of Control Group				Significance Level ‡
		No.	% Anxiety Neurosis	±SE*	No.	% Anxiety Neurosis	±SE	z Score†	
McInnes (1937)[5]	50	289	15.0	±2.1	401	4-5	±1.0	5.00	0.001
							±1.1	4.55	0.001
Brown (1942)[3]	63	354	15.1	±1.9	185	0	±0.0	5.59	0.001
Cohen (1951)[4]	111 (males)	410	15.8	±1.8	336	0.4	±0.3	5.36	0.001

* SE = standard error. † A z score of 1.96 is needed for significance at the 0.05 level; 2.56 at the 0.01 level; and 3.30 at the 0.001 level. ‡ Test of significance of difference between relatives of probands and relatives of controls.

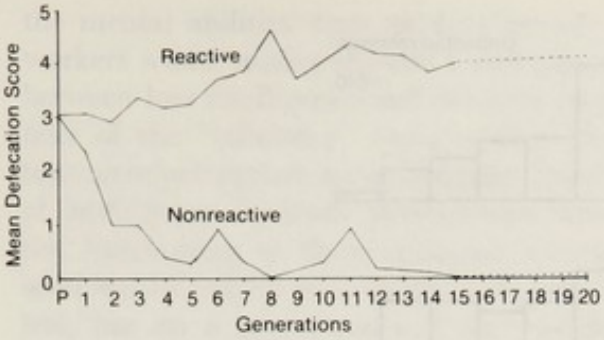

Figure 1. Selection for high and low emotional defecation in the rat. The resulting strains of rats are called the Maudsley Emotionally Reactive and Nonreactive (from Broadhurst, 1967[7]; and Slater and Shields, 1969[4]).

Psychological Tests. Coppen et al were concerned with studies using the Maudsley Personality Inventory (MPI), which has two main scales: "N" for neuroticism, and "E" for extraversion.[11] All patients who entered the Belmont Hospital in London over a period of 18 months and whose conditions were diagnosed with reasonable assurance as neurosis were included in this study. The patients completed the MPI and were asked for names and addresses of relatives, to whom the MPI was also sent. Of the relatives approached, 735 replied (78.3%). The *N* scores for the relatives had a low mean value, considerably below that reported for normal persons and not expected when based on a genetic hypothesis. Coppen et al do not have a satisfactory explanation for this below-normal *N* score but suggest that possibly relatives of neurotic patients presented themselves as less "neurotic" than they actually were as a defense reaction against their relationships to the patient. Figure 2 illustrates the pattern of neuroticism scores in patients and relatives. Rosenberg's study with the MPI also indicated that relatives of neurotics did not rank high in neurotic traits.[12] Assuming a genetic basis for neurosis one would expect to see a raised *N* rate in the relatives of neurotic patients. Coppen's MPI data suggest two possibilities: genetic factors are not operating, or, if operating, the MPI does not measure them.

Vandenberg writes about a series of psychological tests for measuring such variables as cognitive abilities, perceptual abilities, and personality traits conducted on 82 pairs of same-sexed twins, 45 monozygotic (MZ) and 37 dizygotic (DZ) (based on blood typing).[13] Each test was broken down into subunits, and the heritability values were calculated for each. It was found that several subunit variables had statistically significant heritabilities.

Gottesman also studied normal variation in personality traits.[14] His sample consisted of 147 pairs of same-sexed twins: 79 pairs MZ (34 male, 45 female) and 68 pairs DZ (32 male, 36 female). All twins were given the California Psychological Inventory (CPI), the Minnesota Multiphasic Personality Inventory (MMPI), a test of intelligence, and a biographical data sheet to complete. All 18 of the trait intraclass correlation coefficients for the MZ twins were significant for the 18 CPI scales; nine coefficients were significant for the DZ group. Heritability calculations showed that seven traits had within-family variance significantly associated with genetic factors, and a second-order factor, "person-orientation," was estimated to have considerable heritability.

Heritability of personality variables has been measured in children (ages 6–14) by Owen and Sines using the Wechsler Intelligence Scale for Children (WISC) and Missouri Children's Picture Series (MCPS).[15] Their results indicated a genetic component for social introversion-extraversion that is consistent with other reports of heritability for "person-orientation."[16–22] The data also suggested that measures of maturity and of masculinity-femininity may have heritability.

Young et al gave the Middlesex Hospital Questionnaire (MHQ) and a modification of the Eysenck Personality Inventory, the

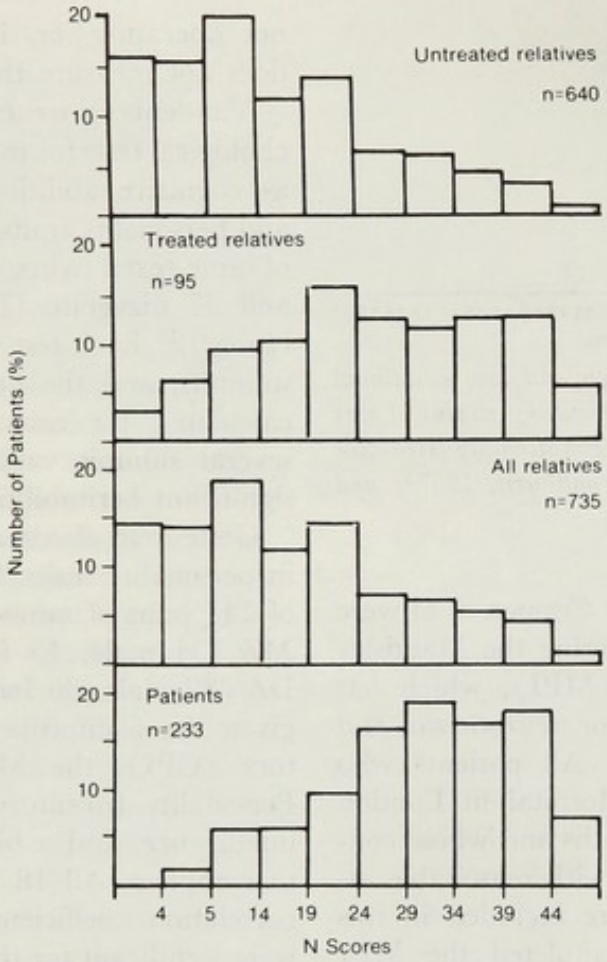

Figure 2. Distribution of neuroticism (N) scores from the MPI (from Coppen et al, 1965).[11]

"Psychoticism, Extraversion and Neuroticism" questionnaire (PEN), to 17 MZ and 15 DZ twins, all medically and psychiatrically normal males aged 19–40.[23] Results suggested genetic components in MHQ subscales measuring anxiety and hysterical personality traits, and in extraversion and neuroticism on the PEN.

The various personality traits that have been studied are all within the normal realm of personality variation; however, they are important to the psychiatric geneticist since they indicate that these personality variables appear to be determined in part by genetic make-up, and may be important in the neuroses.

Neurosis and Intelligence

What relationship, if any, exists between mental illness and intelligence? Eysenck reported data collected from over 3,000 men and women who were given the progressive matrices test of intelligence as they entered the Mill Hill Emergency Hospital and from over 3,000 male recruits who would be considered "normal." [24] These persons were ranked into five grades of intelligence: "I" representing the upper limit equal to 5% of the normal population, "II" equal to 20%, "III" equal to 50% (median intelligence), "IV" equal to 20%, and "V" equal to 5% (lowest intelligence). Eysenck argued that

the mental abilities' tests used by previous workers whose studies showed a correlation between low intelligence and neurosis were tests of the "efficiency" type, whereas his tests were perceptual, measuring the "level" of intelligence. Neurotic persons who were not functioning at their optimum mental level would not do well on an "efficiency" test, but on a perceptual test they would perform in a fashion comparable with nonneurotics.

It can be seen from Fig 3 that the distributions of both male and female neurotics are more platykurtic than the normal curve of male recruits. In other words, there were far fewer cases of average intelligence among the neurotics than among normals and there were more neurotics in both the extremes of the curve. In grade III, the 40.2% seen in male neurotics and the 40.6% in female neurotics are statistically different from the 50% in the male recruits. Also, among the women neurotics there are 31.9% in grades I and II instead of the expected 25%; this difference is statistically significant. Instead of the normal 25% in grades IV and V among the male neurotics, there was a combined percentage of 32.7% in these two categories; this difference is also statistically significant. These data Eysenck concludes, support the view that people of average intelligence tend not to develop neurosis as frequently as people at the extremes of the intelligence curve. This is consistent with a diathesis-stress model of neurosis. A person at either extreme of the intelligence curve may have more adjustment problems and, if he has a genetic predisposition to neurosis, will not be able to cope as well as a person without this genetic predisposition. If the genes associated with intelligence can interact with genes associated with neurosis to produce a lower threshold of resistance to stress, then the phenomenon is known formally by geneticists as "gene interaction."

Twins Studies

Eysenck and Prell studied 25 pairs each of MZ and DZ twins selected at random by searching the schools of five boroughs in South London for same-sexed twins.[25] The subjects were given 17 tests, ranging from those for intelligence, tapping speed, motor speed, and static ataxia to questions from the *Lie* scale of the MMPI, questions about work dislikes, and others. From these a neuroticism factor was computed: the correlation was .85 for MZ twins and .22 for fraternal twins; h^2 (heritability), a mea-

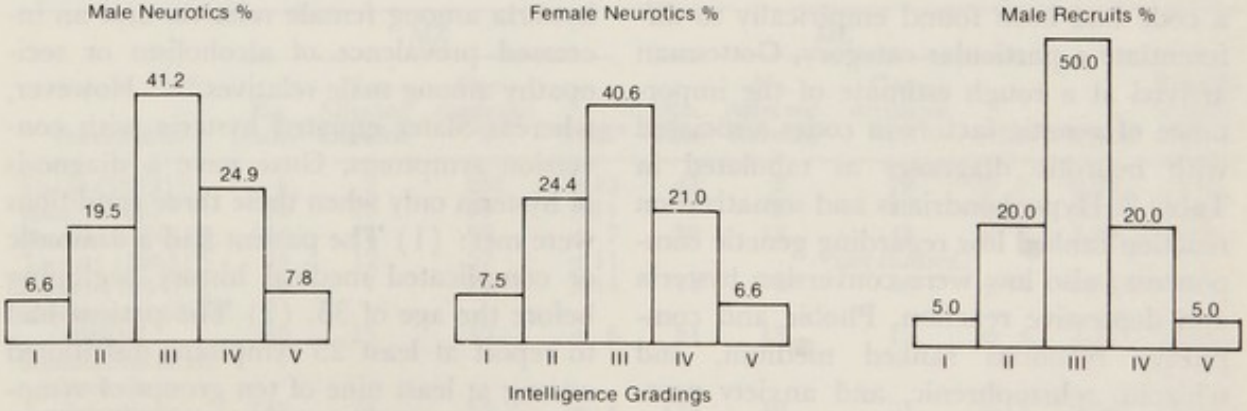

Figure 3. Intelligence in 2,646 male and 439 female neurotics and in 3,665 male recruits (nonneurotic controls). The range of intelligence is divided into five grades. Larger percentages of neurotics than normals fall into the nonmedian grades (I, II, IV, and V) (from Eysenck, 1943[24]).

sure of the degree to which the phenotype is caused by the genotype, was 0.81 (For a further discussion of *heritability,* see pp 47–48 in Rosenthal.[26]).

Gottesman presented data obtained from 34 pairs each of normal, adolescent identical and fraternal same-sexed twins in an attempt to clarify the extent of genetic and environmental components in the etiology of neurosis.[27] Data consisted of personal history sheets, the MMPI, and Cattell's High School Personality Questionnaire (HSPQ). Five factors on the HSPQ configurally define a neurosis. Gottesman found only two of those five to have appreciable heritability. *F*, the scale for depressed vs enthusiastic, had a heritability of 0.56, and *O*, confident vs prone to guilt had a heritability of 0.46. Six of the ten MMPI scales have been found to occur in high frequencies in configurations associated with various psychoneurotic diagnoses. Of these six, four had appreciable heritabilities in Gottesman's study: scale 8, schizophrenia (*Sc*)—.29; scale 7, psychasthenia (*Pt*) —.33; scale 2, depression (*D*)—.34; scale 0, social introversion-extroversion (*SI*) —.69. Using a combination of weights for (1) the number of scales with appreciable heritability in an MMPI code, (2) the magnitude of h^2 for each scale involved, and (3) the degree of accuracy with which a code had been found empirically to differentiate a particular category, Gottesman arrived at a rough estimate of the importance of genetic factors in codes associated with neurotic diagnoses as tabulated in Table 2. Hypochondriasis and somatization reaction ranked low regarding genetic components; also low were conversion hysteria and depressive reaction. Phobic and compulsive reactions ranked medium, and schizoid, schizophrenic, and anxiety reactions ranked high. Gottesman made this important statement: "It is worth noting that the emphasis to the psychoanalytic movement was furnished by the singular success of Freud in treating conversion hysteria." [27(p226)] If hysteria truly does have a low genetic component, as shown by this study, then it would be expected to be highly responsive to environmental manipulation. Slater also came to the conclusion that hysteria did not appear to be a genetic syndrome.[28] He later suggested that organic disease could bring about personality changes leading to hysterical symptoms.[29] Guze and his colleagues collected data from first-degree relatives of hysteric probands that indicated an increased prevalence of hysteria among female relatives and an increased prevalence of alcoholism or sociopathy among male relatives.[30,31] However, whereas Slater equated hysteria with conversion symptoms, Guze gave a diagnosis of hysteria only when these three conditions were met: (1) The patient had a dramatic or complicated medical history beginning before the age of 35. (2) The patient had to report at least 25 symptoms distributed among at least nine of ten groups of symptoms. (3) No other diagnosis could be made to explain the symptoms.[31] Thus Slater and Guze were dealing with different

Table 2. Estimates of the genetic component of variation in the psychoneuroses (from Gottesman, 1962[27])

Snydrome	MMPI Code Type			Magnitude of Genetic Component (Male and Female Combined)
Hypochondriasis/ Somatization Reaction		Hs	Hy	Low
		D	Hs	Low
	Hs	D	Hy	Low
Conversion Hysteria		Hs	Hy	Low
Phobic/Obsessive Compulsive Reaction		D	Pt	Medium
		Pt	Sc	Medium
Depressive Reaction		D	Pt	Medium
		D	Hy	Low
Schizoid/ Schizophrenic Reaction	D	Pt	Sc	High
Anxiety Reaction		D	Pt	High
	D	Pt	Si	High

syndromes although there may have been some overlap.

Inouye reported the results of concordance or discordance in twins suffering from different types of neurosis.[32] His sample size for the DZ twins was small; however, there were 21 pairs of MZ twins, ten of these being concordant for neurosis, eight for obsessive-compulsive reaction and two for dissociative reactions.

Table 3 provides a summary of the studies of neurosis in twins. Although the sample sizes are small for most of the studies, the Shields and Slater sample is large and probably provides a good estimate of twin concordance rates. When all six studies are tabulated, the overall concordance rates are 45% for MZ and 23% for DZ; although combining studies increases the sample size, the unmeasured variance is probably also increased because of differing diagnostic criteria among the investigators.

The data seen in Table 4 are probably less biased than those from previous studies in that the twins were taken from a sample of 192 consecutive admissions (adults) to a hospital between the years 1948–1958 in which each patient had a diagnosis of neurosis or personality disorder. In a follow-up study 7½ years later these probands and their cotwins were blindly rediagnosed from summaries that did not mention the previous diagnosis or zygosity. Forty-six of these twins were then omitted because of psychotic or organic diagnoses, leaving a total of 62 MZ pairs and 84 DZ pairs. It is evident from Table 4 that almost one half of the MZ probands having a diagnosis of anxiety neurosis had cotwins with an identical diagnosis. This was not the case for other types of neurosis.

Shields states that "the data support the view that the particular combination of many genetic factors in the neurotic individual influences the [clinical] form of his neurosis to a greater extent than it influences whether or how severely he breaks down.[33] In other words, environmental stresses are probably the major factor, inducing decompensation and development of a neurosis, but whether this neurosis takes the form of anxiety, hysteria, phobia, or obsession probably depends on genotype.

Pollin et al reported on psychopathology in 15,909 pairs of twins—all male veterans of United States armed services.[40] They found that the MZ concordance rate for schizophrenia was 3.3 times greater than

Table 3. Neurotic illness in cotwins of neurotic probands (modified by the author from data in Slater and Shields, 1969,[4] and Shields, 1973[33])

	MZ				DZ					
Investigator	No. Pairs	No. Affected Cotwins	Concordance %	±SE*	No. Pairs	No. Affected Cotwins	Concordance %	±SE	*z* Score†	Significance Level
Slater (1953)[34]	8	2	25‡	±15	43	8	19	± 6	0.09	ns§
Ihda (1960)[35]	20	10	50	±11	5	2	40	±22	0.10	ns
Braconi (1961)[36]	20	18	90	± 7	30	13	43	± 9	3.04	0.01
Tienari (1963)[37]	21	12	57	±11			(not studied)			
Parker (1964)[38]‖	10	7	70	±14	11	4	36	±14	1.11	ns
Shields and Slater (1966)[39]	62	25	40	± 6	84	13	15	± 4	3.52	0.001
Summation of all above six investigations	141	74	52	± 4	173	40	23	± 3	4.00	0.001

* SE = standard error. † *z* is a measurement of significant difference between MZ and DZ values. ‡ Pairwise concordance. § ns = not significant. ‖ Includes data from an unpublished MD thesis by N. Parker—Twins: A Psychiatric Study (University of Queensland, Australia).

Table 4. Similarity in the diagnoses of cotwins of neurotic probands (modified by the author from data in Slater and Shields, 1969,[4] and Shields, 1973[33])

			MZ				DZ			
	z Score*	Significance Level	No. Pairs	No. Affected Cotwins	Concordance %	±SE†	No. Pairs	No. Affected Cotwins	Concordance %	±SE
Anxiety state in proband										
Any diagnosis in cotwin	1.72	ns‡	17	8	47	±12	28	5	18	±7
Same diagnosis in cotwin	2.73	0.01	17	7	41	±12	28	1	4	±4
Other neurosis in proband										
Any diagnosis in cotwin	0.36	ns	12	3	25	±12	21	5	24	±9
Same diagnosis in cotwin	...	...	12	0	0	...	21	0	0	...
Personality disorder in proband										
Any diagnosis in cotwin	2.20	0.05	33	18	55	± 9	35	10	29	±8
Same diagnosis in cotwin	2.53	0.05	33	9	33	± 8	35	2	6	±4
All probands										
Any diagnosis in cotwin	2.99	0.01	62	29	47	± 6	84	20	24	±5
Same diagnosis in cotwin	3.75	0.001	62	18	29	± 6	84	3	4	±2

* *z* score tests significant differences between values for MZ and DZ. † SE = standard error. ‡ ns = not significant.

the DZ rate. In contrast, the MZ concordance rate for neurosis was only 1.3 times as great as the DZ rate. They concluded that this difference suggested the presence of a genetic factor in schizophrenia but its relative absence in neurosis, although they tended to dismiss the genetic factor in schizophrenia as a limited one, since 85% of their pairs of MZ twins were discordant for schizophrenia. Although this study contains a large number of twins, it should be noted that hospital chart diagnoses were used, and if a diagnosis had been made more than once, the worst diagnosis was recorded. So, although the sample size is large, the diagnoses are not standardized. Twin studies using a blind consensus diagnosis method are probably more accurate.[41] Moreover, there is further bias in that both members of the pair had to have served with armed forces, which suggests selection for health and male sex, and both had to attend Veterans Administration Hospitals and clinics, suggesting socioeconomic and probably other selective factors.

The twin studies discussed above indicate that genetic factors must be involved in the development of certain types of neurosis, and that genetic factors are possibly absent in others.

Biochemical Aspects of Anxiety Neurosis

Genetic mechanisms must involve DNA, RNA, enzymes, proteins, hormones, and physiological processes. To this end Pitts and McClure have done some important biochemical research on anxiety neurosis.[42] They point out that four investigations conducted in four countries have shown excessive lactate production in patients with anxiety neurosis.[43–46] Anxiety symptoms were often brought on with standard exercises, and correlated with the symptoms was a rapid rise in blood lactic acid. This caused the patients to be unable to perform as much work per unit time as controls.

Pitts and McClure conducted their research based on the hypothesis: "... that perhaps the lactate ion itself can produce anxiety attacks in susceptible persons." [42(p1329)] A pilot study with nine patients and nine controls showed that all patients and two of the controls developed anxiety attacks with lactate infusion sufficient to raise the venous lactate to 12–15 millimoles/liter (normal resting venous lactate—0.2–1.5 millimoles/liter). A double-blind experiment was conducted with 14 patients (mean age, 33 ± 2.1) and 10

controls (mean age, 31.7 ± 2.3). To be included each of these patients had to meet five criteria: To have had (1) an anxiety attack at the interview, (2) severe feelings of tenseness or free-floating anxiety nearly daily for at least two years, (3) at least 10 of 16 anxiety symptoms, (4) no other psychiatric disease or serious medical disorder, and (5) the first anxiety syndrome symptoms before the age of 30. The patients and controls were infused with lactate ion, lactate plus calcium, or glucose in saline. The results demonstrated that anxiety symptoms developed when lactate ion was infused into the patients diagnosed as having anxiety neurosis. These symptoms were largely prevented when calcium ion was added to the lactate, and did not occur when glucose in a saline solution was administered. The lactate infusion caused some anxiety symptoms in controls, but these symptoms were fewer in number and of less severity than those of the patients. In 13 of 14 subjects diagnosed as anxiety neurotics, anxiety attacks developed with infusion of lactate. The attack began one or two minutes after infusion had started, decreased rapidly after completion of infusion, but was often followed by a prolonged period of 24 to 72 hours of exhaustion and symptom-exacerbation. Only two of the control subjects had such attacks ($P < .002$). In one subject diagnosed as an anxiety neurotic, a probable anxiety attack developed with lactate-plus-calcium infusion. No attacks occurred in controls with similar treatment ($P < .20$). Statistically the group of anxiety neurotics differed from the controls only in the response to lactate infusion. No symptoms characteristic of depression, hysteria, schizophrenia, or obsessive-compulsive neurosis developed.

Pitts and McClure concluded that there may be something highly specific about lactate ion in producing the naturally occurring hypocalcemic anxiety symptoms in human beings. They developed the following theory:

> Anxiety symptoms may have a common determining biochemical end mechanism involving the complexing of ionized calcium at the surface of excitable membranes (in the interstitial fluid) with lactate ion produced intra-cellularly. According to our theory, anxiety symptoms could occur in the normal person under stress as a consequence of marked increase in lactate production in response to increased epinephrine release; the patient with anxiety neurosis would be someone especially subject to this mechanism because of chronic overproduction of epinephrine, overactivity of the central nervous system, a defect in aerobic or anaerobic metabolism resulting in excess lactate production, a defect in calcium metabolism or some combination of these.[42(p1335)]

Pitts and McClure's study has generated controversy and a recent study by Grosz and Farmer[47] indicated that the lactate ion is not directly related to anxiety neurosis. Grosz and Farmer pointed out that sodium lactate is rapidly converted to sodium bicarbonate, which creates an alkalosis. They administered sodium lactate, sodium bicarbonate, or glucose randomly in a double-blind fashion, on different days to ten healthy young men. Anxiety symptoms appeared to be elicited equally well by either the lactate or bicarbonate but not by glucose. Hyperventilation, characteristic of anxiety neurosis, also leads to alkalosis and is associated with anxiety symptoms. There is less free ionized calcium in an alkaloid state so that the infusion of calcium should counteract alkalosis and hence anxiety symptoms; this could explain the results of Pitts and McClure's lactate plus calcium infusion experiments. It appears that lactate ion may be only one factor of an underlying mechanism in anxiety neurosis.

It seems that the studies done by Pitts and McClure and those done by Grosz and Farmer are the type of investigation needed to elucidate the biochemical mechanisms that almost certainly must be involved in the genetic-environmental interaction taking place to produce some of these illnesses.

Marriage and Fertility in Neurotics

If neurosis has a hereditary component then it is important to study marriage and fertility patterns in neurotic persons to see what is happening to the population frequency of the genes involved in neurosis. Several studies[25–32] have discussed marriage and fertility patterns, but the first to provide worthy information is that of Slater et al.[33] They collected data on marriage and fertility from both inpatient and outpatient records on first attendance at the Royal Bethlem and Maudsley Hospitals during the period 1952 through 1966. Patients were separated into five classifications: schizophrenia (1,003 males, 1,086 females), manic-depression (1,606 males, 2,692 females), personality disorder (2,158 males, 932 females), obsessional neurosis (229 males, 235 females), and neurosis other than obsessional (3,908 males, 5,596 females). Since most inpatients were hospitalized only for a short time or, if longer, were permitted frequent leaves, inpatient treatment was not considered to affect the patient's chance of marriage or fertility. The controls with which the psychiatric patients were compared were taken from the registrar-general's data for England and Wales during the 1961 census. The data indicated that various psychiatric disorders were associated with shortness of time spent in the married state during the reproductive years (age 20–44); ratios of mean years in married state of the diagnostic group divided by that for the controls gave 0.42 (males) and 0.60 (females) for schizophrenia, and 0.87 (males) and 0.92 (females) for neurosis. Neurotics were closest to normal for the illness categories studied.

$$\text{Fitness} = \frac{\text{Proportion of offspring observed}}{\text{Proportion of offspring expected}} =$$

$$\frac{\text{observed number of children at each age}}{\text{expected number of children at each age (calculated from census data, allowing for age at marriage)}} \times \frac{\text{expectation of being ever married at this age}}{\text{census expectation of being ever married at this age}} \times 100$$

This estimate showed that fitness in female neurotics was consistently lowered by about 30% (range = 61–75) over age of first hospitalization ranging from 20 to 65 years, whereas fitness in female schizophrenics was lowered from 80% at age 20 to only 4% if the first hospitalization was at age 65, averaging to only a slightly lower fitness estimate in neurotics. These

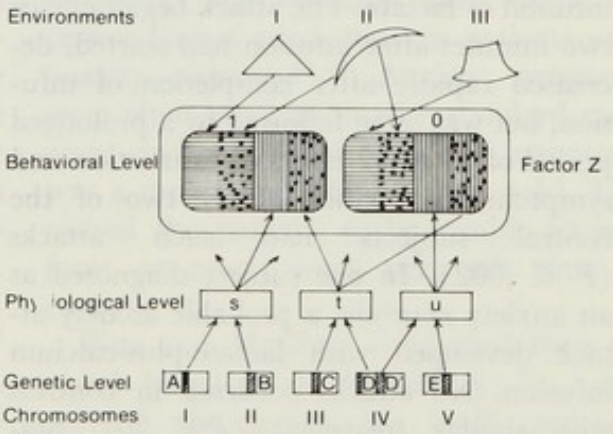

Figure 4. Gene and chromosomal communality and specific and common variances of the pathway between the gene and behavior (from Fuller and Thompson, 1960; and Gottesman, 1968[55,56]). I, II, and III (top): types of environments; 1 and 0: behavior traits; Factor Z: general behavior; s, t, u: enzymes, hormones, and neurons; A, B . . . E: genes; I, II . . . V: chromosomes; horizontal lines: environmental variance; vertical lines: genetic variance; dotted areas: variances between the two behavioral traits.

data, showing that neurotics are less fertile, would indicate, on first inspection, that the hereditary component in neurosis is decreasing in the population. Whether or not this actually is the case, however, remains to be elucidated. Reed has speculated that a balanced polymorphic system may be operating in psychoses,[54] and one could also postulate this genetic mechanism for neuroses. In such a system some genotypes would have a reproductive advantage compensating for those who develop illness resulting in a reproductive disadvantage, thus keeping the frequencies of the alleles of the genes involved relatively constant.

A Genetic-Environmental Interaction Model of Neurosis

If one postulates a genetic component to neurosis, or for that matter any mental illness, then one has to take into account the pathway between the gene and the behavioral phenotype. This pathway has to involve biochemical and neurophysiological mechanisms. Figure 4 illustrates a model originally presented by Fuller and Thompson[55(p341)] for this gene-to-behavior pathway in which some factors act on more than one element of another level (communality) and various factors interact to produce the behavior. Looking at the evidence on neurosis, it seems that there must be many different genetic loci acting as contributors to a genetic predisposition. The alleles at these loci could interact in different ways:

1. The alleles at one locus may show a dominance-recessive type of action or may show incomplete dominance; ie, at a locus called, for example, "anxiety," allele "A" may be dominant over allele "a," or "Aa" may produce a phenotype different from either "AA" or "aa."

2. Alleles at another locus may suppress or enhance the action of alleles at other loci; ie, allele "o" at locus O may give a certain quantitative predisposition to obsessional neurosis. When allele "m" is present at locus M the quantitative predisposition is doubled, but if "m" is present without "o" there is no predisposition.

3. Alleles in a certain set of loci may show additive characteristics, whereas other loci may show nonadditive characteristics; ie, allele "a" at locus A may give a neurotic predisposition equal to x; allele "b" at locus B may give a neurotic predisposition equal to y; when both alleles "a" and "b" are present in the same individual the neurotic predisposition equals $x + y$—this is an additive effect, but if the neurotic predisposition did not equal $x + y$ it would be a nonadditive effect.

4. The importance of any one genetic locus in the total genetic predisposition may be relative to the particular set of environmental stresses; ie, two individuals genetically identical, but subjected to two different sets of environmental stresses may develop similar neuroses in which in one individual genetic locus A is most important and in the second individual genetic locus B is most important.

Another way of stating this is: A neurosis is dependent on both genetic and environmental factors; the genetic aspect is dependent on many alleles at many loci. Some of these alleles will exert greater effects contributing to an illness and some lesser effects, and the exact type of neurosis, be it hysterical, anxiety, obsessional, or depressional, will then probably be dependent on the exact "set" of genes that an individual has, therefore giving him that particular predisposed "neurotic set."

It should be emphasized that this model intends that environmental stress must be an important component in the development of a neurosis.[1,2] An example of the interaction between the genotype and environment was suggested earlier in this paper in the work by Pitts and McClure.[42] Anxiety symptoms were brought on in pa-

tients previously diagnosed as anxiety neurotics by physical exercise—an environmental stress. Presumably, if persons having a genetic predisposition to anxiety neurosis are never subjected to physical exercise plus the remainder of environmental stresses comprising a spectrum of stresses specific for anxiety neurosis, then they will never develop the neurosis.

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Modern Biochemical Concepts of Anxiety

Implications for Psychopharmacological Treatment

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Evidence from clinical studies suggest that corticosteroids produce agitation and enhance anxiety. It is proposed that anxiety results from the neurochemical changes induced by corticosteroids. Evidence was presented to show that the critical changes for anxiety are due to modifications in serotonin pathways in the tegmental region of the midbrain. In support of this, known antianxiety agents block these changes and so it is argued that the future search for anxiolytic drugs should focus on these neurochemical pathways.

All normal people are subject to anxiety prior to critical and uncertain events, like examinations, public appearances and so on. Pure pathological anxiety reactions are rarely seen in clinical practice (*Mayer-Gross et al.*, 1954) and more often anxiety is found as an accompanying symptom of depression and occasionally schizophrenia, where the patient is preoccupied with impending disaster, without any idea of the source of the threat, or if the threat can be recognized, it is trivial compared with the reaction. Anxiety can be characterized as an unpleasant emotional state which is directed towards the future, and this anticipatory element distinguishes it from fear which is the result of a response to an actual threat. Thus, following *Pribram* (1967), anxiety will be viewed as a passive state representing awareness of a response to certain internal and external stimuli. The magnitude of the emotional experience will depend on the amount of arousal measured in information theory terms as the amount of uncertainty in the environment. Amount of arousal is thus viewed as the size of the match and mismatch between expectancy and stimulus input.

Warburton (1972) suggested that redundant stimuli from the external and internal milieu are prevented from arousing the cortex by the functioning of the hippocampus and this implies that the system is more than a simple negative feedback loop because there must be some sort of storage of information about stimulus regularities in the internal and external environments. This characterization was based on the hypothesis that the limbic midbrain maintains stability by diminishing the response

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to recurrent events in the internal and external milieux (*Pribram*, 1969). It will be part of the argument in this paper that the hippocampus 'recognizes' a state of mismatch, produces specific changes in the output to the hypothalamus and the tegmental region. As a result, corticosteroids are released from the adrenal glands. It is argued that it is the action of this hormone on the brain chemistry, combined with the cognitive interpretation of the situation that constitutes the response that is experienced as the emotion 'anxiety'.

The organization in this paper will involve expansion of the following logical steps (*Schildkraut*, 1969) in the search for the biochemical bases of anxiety: (a) corticosteroids produce anxiety in man; (b) corticosteroids produce equivalent changes in animal behaviour; (c) it is assumed that the anxiety results from neurochemical changes induced by corticosteroids. Thus the biochemical changes produced in animals may be used to infer the biochemical bases of anxiety in man and so the nature of drugs which would reduce anxiety, and (d) the biochemical mode of action of known antianxiety drugs is examined to see if this action conforms to the pattern predicted from (c), and so test the hypothesis that an 'ideal' antianxiety agent should have these properties.

Corticosteroids and Anxiety in Man

There have been a number of studies correlating cortisol production and psychiatric state, but few of these have focussed on anxiety. In a summary of his own work *Sachar* (1970) found that patients who had little anxiety and emotional arousal also showed little change in cortisol production during recovery, while patients with symptoms of anxiety had a moderate 25-percent elevation in their cortisol production compared with their recovery levels. In cases of psychotic disorganization in depression and schizophrenia there was disintegrative anxiety and very large, 50-percent, increases in cortisol levels. Of course it is unclear in these studies whether the anxiety results from the steroid release produced by the stress of the disorder or whether the stress of the disorder, including the anxiety, causes the release of the cortisol. Some evidence for the former mechanism comes from studies of patients with Cushing's disease in which there is cortisol hypersecretion; as well as the physical disorder, patients display a number of psychiatric symptoms, including agitation, and anxiety (*Cleghorn*, 1957).

The most convincing evidence for the steroid causing anxiety comes from the effects of administering corticosteroids to man. When cortisone therapy was first introduced there were numerous reports of emotional disturbance (*Cleghorn*, 1957). This was described as an alerted state marked by anxiety, irritability, tension and emotional lability. In these studies anxiety was not necessarily increased although the subjects invariably became more tense. In a more systematic investigation the plasma corticosteroid level was raised rapidly by intravenous injection of hydrocortisone (F) and the subjects' anxiety levels assessed by a battery of tests. It was found that this steroid did not affect the immediate experience of anxiety, but their proneness to anxiety was enhanced (*Weiner et al.*, 1963). In order to examine whether corticosteroids play a role in modulating the effects of anxiety-provoking situations, subjects were given an injection and an anxiety-provoking suggestion while in a hypnotic trance. These subjects responded to the suggestion with a more prolonged anxiety response than subjects receiving a placebo injection (*Levitt et al.*, 1963). In a later study *Persky et al.* (1971) found slight increases in anxiety measured on the same anxiety scales as *Weiner et al.* (1963)

with small doses of the naturally occurring corticosterone B and corticosterone F given intravenously.

Corticosteroids and Animal Behaviour

It is difficult to devise methods of inducing 'normal' anxiety in animals. One experimental situation was devised by *Estes and Skinner* (1941) in which animals were trained to press a lever for positive reinforcement and after this training the animals were placed in a box and a warning stimulus presented prior to a shock to the feet. Thereafter, presentation of the warning signal while the animal was pressing resulted in suppression of responding and measures of the corticosteroids during sessions, when the warning signal but no shock was given, showed that the adrenocortical secretion was increased progressively on successive sessions (*Mason et al.*, 1957). In the same study, measures were made in a second situation, non-discriminated avoidance (*Sidman*, 1953), where animals could reset a clock by pressing a lever, but if the clock timed out they received a shock. Here the animal has no signal, but must press in anticipation of shock. Measures of plasma corticosteroids showed elevated levels, but in the later experiment, when the animal was given a warning signal for the avoidance response i.e., discriminated avoidance, the steroid secretion was decreased. Elimination of the warning signal resulted in an elevation of the steroids again, although they did not return to their original level. In addition to this, there was also release of norepinephrine and epinephrine, from the adrenal medulla, during these experiments. From the pattern of release in different situations it was concluded that norepinephrine release occurred in situations which were unambiguous and familiar, while the epinephrine and corticosteroid response occurred when there was an element of uncertainty and unpredictability (*Mason et al.*, 1961). A similar phenomenon occurs in human subjects where a subject feels 'uncertain and helpless' when he receives unpredictable and uncontrollable shocks (*Frankenhauser and Rissler*, 1970) or when he plays a game of chance like 'bingo' (*Patkai*, 1971). Here it should be noted that uncertainty has produced similar physiological states in humans, but the interpretation in cognitive terms depends on situational variables, and so anxiety is not experienced in bingo sessions (*Schachter and Singer*, 1962).

This situation can be interpreted in terms of 'uncertainty' and 'control'. In the first situation a signal is presented, which had previously been paired with shock, but no shock is given; the animal's expectancy has been contradicted. In the second situation, the animal has no exteroceptive cue which signals when an avoidance response should be made, so it is not predictable, and greater amounts of steroids are secreted but introduction of the warning signal makes the situation predictable and the steroid levels fall. Another way of talking about this expectancy and control is proposed by *Mandler* (1967) when he argues that by 'anticipation', or expectancy, we mean that the organism has some appropriate behaviour pattern that can be performed when the proper stimuli occur. A situation is 'ambiguous', unpredictable, when no single set of behaviours is directly or dominantly relevant to the situation, and 'anxiety' occurs when no situationally relevant behaviour is available to the organism.

In the previous experiments it was argued that corticosteroid release was the result of the uncertainty in the situation. However, all of these experiments used shock, which releases steroids and unequivocal support for the uncertainty argument can only come from studies using appetitive reinforcement. In a study of *Coover et al.* (1971), uncertainty was introduced by changing the rat's schedule of reinforce-

ment after training; rats were trained to lever press on a continuous reinforcement schedule, and then reinforcement was withheld. Measures of the stress steroids demonstrated a rise in plasma corticosterone during extinction. That the phenomenon was not due to removal of reinforcement *per se* was shown by *Levine et al.* (1972) in another study in which animals were trained on either a variable interval schedule with reinforcement at irregular intervals, or a fixed interval schedule with the same density of reinforcement but given regularly. Then the two groups were switched to the other schedule, and it was found that animals switched from unpredictable variable interval schedule to the predictable fixed interval schedule showed no change in plasma corticosterone, but rats switched from the predictable fixed interval to the unpredictable variable interval showed an elevation of plasma corticosterone levels.

A third experiment by *Coover et al.* (1972) also showed that this phenomenon was not confined to negative reinforcement situations. During training on discriminated avoidance, blood samples were taken from the rats during acquisition, stable performance and extinction when the response was prevented. During acquisition there was a high level of corticosterone which one might expect from the high shock density, and the levels fell when stable performance was achieved, and the number of shocks decreased. However, shock was not the only reason for elevated steroid levels, because during extinction with the lever removed the levels were again elevated. *Levine et al.* (1972) suggested that during acquisition the situation becomes more predictable for the animal and the corticosterone levels fall, but during extinction 'when the predictability and control that the rats had acquired no longer exist, an apparent increase in arousal and an increase in pituitary-adrenal function result.'

These studies show that in situations involving uncertainty, animals show increased steroid release similar to that found in humans. This suggests that it may be profitable to analyze the influence of corticosteroids on performance in these anxiety situations. The physiological consequences of increased ACTH secretion, and the resulting enhanced corticosteroid release, are well documented, but until recently there has been very little strong behavioural data available.

The effects of corticosterone can be studied by either injecting ACTH into normal rats, or by using the synthetic corticosteroid, dexamethasone. The advantage of the latter procedure is that ACTH levels are not high at the same time as the corticosterone, enabling separation of the two effects. One study (*Wertheim et al.*, 1967) compared the two sorts of treatment on animals trained in a non-discriminated avoidance of *Sidman* (1953), described earlier as a model of human anxiety, until all subjects had achieved stable performance. Injections of both ACTH and dexamethasone resulted in a marked decrement in shock rate during the avoidance testing, but the greatest decrements occurred with dexamethasone, suggesting that the effects of corticosterone were confounded with those of ACTH. The distribution of responses was also modified by dexamethasone, and to a lesser extent by ACTH, so that there were fewer short-latency responses and concomitantly a slight reduction in response rate, representing a greater efficiency of avoidance responding.

This conclusion was supported by a companion study by the same authors (*Wertheim et al.*, 1969) which correlated both the baseline endogenous steroid levels, and their steroid response to either stress with avoidance performance. Initially, the rats did not differ in basal levels of corticosterone, but the stress of anesthetization revealed marked individual differences in responsiveness and there was a one-to-one

correlation with avoidance proficiency of the animal after training. It was also discovered that marked individual differences in baseline steroid levels developed during training, and these correlated with the individual differences in avoidance performance as training progressed. Other studies which have demonstrated this relationship are those of *Pagano and Lovely* (1972) and *Lovely et al.* (1972).

These experiments demonstrate a relationship between plasma corticosteroid and avoidance performance. This implies either that the release of stress steroids and avoidance performance reflect activation of a generalized arousal system (*Wertheim et al.*, 1969), or that the corticosterone feeds back to modulate a generalized arousal system which facilitates avoidance behaviour. As we pointed out in the introduction, the latter position will be taken, and it will be argued that the feedback of corticosteroids acting on ascending neurochemical systems in the brain, resulting in increased arousal which forms part of the sensations experienced subjectively as anxiety. In the next section we will discuss the interactions between brain chemistry and corticosteroids.

Neurochemical Control of Corticosteroid Secretion

The adrenal gland located just below the stomach in man is controlled from the hypothalamus by means of hormones released into the blood stream from the pituitary. Hypothalamic regions close to the median eminence translate the neural stress information into chemical information in the form of corticotrophin-releasing factor, which is secreted into a specialized blood vessel system, the hypophyseal portal, by cells in the hypothalamus. The blood flow carries the releasing factor to the adrenohypophysis where it triggers the release of ACTH into the general blood stream and so it reaches the adrenal cortex to release cortisol and corticosterone in man and corticosterone alone in rats.

Neural Control

The levels of corticosterone are controlled by a negative feedback system to receptors in the hypothalamus (*Yates and Urquhart*, 1962), and the administration of corticosteroids into the hypothalamus has decreased the secretion of CRF (*Chowers et al.*, 1963). Cells in the basomedial hypothalamus were investigated by *Ruf and Steiner* (1967), using a potent synthetic corticosteroid called dexamethasone, introduced close to the cells by microelectrophoresis and the firing rate of these cells recorded by means of another barrel of the pipette group of cells was found in the periventricular gray close to the third ventricle, which were depressed instantaneously by the dexamethasone. These cells were either receptor cells monitoring the circulating corticosteroid levels and controlling the effect, or cells synthesizing the CRF for release to the pituitary, or perhaps the effector cells themselves which were sensitive to the end produce of CRF release.

The studies of *Ruf and Steiner* (1967) found that hippocampal cells were not responsive to dexamethasone, yet *Gerlach and McEwen* (1972) found that radioactive corticosterone was taken up and bound in the hippocampus of adrenalectomized rats suggesting that adrenalectomy eliminated competition for binding sites in the brain by endogenous corticosterone that would have been released by the stress of injection. The greatest incorporation of the tritiated corticosterone was in the pyramidal cells, particularly in region CA1 and CA2, the alveus region next to the ventricles, whose fibres project to the mamillary bodies, among other structures (*Raisman et al.*, 1966) as well as the granule cells, the dentate gyrus. This study relates very neatly with an electrical recording study from the same laboratory (*Pfaff et al.*,

1971) which found that corticosterone produced decreases in hippocampal unit activity, starting 10–40 min after injection and lasting for at least 2 h after injection which would be characteristic of a substance binding intracellularly, and inhibiting activity to the pyramidal cells in the CA1 and CA2 region of the hippocampal formation. Studies in which the hippocampus formation has been stimulated have shown clearly the inhibitory influence of the hippocampus on steroid release; for example, one study (*Rubin et al.*, 1966) found that stimulation of the hippocampus in human patients induced a fall in plasma corticosteroids within 5–30 min while the same study using different patients, who were stimulated in the amygdala and demonstrated that the plasma corticosteroids increased with this treatment. The interaction between these structures was demonstrated by *Mason* (1958) when he found that the release of ACTH after amygdaloid stimulation could be reversed by stimulation of the hippocampus.

These studies show that corticosteroid levels in the plasma are controlled by feedback mechanisms to the hypothalamus and hippocampus, while the releasing mechanisms are associated with the amygdala.

Cholinergic Control of ACTH Secretion

The neuronal pathways regulating anterior pituitary function are thought to converge on the hypothalamus and in a search for the possible neurochemical systems involved in corticosteroid control it would seem logical to evaluate the effects of injecting various presumed transmitter substances into hypothalamic regions as well as the limbic system structures implicated by lesion studies. This sort of study was performed by *Krieger and Krieger* (1970), and they found that carbachol, a cholinomimetic, implanted in the median eminence region, mid-mamillary body area and amygdala area, induced an abrupt rise in corticosteroid levels reaching a peak within 45 min of injection, but little response was obtained from hippocampal and septal implants. The effects of carbachol were blocked by means of atropine, but not by dexamethasone, suggesting that corticosteroid feedback inhibition was not anatomically associated with this cholinergic steroid release system.

In an earlier investigation of cholinergic involvement in ACTH release, *Hedge and Smelik* (1968) implanted cannulae in the septum, anterior hypothalamus and posterior hypothalamus. The stress of implantation resulted in a prolonged release of ACTH lasting over 1 h, which was reflected in enhanced plasma corticosterone levels. If the cannula was filled with crystalline atropine and placed in the anterior hypothalamus, just rostral to the paraventricular nuclei, the plasma corticosterone levels were reduced, but atropine stimulation of the other two structures was without effect, which showed the specificity of the effect to the particular neural locus. In this instance, the anterior hypothalamic site was the median eminence region found to be sensitive to carbachol by *Krieger and Krieger* (1970).

Adrenergic Inhibition of ACTH Secretion

Some of the first studies that gave indirect evidence for adrenergic inhibition came from the laboratory of *Brodie and Maickel* in which they examined the effect of reserpine on the stress response, and found that reserpine induced a pattern of change similar to stress, including an increase in plasma corticosteroids, a fall in adrenal ascorbic acid and an increase in the weight of the adrenal glands (*Maickel et al.*, 1961). These effects did not occur in hypophysectomized rats, and so were attributed to the secretion of ACTH and it was found that a medium dose produced a 75-percent de-

pletion of this pituitary hormone in 20 h. Reserpine impairs the binding of dopamine, noradrenalin, and serotonin in brain neurons, and so one obvious set of hypotheses was that stress steroids were inhibited by one of these monoamines. This was supported by *Westerman et al.* (1962) using concomitant measures of noradrenalin, serotonin and plasma corticosteroids which demonstrated similar dose-response and time-response effects for monoamine depletion and increased corticosteroid release. Pharmacologically enhanced release of ACTH could also be produced by chlorpromazine which blocks noradrenalin and serotonin synapses (*de Wied*, 1967).

In an attempt to separate the function of the two monoaminergic systems *Westerman et al.* (1962) injected α-methylmetatyrosine, which inhibits catecholamine synthesis, and observed that plasma corticosterone increased, although the increase was not as large as that produced by reserpine. In a second study α-methylparatyrosine produced an increase in plasma corticosterone in most animals, and that in those animals in which corticosterone was not increased α-methylparatyrosine did not deplete hypothalamic catecholamines (*Scapagnini et al.*, 1970). In order to distinguish between the two catecholamines intraventricular injections of *l*-dopa, dopamine, *l*-noradrenalin and *l*-isoproterenol, an adrenomimetic, were investigated for their inhibitory properties (*Van Loon et al.*, 1971). All these compounds produced inhibition, and since the first two are precursors of noradrenalin and dopamine, it looks as if noradrenalin is the inhibitory transmitter for ACTH release. This was confirmed by means of an inhibitor of dopamine β-oxidase, FLA-63, which prevented the synthesis of noradrenalin from dopamine and the reduced hypothalamic levels of noradrenalin were correlated with increased plasma corticosterone (*Ganong*, 1972).

At this point it should be mentioned that there is some contradictory evidence. In an extensive study *Carr and Moore* (1968) found that combined injections of reserpine and α-methylparatyrosine markedly reduced the brain levels of dopamine and noradrenalin, but not the baseline levels of corticosteroids although the release of steroids induced by stress was slightly, but not significantly, increased by depletion. In addition, *Krieger and Krieger* (1970) implanted crystalline noradrenalin in the median eminence and induced rises in steroid levels. This discrepant result has not been explained, but one suggestion would be that the crystalline noradrenalin was producing a depolarization blockade of the adrenergic synapses, rather than stimulating them.

Indirect evidence for an adrenergic inhibitory system comes from studies of the effects of stress steroids on brain chemistry. Brain levels of noradrenalin have been found to decrease after exposure to cold (*Maynert and Levi*, 1964), electric shock (*Levi and Maynert*, 1964) and immobilization stress (*Corrodi et al.*, 1971). This suggests that feedback of stress steroids to the brain activates the adrenergic inhibitory neurons in the median eminence to reduce the production of corticotrophic releasing factor. This activation could be by increased release or reduced reuptake and some evidence for the latter mechanism has been provided by *Iverson and Salt* (1970).

Serotonin Control of ACTH Secretion

The evidence for the involvement of serotonin in the control of stress steroids is consistent with the hypothesis that this transmitter is involved in the inhibition of corticotrophic releasing factor and so ACTH secretion by the pituitary. Indirect evidence consistent with this hypothesis has

come from assays of the brain after acute stress, such as immobilization stress for 3 h (*Fuxe et al.*, 1970; *Curzon and Green*, 1968) depleted serotonin when tryptophan hydroxylase, the rate-limiting, synthesizing enzyme, was inhibited. These results in themselves are not convincing, but cortisol (*Curzon and Green*, 1968) and corticosterone (*Scapagnini et al.*, 1971) also produce depletion showing that it is the feedback that releases the serotonin. This increased rate of release would be expected to reduce the functional serotonin eventually if there was not a compensatory increase in synthesis. Some evidence for corticosteroid control of synthesis has come from studies where synthesis inhibitors were not injected and the serotonin levels remained constant after stress (*Levi and Maynert*, 1964; *Maynert and Levi*, 1964) and injections of cortisone (*McKennee et al.*, 1968). Increased synthesis appears to be due to increased tryptophan hydroxylase activity produced by corticosteroids. In bilateral adrenalectomized rats with high levels of plasma ACTH, but low levels of plasma corticosterone, the activity of midbrain tryptophan hydroxylase was reduced by 75% compared with sham-operated rats (*Azmitia and McEwen*, 1969) and as a result there was reduced conversion of tritiated tryptophan to tritiated serotonin (*Azmitia et al.*, 1970). Injections of corticosteroids restored the activity of tryptophan hydroxylase towards normal in these adrenalectomized animals (*Azmitia and McEwen*, 1969) and returning serotonin turnover to normal (*Fuxe et al.*, 1970), suggesting that it was the low level of corticosterone that was responsible for the reduced serotonin synthesis. Cold and electric shock stress also stimulated tryptophan hydroxylase synthesis, but this did not happen in adrenalectomized rats (*McEwen et al.*, 1970) confirming that feedback corticosteroids enhanced serotonin synthesis.

At the moment the balance of evidence favours the hypothesis that there is adrenergic inhibition of ACTH release together with a cholinergic releasing system and perhaps a serotonin-releasing mechanism. It seems that part of the adrenergic inhibition is mediated via the hippocampus. Another likely source of adrenergic inhibitory input is the median forebrain bundle believed to control mood (*Schildkraut and Kety*, 1966). The cholinergic control of secretion is probably mediated by pathways related to the cholinergic fibres ascending from the reticular formation, thought to be involved in electrocortical arousal (*Shute and Lewis*, 1967).

Neurochemistry of Known Antianxiety Drugs

The debilitating effects of pathological anxiety have been reduced to a remarkable extent by a number of psychoactive drugs. The first drugs used for the treatment of anxiety, besides alcohol, were the barbiturates, but they tend to induce sleep during the day and repeated use results in physical dependence. The first modern antianxiety drug, meprobamate (Miltown; Equanil) was developed at the beginning of the 1950s and released for general use in 1955, when it was an instant success.

At the same time as the clinical introduction of meprobamate, another group of compounds, the benzodiazepines, were under test, and the first useful compound to be discovered was chlordiazepoxide (Librium) and more recently diazepam (Valium), nitrazepam and oxazepam. The first clinical reports (*Harris*, 1960) collated the results of using chlordiazepoxide with 212 patients whose main symptoms were anxiety and tension, and had failed to respond to meprobamate and barbiturates. After treatment, both the psychiatrists and the

patients evaluated the drug, and it was found that over 80% of the cases demonstrated clinical improvement. The doctors felt that it had a more specific effect on anxiety than meprobamate and did not produce any lowering of mood. On the contrary, the patients reported feelings of well-being and increased drive which was reflected in wider social interests, and return to work. More recently, oxazepam has been given clinical trials. One of these was an extensive survey by *Wittenborn* (1966) of 613 patients treated with oxazepam and 261 given placebo. In addition, a number of chlordiazepoxide patients were used for comparison. The patients given placebo were matched by computer with oxazepam patients on the basis of age, diagnosis, sex, severity of anxiety and the treatment specialty of the prescribing psychiatrist. Over a 5-week period the proportion of patients rated as having severe anxiety decreased in both groups, but the diminution of severe rating was far greater in the oxazepam group. It is significant from the point of view of our hypothesis that oxazepam is considered to be more effective in the suppression of stress hormones released during fear situations than chlordiazepoxide or diazepam (*Wittenborn*, 1966).

The antianxiety drugs have different effects on the two situations mentioned in the section on corticosteroids and animal behaviour. Tests of the major tranquillizers and the antianxiety drugs on performance in continuous avoidance (*Heise and Boff*, 1962) showed that barbiturates, meprobamate, chlorpromazine, and the benzodiazepines decreased responding in continuous avoidance. The major difference between the compounds was the dose-range which was the range of doses over which the drug affected behaviour, but did not impair the capacity to press a lever; a compound producing a non-specific behavioural decrease would have a ratio close to one. Thus alcohol, the shorter acting hypnotics, and muscle relaxants had values close to one, and the antianxiety agents e.g., benzodiazepines had values ranging from 3.8 (chlordiazepoxide) to 19 (nitrazepam) with the major tranquillizers like chlorpromazine intermediate.

As *Heise and Boff* (1962) point out, the boundaries between the three groups were quite arbitrary and so this situation only discriminates between them quantitatively, but the discrete trial avoidance situation does provide some qualitative distinction. From the earlier discussion of discrete trial avoidance we would not expect antianxiety agents to have much effect since there was little uncertainty associated with them, and so only small increases in corticosterone. As predicted, meprobamate and chlordiazepoxide only produced a 25-percent loss of avoidance responses at doses which were clearly ataxic (*Randall et al.*, 1960) compared with the marked effects of low doses of chlorpromazine (*Heise and Boff*, 1962). To give a clear comparison of the doses required to modify performance in the two avoidance situations the actual doses will be given from this paper. Thus, 28–115 mg/kg of meprobamate and 49 mg/kg of chlordiazepoxide orally produced a 75-percent decrement in continuous avoidance, 640 mg/kg of meprobamate and 60 mg/kg of chlordiazepoxide orally decreased locomotor activity by 50%, while 400–1,300 mg/kg of meprobamate and 125–480 mg/kg of chlordiazepoxide orally were required to reduce discrete trial avoidance by 25%.

These drugs which ameliorate human anxiety and reduce 'anxiety' behaviour in animal situations will now be used to test the hypothesis that a suitable antianxiety agent will either reduce ACTH release or reduce the effects of corticosteroid on the brain. An ideal agent reducing stress steroid release would be a drug which increased functional noradrenalin and decreased functional acetylcholine, whereas a

drug reducing corticosteroid effects on the brain would be a drug reducing functional noradrenalin and serotonin.

As additional evidence for the hypothesis it is possible to examine the biochemical mode of action of known antianxiety drugs to see whether they conform to the pattern of action required by the hypothesis; these are increased functional noradrenalin and decreased functional serotonin and acetylcholine. The effects of the drug on acetylcholine have only been studied in preliminary experiments (*Ladinsky et al.*, 1973) which suggested that the diazepam increased the cortical levels of the transmitter which may represent an inhibition of release, but further studies are required before firm conclusions can be drawn, and the rest of the section will be devoted to noradrenalin and serotonin.

Although there are sensitive assay techniques developed for monoamines, there have been very few studies which have studied the effects of the benzodiazepines and other tranquillizers on the synthesis, storage, release, receptor interaction and inactivation of these transmitters. In a pioneering study *Taylor and Laverty* (1969) found that the major benzodiazepines, chlordiazepoxide, diazepam and nitrazepam, and barbiturates did not change the levels of noradrenalin in any part of the rat brain. In addition, there was no evidence for a reduction of reuptake or inhibition of catechol-*O*-methyltransferase, the inactivating enzyme, showing that inactivation mechanisms were unaffected by these drugs (*Taylor and Laverty*, 1969). However, the static levels of transmitter are not good indicators of functional transmitter and so *Taylor and Laverty* (1973) examined the effect of the three benzodiazepines on noradrenalin turnover in animals stressed with electric shock. This form of stress increased turnover in all regions of the rat brain (*Bliss et al.*, 1968) as one would expect from the action of corticosteroids on noradrenalin, but the benzodiazepines blocked this effect and maintained the noradrenalin levels close to their control values. It is important for the hypothesis that the human antianxiety potency order was found in these studies, so that nitrazepam was the most effective and chlordiazepoxide was the least effective in maintaining the noradrenalin turnover. From the point of view of the neural pathways involved, this effect was maximal in the midbrain sample, containing the hypothalamus, and the cortical sample, and least in the brain stem sample.

The depletion of noradrenalin from the cortical and hypothalamic neurons after injection of a noradrenalin synthesis inhibitor was measured by means of a histochemical fluorescence technique (*Corrodi et al.*, 1971). The animals were stressed by restraining them, which accelerated the depletion of the noradrenalin, but chlordiazepoxide and diazepam reduced the rate of depletion. This result shows that these drugs were probably acting to reduce turnover by blocking release of noradrenalin. However, the reduction in turnovers was not detectable after six daily injections of the benzodiazepine, oxazepam, showing the development of tolerance.

A similar sort of result was obtained when the serotonin neurons were examined after an injection of a tryptophan hydroxylase inhibitor, which prevented *de novo* synthesis of serotonin. Benzodiazepines and pentobarbital reduced the rate of depletion of serotonin in the cortex, but the effects did not occur in all parts of the brain (*Lidbrink et al.*, 1973). The notion that this result might be due to the benzodiazepines blocking serotonin release was supported by the finding that intracisternally injected radioactive serotonin was retained in the brain longer after diazepam (*Chase et al.*, 1970). This finding has been confirmed by single and repeated doses of oxazepam (*Wise et al.*, 1972) which reduced seroto-

nin turnover in the midbrain-hindbrain region, and contrasts with the marked tolerance that developed in the noradrenalin system after repeated doses. This biochemical difference immediately suggests a psychopharmacological experiment examining the behaviour after injections of oxazepam. *Margules and Stein* (1968) found that the slight non-selective decreased responding disappeared after a few days, but the release of suppressed responding in the *Geller and Seifter* (1960) conflict situation remained unchanged. This circumstantial evidence points to the involvement of the serotonin system in the antianxiety action of the drug.

Direct tests of the hypothesis that it is either the reduction in functional noradrenalin or the reduced functional serotonin which is responsible for the antianxiety properties of the benzodiazepines have been carried out by workers at Wyeth Laboratories in the United States. They argued that if it was a reduction of adrenergic function then adrenergic blockers should have similar effects as benzodiazepines in the conflict situation of *Geller and Seifter* (1960), but tests with α-adrenergic blocker, phentolamine, and the β-adrenergic antagonist propranolol injected into the ventricles were negative. Propranolol had no effect, while phentolamine reduced punished and non-punished responding, showing a non-specific effect of the latter drug (*Stein et al.*, 1973). In the second part of the studies, serotonin blockers and a serotonin synthesis inhibitor were tested to produce the reduction of functional serotonin also produced by the benzodiazepines. They injected methysergide, the antagonist, and released the suppressed responding in the conflict situation (*Stein et al.*, 1973). Similar results were obtained with parachlorphenylalanine, the synthesis blocker, and the suppressed behaviour could be reinstated by repletion of serotonin by injecting the precursor 5-hydroxytryptophan (*Stein et al.*, 1973). The serotonin agonist, α-methyltryptamine and serotonin both enhance the suppression of responding in the conflict situation (*Stein et al.*, 1973), as one would have predicted from the other results.

In a final test of the hypothesis, *Stein et al.* (1973) injected oxazepam releasing the suppressed responding, and then introduced serotonin directly into the ventricles which restored the suppression.

The neurochemical pathways on which the oxazepam was acting are not known, although *Stein et al.* (1973) suggested serotonin fibres arising in the dorsomedial tegmental region of the midbrain. The terminal of these pathways is mainly in the limbic system including the amygdala and septal area (*Anden et al.*, 1966). As we saw earlier, these were the regions involved in the control of corticosteroid release.

Studies of the antianxiety drugs show that they act on these structures. Barbiturates block hippocampal seizures after fornix stimulation, and suppress post-tetanic potentiation in the hippocampus after amygdala and hypothalamic stimulation (*Takagi and Ban*, 1960). Meprobamate acts on the hypothalamus and septal area and hippocampus (*Schallek et al.*, 1962). Both barbiturates and meprobamate suppressed hippocampal seizures produced by stimulation of the fornix, but only barbiturates suppress the hippocampal discharges after stimulation of the amygdala (*Kletzkin and Berger*, 1959; *Schallek et al.*, 1962). Tests of chlordiazepoxide disclosed some similarities with decreased duration of discharge after stimulation of the septal area, and hippocampus, and decrease amplitude of responses in the amygdala. Chlordiazepoxide also slowed the electrical activity in the septal area, amygdala and hippocampus, but not the cortex, of the unanesthetized animals just like meprobamate (*Schallek et al.*, 1962).

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5. The Hyperactive Child Syndrome

Clinical Description

The hyperactive child syndrome,* also often referred to as minimal brain dysfunction (MBD) or hyperkinesia, appears to be a heterogenous group of childhood behavioral disorders characterized by restlessness, hyperactivity, impulsivity, excitability, and decreased attention and concentration. Other symptoms which are frequently observed include aggression, antisocial behavior, learning disabilities, and depression.

This syndrome has been reported to occur in as many as 5% to 20% of preadolescent school-age children, most of them boys. However, as Omenn[78] points out, the available epidemiological information regarding prevalence must be interpreted with caution, in part because factors such as race, ethnic background, and socioeconomic status have not been properly evaluated.

Contrary to earlier beliefs that this syndrome ends in childhood, recent evidence indicates that although hyperactivity seems to diminish as the child moves into adolescence, impulsivity, distractability, restlessness, and excitability persist. Aggressive antisocial behavior, learning problems, and poor self-image are common when these children reach adolescence. Psychopathology also appears to be present in adulthood, especially in the forms of sociopathy, alcoholism, hysteria, and sometimes psychosis.

Evidence suggests that genetic factors contribute significantly to the etiology of the hyperactive child syndrome. Some reports indicate that first- and second-degree relatives of hyperactive children show a high incidence of sociopathy, alcoholism, and hysteria (all of which are common in hyperactive children when they reach adulthood), and that many of the parents of hyperactive children were themselves hyperactive as children. Adoption and twin studies also support a genetic role. The results obtained from these genetic studies as well as data regarding the apparent natural course of this disorder suggest that the hyperactive child syndrome may be a precursor to significant psychopathology in adulthood. However, adequately designed prospective studies must be completed before the relationship between hyperactivity in childhood and various forms of psychopathology in adults can be elucidated.

* Much of the clinical information in this section was obtained from *The Hyperactive Child.*[77] This book is an excellent reference for a more extended discussion of this syndrome.

Treatment

For purposes of treatment the hyperactive child is best considered as multihandicapped, and therefore a treatment approach that addresses each of the problem areas promises the greatest benefit. Individualized treatment plans should be based upon a comprehensive assessment of each child, the family, and the child's school situation.

Unfortunately, very little is known about the long-term effects of any of the treatments currently used, including drugs and psychological therapies. While drug treatment has been best studied and offers considerable symptomatic benefits, at least over short periods of time, drug treatment alone is not sufficient. In every case optimally successful treatment requires involvement of the family and of the child in counseling and therapy. Educational and other remedial therapies are often required to help change some of the child's maladaptive behaviors; moreover, in addition to their hyperactive syndrome, many of the children have specific perceptual problems. Recently, diets free of artificial food additives and natural salicylates have received attention in the treatment of hyperactive children, but these efforts are new and as yet difficult to evaluate.

Stimulant drugs, particularly amphetamines and methylphenidate (Ritalin®), have been widely used. About 60% to 70% of hyperactive children will experience increased attention span, decreased hyperactivity, and increased motivation and interest in the social setting. However, even for children who benefit, the stimulants are effective for only some symptoms.

Because hyperactive children appear to act more calm on stimulants, this quieting effect has been thought to be a paradoxical effect of the drugs. However, these drugs may work the same way in hyperactive children as they do in normal children and in adults, by increasing arousal. Some physiological evidence suggests that many of the children who respond to stimulants are in an underaroused state prior to treatment, and that the drugs bring them closer to a normal level of arousal. This formulation is consistent with the suggestion made by some clinicians that the irritability, excitability, and hyperactivity seen in the hyperactive child syndrome is reminiscent of normal children when they are fatigued. Some studies have shown that the total amount of bodily activity is actually increased by the stimulant drugs and that the increase is in directed or controlled motor activity.

Some hyperactive children respond better to other medications than to the stimulants. If a child will benefit from stimulants, results are often obvious within hours. Fish[79] suggests that if a child doesn't begin to act normally after an adequate clinical trial of stimulants, serial clinical trials of other medications may be undertaken, starting with milder drugs such as the antihistamine diphenhydramine (Benadryl®), and following, if necessary, with major tranquilizers, including chlorpromazine (Thorazine®), haloperidol (Haldol®), and thiothixene (Navane®). Some investigators have found tricyclic antidepressants effective in treating hyperactive children with concomitant depressive disorders.[80,81]

Reading Selections

Wender in his book entitled *Minimal Brain Dysfunction in Children*[82] discusses evidence of an abnormality in the functioning of brain biogenic amines, especially the catecholamines (CAs) norepinephrine (NE) and dopamine (DA) in MBD. And in a recent paper Brase and Loh[83] have reviewed the literature which supports a possible role of

brain serotonin (5HT). Although all of these as well as other neurochemical systems may ultimately be shown to contribute to the pathophysiology of the hyperactive child syndrome, some recent clinical investigations involving the effects of amphetamine have led to strong support for the involvement of CAs in the etiology of this disorder. Amphetamine, often effective in the treatment of MBD, is believed to exert some of its behavioral effects by its action on brain DA and NE. In the following articles the primary focus of interest is on the relative involvement of brain DA and NE systems in the therapeutic effects of amphetamine in MBD. In these studies the researchers employ a technique called pharmacological dissection, using the D and L isomers of amphetamine to distinguish between the behaviors subserved by NE and DA systems in the brain. The rationale for this procedure is based on the finding that *d*-amphetamine is considerably more effective than *l*-amphetamine in facilitating transmission at NE synapses, whereas the two isomers have a relatively similar effect at DA synapses.[84,85] Therefore, if the potency of *d*-amphetamine in eliciting a particular behavior is much greater than that of *l*-amphetamine, NE may be thought of as playing the more significant role. In contrast, if the behavioral potencies of the two isomers are similar, DA would be considered the more prominent transmitter in mediating that behavior. Some investigators have found that DA pathways may mediate certain amphetamine-induced behaviors (eg, stereotypy), while NE pathways may mediate others (eg, locomotion).

Snyder and Meyerhoff describe the results of a preliminary study in which they examined the relative effects of *d*- and *l*-amphetamine in one child with MBD. The two isomers appeared to have comparable therapeutic potencies, so it was tentatively concluded that DA mediated the beneficial effects of amphetamine in the treatment of MBD.

The second article reports results from a more extensive study designed to test this hypothesis further. Eleven hyperkinetic children were each tested for three weeks with placebo, *d*-amphetamine, or *l*-amphetamine. The treatments were administered according to a counterbalanced design, thus allowing each subject to serve as his own control. Either isomer was more effective than placebo, and although *l*-amphetamine had a slower onset, *d*-amphetamine was not significantly more potent than *l*-amphetamine with respect to most of the clinical measures employed. These results were also interpreted as implicating brain DA pathways in the beneficial effects of amphetamine for MBD, NE pathways playing a lesser role.

This interpretation has been modified on the basis of results obtained by the same investigators in a subsequent study.[86] They found that in hyperkinetic, untrainable dogs *d*- and *l*-amphetamine were equally effective in diminishing aggressive behavior, but that the *d*-isomer was three to four times more potent in suppressing nervousness and hyperactivity. In view of the indications that the action of amphetamine on hyperactive and aggressive behavior may be mediated by different neurochemical systems, the data obtained from the earlier clinical study were reevaluated. The children were assigned to one of two categories, an unsocialized-aggressive group or an overanxious-hyperkinetic group, and the relative efficacy of *d*- and *l*-amphetamine on these two groups was assessed. In accord with the animal data, the aggressive group of children improved to about the same extent with either isomer of amphetamine. The hyperactive group, in contrast, showed significantly greater improvement with *d*-amphetamine. These studies were interpreted as indicating that the beneficial effects of amphetamine on aggression and hyperactivity may be mediated by brain DA and NE pathways, respectively. In a still more recent study,[87] which included a larger and more representative sample of children, there was

not a clear differential effect of *d*- and *l*-amphetamine on these subgroups of MBD children.

While they do provide a potentially valuable insight into the cause(s) of this disease, these studies do not necessarily indicate that a defect in brain CA functioning is responsible for MBD. The therapeutic effects of amphetamine may be only remotely related to the mechanisms responsible for this syndrome. In fact, MBD may not have a single underlying cause, rather it may represent a variety of abnormalities in brain function.

How Amphetamine Acts in Minimal Brain Dysfunction

Solomon H. Snyder, MD, and James L. Meyerhoff, MD

In searching for mechanisms of amphetamine action, pharmacologists have a head start. Because of the close chemical resemblance of amphetamine to the catecholamines, dopamine and norepinephrine (see FIGURE 1), most pharmacologists agree that it is via these putative neurotransmitters in the brain that amphetamine exerts its behavioral effects. This generalization probably also holds true for the minimal brain dysfunction (MBD) syndrome. For other drugs, such as methylphenidate and the tricyclic antidepressants,[24,30] that appear to give effective theory for MBD, facilitate synaptic effects of brain catecholamines in a way similar to the actions of amphetamine.

A vast number of interactions of amphetamines and the catecholamines have been reported, both in the peripheral sympathetic nervous system and in the brain. Amphetamine can mimic catecholamines at their receptor sites; it inhibits monoamine oxidase, an enzyme that degrades the catecholamines; amphetamine impairs the reuptake inactivation of the catecholamines (a mechanism that will be explicated in greater detail later); and it also can release catecholamines directly into the synaptic cleft. Most neuropharmacologists currently consider inhibition of reuptake inactivation and direct synaptic release to be the major mechanisms of amphetamine action in the brain.[32] Thus, by one or another means, amphetamine increases the amount of norepinephrine or dopamine available at synapses for receptor stimulation.

Scientific common sense dictates that particular behavioral actions should be mediated via highly localized neuronal tracts containing each of these transmitter substances. Until 1962–65, however, it was not possible to delineate the course of the catecholamine-containing tracts in the brain. Then, a histochemical fluorescent technique developed by a group of Swedish investigators[21] was applied to brain tissue.

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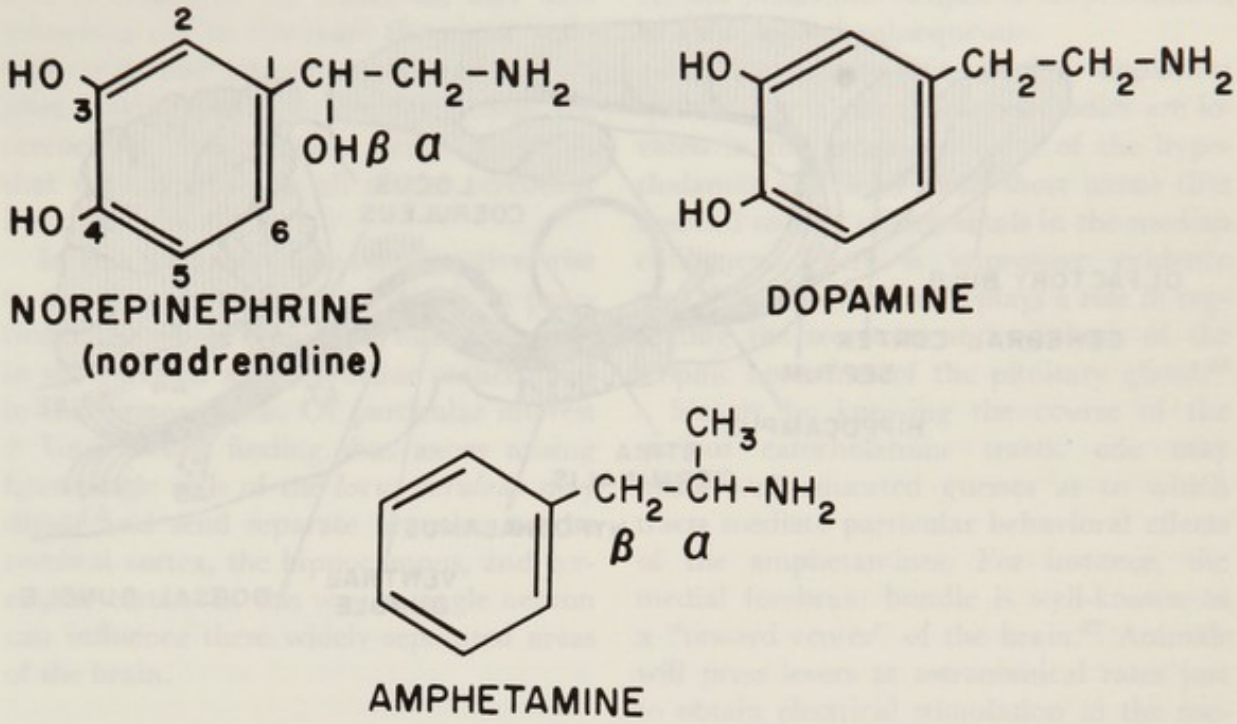

Figure 1. Structures of norepinephrine, dopamine, and amphetamine.

When brain tissue was treated with paraformaldehyde vapors, dopamine and norepinephrine developed an intense green fluorescence. By a variety of pharmacological maneuvers, it was possible to discriminate between norepinephrine and dopamine. Accordingly, neurons containing these amines in the brains could be visualized directly, and the course of the catecholamine-containing tracts could be described. The most recent and thorough evaluation of these tracts has been performed by Ungerstedt.[39]

Course of Catecholamine-containing Tracts

Norepinephrine Pathways

1. Ventral norepinephrine system (see Figure 2): Major norepinephrine tracts ascending from the lower brain stem are referred to by Ungerstedt[39] as "the ventral norepinephrine pathway." Cell bodies occur in approximately four different groupings in the *medulla oblongata-pons*. The axons ascend in the reticular formation and then continue upward mainly within the medial forebrain bundle. All along their course, they give off terminals, first in the lower brain stem, then in the midbrain, and finally in large numbers throughout the hypothalamus.

2. Dorsal norepinephrine system: The other major norepinephrine tracts have cell bodies in the *locus ceruleus*. Some fibers proceed downward to innervate lower brain stem areas, overlapping here with nerve terminals of the ventral norepinephrine pathway. A larger proportion of these neurons, however, send axons that ascend more dorsally than the "ventral norepinephrine pathway," and are hence referred to as the "dorsal norepinephrine pathway." These axons pass into the medial forebrain bundle and the septum, giving off branches to

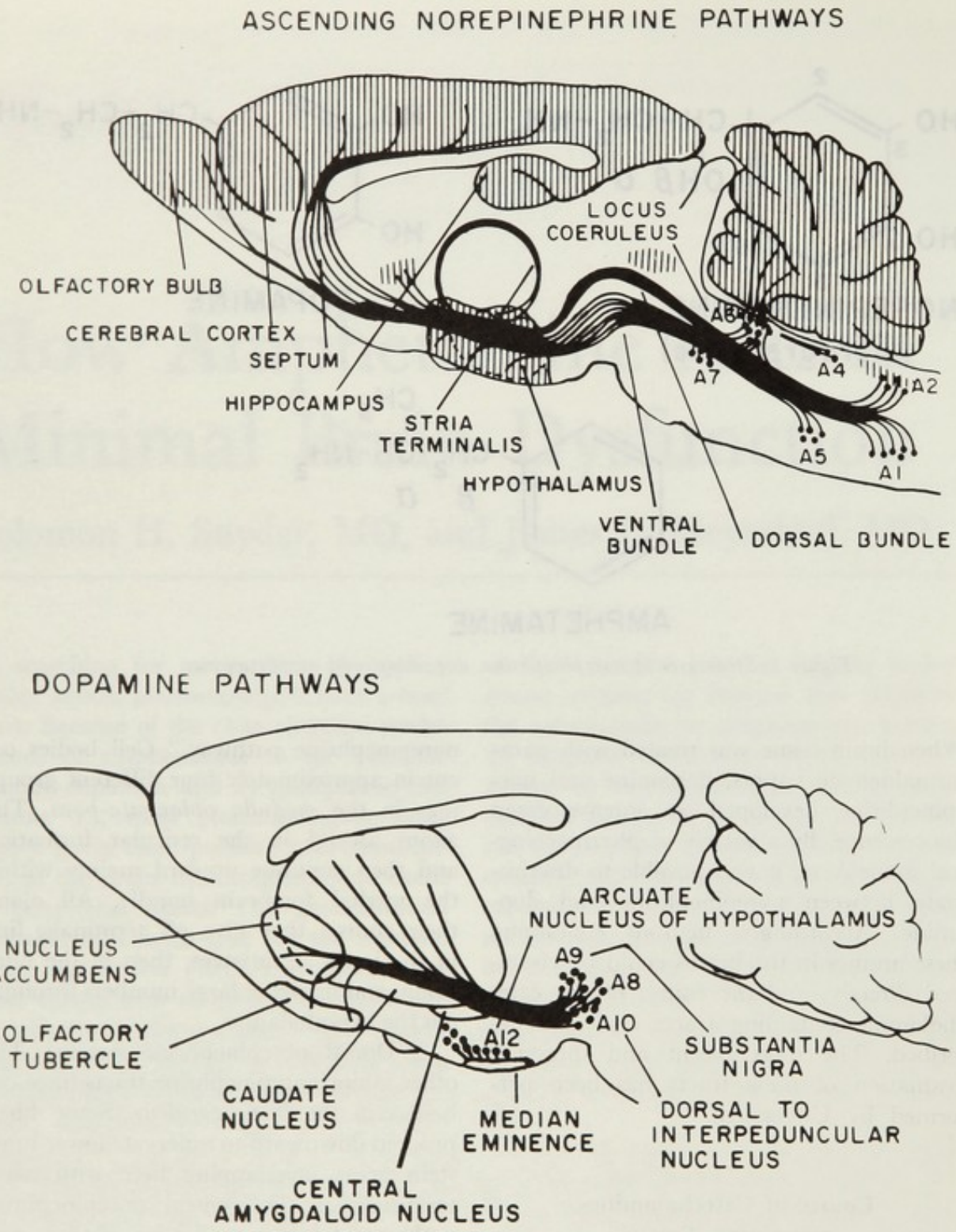

Figure 2. Pathways of ascending norepinephrine and dopamine tracts in the brain. Adapted from Ungerstedt.[39]

the medial and lateral geniculate bodies and to nuclei of the thalamus, and then spreading out to innervate the entire cerebral cortex and hippocampus. Some axons, after leaving the *locus ceruleus,* enter the cerebellum and provide nerve terminals that may synapse on all of the cerebellar Purkinje cells.

In this way, the *locus ceruleus* gives rise to norepinephrine nerve terminals in practically the whole brain, and most especially in the cerebral and cerebellar cortices and in the hippocampus. Of particular interest is Ungerstedt's finding that axons arising from single cells of the *locus ceruleus* may divide and send separate branches to the cerebral cortex, the hippocampus, and cerebellar cortex. In this way, a single neuron can influence these widely separated areas of the brain.

Dopamine Pathways (see Figure 2)

1. The nigrostriatal dopamine system: The best known dopamine tract has cell bodies in the *zona compacta* of the *substantia nigra* in the midbrain and sends axons up through the lateral hypothalamus, close to the medial forebrain bundle, to terminate in the caudate nucleus and putamen of the *corpus striatum,* as well as in the central portion of the amygdaloid nucleus. The nigrostriatal system is degenerated in the brains of patients with Parkinson's disease, and the attendant dopamine deficiency appears to account for many parkinsonian symptoms.[22]

2. The mesolimbic dopamine system: Dopamine cell bodies situated dorsal to the interpeduncular nucleus in the midbrain ascend along with axons of the nigrostriatal dopamine system but subsequently proceed more medially to give off terminals in the nucleus accumbens and the olfactory tubercle. These two poorly understood parts of the brain may conceivably mediate certain behavioral actions of amphetamine, to be discussed subsequently.

3. The tubero-infundibular dopamine system: Some dopamine cell bodies are located in the arcuate nucleus of the hypothalamus and send forth short axons that descend to give off terminals in the median eminence. There is impressive evidence that this dopamine tract plays a role in regulating the secretion and synthesis of the trophic hormones of the pituitary gland.[23]

Simply by knowing the course of the various catecholamine tracts, one may make well educated guesses as to which tracts mediate particular behavioral effects of the amphetamines. For instance, the medial forebrain bundle is well-known as a "reward center" of the brain.[27] Animals will press levers at astronomical rates just to obtain electrical stimulation in the medial forebrain bundle. Stein[35] demonstrated that amphetamine greatly facilitates self-stimulation in the medial forebrain bundle. Since the ventral norepinephrine pathway accounts for the majority of catecholamine axons and terminals in the medial forebrain bundle area, it would be reasonable to suppose that effects of amphetamine on this norepinephrine tract account for the euphoriant and conceivably the sexually stimulating actions of the drug. Wise and Stein[42] obtained pharmacological evidence that norepinephrine neurons in the medial forebrain bundle are responsible for self-stimulating behavior. They found that disulfiram, which inhibits the conversion of dopamine to norepinephrine, reduces self-stimulation in this part of the brain and that the suppressed behavior can be reinstated by intraventricular injections of norepinephrine.

It is widely held that brain stem influences on the cerebral cortex are largely responsible for maintaining a state of alertness. Some years ago, Bradley and Elkes[6]

showed that the alerting effects of amphetamine are mediated by influences of the brain stem reticular formation on cerebral arousal mechanisms. Perhaps the brain stem site responsible for the results of Bradley and Elkes[6] is the *locus ceruleus* and its norepinephrine fibers ascending to the cerebral cortex. Conceivably, the norepinephrine fibers that the *locus ceruleus* sends to the cerebellum might account for the enhancement by amphetamine of motor coordination. Since alertness and muscle coordination are mutually interdependent processes, their interrelation might be subserved by the neuronal architecture, whereby single norepinephrine neurons in the *locus ceruleus* project both to the cerebrum and the cerebellum.

The therapeutic efficacy of L-DOPA in Parkinson's disease appears to depend largely on its decarboxylation to dopamine, hence ameliorating the dopamine deficiency in the brains of these patients.[3,10,44] Dextroamphetamine has been employed in the past as an effective therapeutic agent in Parkinson's disease.[13,18] It is possible that its therapeutic efficacy was attributable to potentiation of the limited amounts of dopamine remaining in the brains of parkinsonian patients.[22] Consonant with this hypothesis is our recent finding[11] that antiparkinsonian agents having a wide variety of chemical structures all share the ability to inhibit the reuptake inactivation of dopamine in the *corpus striatum*, a finding that might explain in part their therapeutic activity.

The functions of the mesolimbic dopamine system are obscure. Since some of the terminals of these neurons occur in the olfactory tubercle, one might hypothesize that they play a part in the olfactory hallucinations that frequently occur in individuals, children, or adults who have ingested overdoses of amphetamine, as well as in amphetamine addicts who have developed a drug-related psychosis.

Behavioral Effects of Amphetamine
The Neuropharmacology of Amphetamine Isomers in Animals and in Children with Minimal Brain Dysfunction

How might one determine in animals which brain tracts mediate particular behavioral effects of amphetamine? One might place lesions in selected brain regions and determine if responses to the drug are altered. But it is difficult to make a brain lesion that will selectively affect a particular norepinephrine or dopamine tract. In most areas of the brain, the catecholamine neurons account for only a small percentage of the total neuronal population, a fact often forgotten by neuropharmacologists, who have a major professional investment in these substances. A more fruitful approach has been to make selective chemical lesions of the catecholamine neurons. This approach is possible with 6-hydroxydopamine, a drug that is selectively accumulated by catecholamine neurons, which it subsequently destroys, presumably by a process of autooxidation.[38] Once destroyed, neurons in the brain do not regenerate, so that a permanent depletion of brain catecholamines can be obtained with this drug. If 6-hydroxydopamine is implanted into selected groups of catecholamine cell bodies, the axons and nerve terminals that derive from these groups of cells degenerate.[40] Thus, after injections of 6-hydroxydopamine into the *substantia nigra*, the nigrostriatal dopamine system degenerates, resulting in an elegant model of the specific neuronal dopamine deficiency of Parkinson's disease.

Such approaches are fine for evaluating the roles of different catecholamine systems in animals. But what about disorders such as MBD, for which there is yet no animal model? One would like a technique to explore responsible neurochemical systems without making brain lesions. Ideally, one

would desire drugs that might exert selective effects upon individual neuronal pathways. Although drugs with such selective actions are not yet available, it is possible, by using amphetamine isomers, to distinguish between behavioral effects mediated by norepinephrine and those mediated by dopamine neurons in the brain. Already, this technique for pharmacological "dissection" of the brain has been applied to humans in analyzing pathophysiological mechanisms in amphetamine psychosis,[1] Gilles de la Tourette's disease,[26] and, of greatest relevance for this review, in children with MBD.[2] First, we should explain the neurochemical basis for this approach.

Neurochemical Basis

In our laboratory, attempts to differentiate between the involvement of dopamine or norepinephrine in certain behavioral effects of amphetamine have been based on chemical differences we observed between dopamine and norepinephrine nerve terminals.[12] As already mentioned, these catecholamines appear to be inactivated after synaptic release primarily by reuptake into the nerve terminals that released them. This reuptake system can be studied in isolated nerve terminals, "synaptosomes," obtained after homogenizing brain tissue in isotonic sucrose and subjecting the homogenate to differential and/or density gradient centrifugation. In this way, the reuptake inactivation mechanism and its interaction with a variety of drugs can be studied in a relatively simple *in vitro* system. Drugs that block this reuptake are assumed to be capable of potentiating the effects of synaptically released norepinephrine or dopamine. Since dopamine accounts for more than 90% of the catecholamine content of the *corpus striatum,* synaptosomes from this brain region can be taken to represent primarily dopamine nerve terminals. In other brain areas, especially the cerebral cortex and hypothalamus, the content of norepinephrine greatly exceeds that of dopamine, so that in these brain areas, catecholamine uptake is mediated predominantly by norepinephrine neurons.

We found that *d*-amphetamine (dextroamphetamine) was considerably more potent than its optical isomer *l*-amphetamine in inhibiting the reuptake process of norepinephrine neurons.[12,34,36,37] Catecholamine reuptake by the dopamine neurons of the *corpus striatum,* however, was affected similarly by *d*- and *l*-amphetamine. We also obtained evidence suggesting that *d*-amphetamine was much more potent than its *l*-isomer in eliciting catecholamine release in norepinephrine areas of the brain, although the two isomers had similar potencies in evoking catecholamine release from the dopamine neurons of the *corpus striatum.*[45] Thus, for the two major modes of amphetamine action, inhibition of reuptake inactivation and synaptic release, *d*-amphetamine is considerably more potent than *l*-amphetamine in affecting norepinephrine neurons, whereas the two isomers have similar potencies, in affecting dopamine neurons.

Assuming that these biochemical actions are responsible for the behavioral effects of amphetamine, there emerges a simple way to determine whether a particular animal or human behavior involves brain dopamine or norepinephrine. If *d*-amphetamine is much more potent than *l*-amphetamine in eliciting a behavioral effect, norepinephrine might be thought to be responsible. On the other hand, if *d*- and *l*-amphetamine have similar behavioral potencies, dopamine would be the implicated neurotransmitter.

Effects of Amphetamine Isomers on Animals

Earlier, we reported comparisons of the two amphetamine isomers on two behav-

ioral effects of amphetamine in animals, locomotor stimulation and stereotyped behavior.[34,36,37] At relatively low amphetamine doses, animals appear excited tending to run around their cages at a rapid rate, an effect that has been thought to mirror the central stimulant actions of amphetamine in man. In our experiments, *d*-amphetamine was ten times as potent as *l*-amphetamine in enhancing locomotor activity in rats, paralleling the ten-fold different potency of these isomers in inhibiting the catecholamine reuptake mechanism of the norepinephrine neurons.[12] Similar differences in the potencies of amphetamine isomers in enhancing locomotor activity and analogous performances in rats and mice have been reported by other workers.[31,43] These results suggested that locomotor stimulation in animals, and possibly the central stimulant properties of amphetamine in man, might involve brain norepinephrine. It is difficult to conclude with certainty that locomotor stimulation in animals has a neurochemical substratum like that of central stimulation in man. However, the powerful ability of locomotor stimulatory drug potency in animals to predict central stimulant potency in man strongly supports such a hypothesis.[31,34,36,37,43]

Drugs that block the conversion of dopamine to norepinephrine diminished the locomotor stimulant actions of amphetamine, also suggesting that norepinephrine rather than dopamine was the catecholamine responsible for mediation of this behavior.[8] Although these experiments fail to identify the responsible norepinephrine tract, a likely candidate might be the dorsal norepinephrine pathway, with cell bodies in the *locus ceruleus* and terminals in the cerebral cortex.

At somewhat higher doses, amphetamine elicits a stereotyped compulsive behavior in animals, the exact pattern varying with different species. In rats, whose major means of exploring their environment is olfactory, animals will stay in one portion of the cage, sniff, lick, and especially gnaw. Previously, we emphasized the analogy between this behavior and the involuntary movements produced in parkinsonian patients by large doses of L-DOPA and to the motor tics of Gilles de la Tourette's disease.[34]

d-Amphetamine was only twice as potent as the *l*-isomer in eliciting stereotyped behavior in rats, considerably less than the ten-fold difference in the capacity of these drugs to stimulate locomotor activation.[34,36,37] This finding implicates dopamine as the catecholamine of major importance in mediating this behavior, which accords with results using drugs that block the conversion of dopamine to norepinephrine[8,29] or employing lesions[19,25,28] or stimulation[15,17] in brain areas that contain dopamine. The fact that the two isomers were not quite equal in activity suggests that norepinephrine may play some role, conceivably in triggering the stereotyped behavior.

Effects of Amphetamine Isomers on Humans

The exact relevance of stereotyped behavior in animals to the clinical actions of amphetamine in man is not altogether clear. This behavior is observed regularly, however, in a number of animal species, including cats and monkeys, in which it includes side-to-side looking patterns as well as self-picking and grooming behavior extremely similar to the compulsive, stereotyped, repetitive behavior classically evinced by amphetamine addicts.[14,16]

Amphetamine addicts also often develop a psychosis that may be clinically indistinguishable from acute paranoid schizophrenia.[4,5,9,33] Amphetamine psychosis occurs quite frequently in heavy amphetamine addicts and can be experimentally elicited consistently in human subjects (former am-

phetamine addicts).[1,20] Angrist and coworkers[1] found that *d*- and *l*-amphetamine were similarly efficacious in evoking amphetamine psychosis in human volunteers, suggesting that brain dopamine was responsible for the symptoms of the psychosis.

Quite recently, it has been possible to compare *d*- and *l*-amphetamine in the treatment of MBD. In one study, we evaluated the effects of these isomers in an eight-year-old girl with classic symptoms of Gilles de la Tourette's disease, a condition of unknown etiology with body tics and barking noises developing into coprolalia as the predominant symptoms. She also displayed classic symptoms of MBD, including hyperactivity, short attention span, and poor impulse control.[28] She was maintained at the Johns Hopkins Hospital as an inpatient on a research ward for a period of 60 days, during which three separate double-blind cross-over comparisons of *d*- and *l*-amphetamine and placebo were performed. To evaluate relative potencies, dosages of amphetamine during each trial were gradually escalated each day for up to five days.

Tics were graded by a team of two ward personnel who had no knowledge of the patient's medication. At the same time each day, they counted the number of tics occurring during a five-minute period, when the patient was engaged by one of the team in an interesting activity that minimized volitional motor behavior, i.e., a game of dominoes. Hyperactivity was evaluated daily by the nursing staff with a rating scale that included indicators of hyperactivity such as: agitation, irritability, rule breaking, hyperactivity, inability "to cooperate," "short attention span." Care was taken to distinguish between "hyperactivity" and the tic syndrome. Ratings were made on a scale from minimal (1) to very severe (6).

Treatment with *d*-amphetamine dramatically exacerbated the tics (see FIGURE 3) and *l*-amphetamine failed to alter the tics at any dose. These results suggest that norepinephrine is the catecholamine primarily responsible for the exacerbation of tics by amphetamine.

In contrast with the marked difference in the actions of the two amphetamine isomers on the tics, the patient's hyperactivity appeared to respond similarly to the two drugs (see FIGURE 4). Of interest is the very rapid therapeutic response to amphetamine as well as the equally rapid reappearance of hyperactivity during the institution of placebo. This result confirms numerous previous observations on the almost immediate beneficial effects of *d*-amphetamine in this condition and on the equally abrupt recrudescence of symptoms upon discontinuation of the drug.[41]

The similar potency of amphetamine isomers in alleviating MBD symptoms in this patient is consistent with a dopamine mediated therapeutic effect of the drug. Since the duration of the drug trials was relatively brief, however, and because only a single patient was examined, we cannot conclude definitively that *d*- and *l*-amphetamine are truly equal in potency. Quite recently, however, these results have been partially confirmed in a more extensive trial. In a double-blind cross-over comparison of *d*- and *l*-amphetamine in 11 hyperactive children, *d*-amphetamine was only slightly more effective than *l*-amphetamine.[2]

Conclusion

What do these data tell us about how amphetamine works in MBD? If we very cautiously conclude that brain dopamine is involved in the effects of amphetamine upon symptoms of MBD, what are the particular dopamine tracts affected? Of course, there is no answer at the present

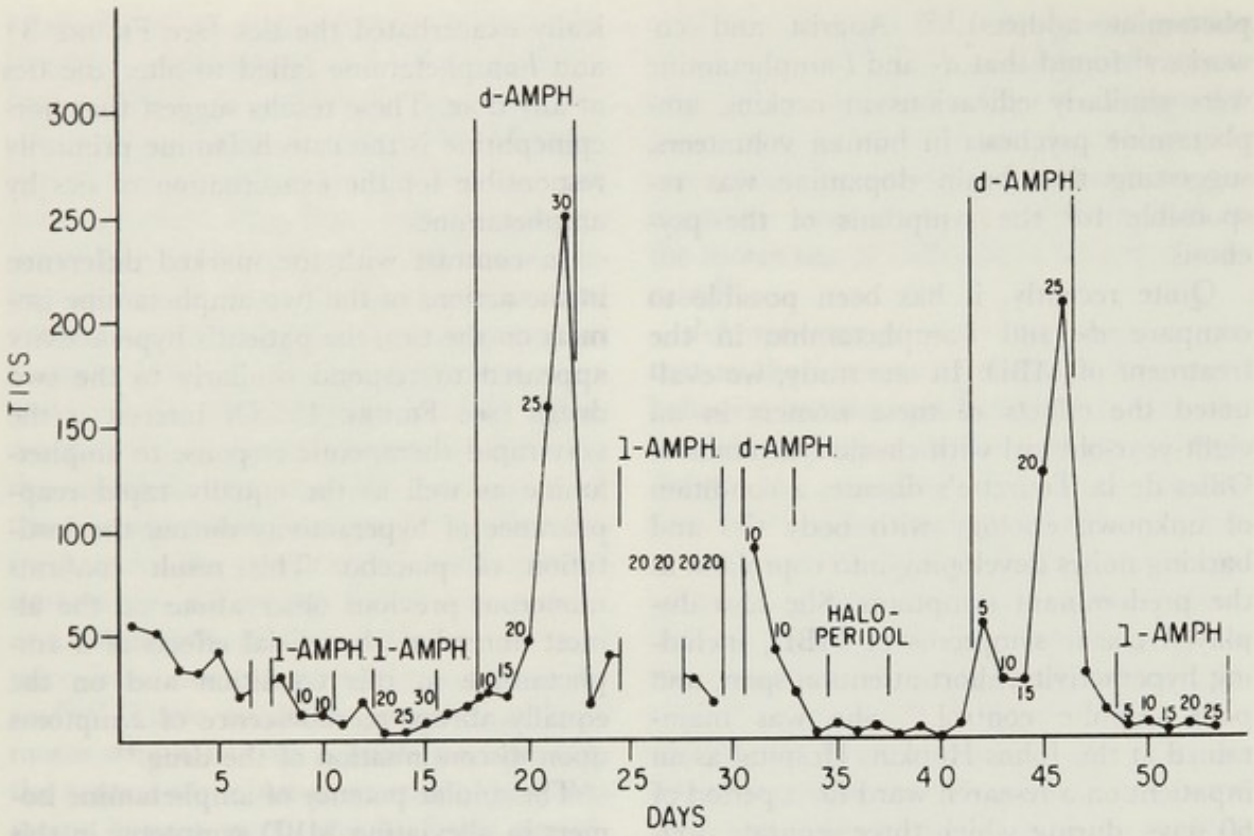

Figure 3. Effects of d- *and* l-*amphetamine on tics of a patient with Gilles de la Tourette's disease and minimal brain dysfunction syndrome. Amphetamine dosage in milligrams of* d- *or* l-*amphetamine sulfate equivalents is indicated above the tic ratings. Ratings represent the total number of tics recorded during a standardized five-minute daily observation period. Haloperidol dosage is described in the text.*

time. The three candidates are the nigrostriatal pathway, known to be degenerated in Parkinson's disease, and the two little understood tracts with cell bodies near the interpeduncular nucleus and terminals in the nucleus accumbens or olfactory tubercle. These latter two regions are parts of the "septal" area of the brain, which has long been implicated in emotional behavior. Hence, insofar as MBD reflects an "emotional disorder," these tracts might be good candidates. On the other hand, the most conspicuous symptomatology of MBD is motor, i.e., hyperactivity, which might suggest a role for the *corpus striatum*. Yet another formulation is possible if one thinks of children with MBD as manifesting "emotionally determined hypermotility." In this case, combined effects of amphetamine on all three dopamine tracts would best explain the therapeutic actions of the drug.

In one sense, it is disquieting to speculate about dopamine tracts as mediating amphetamine actions in MBD. Much evidence favors norepinephrine pathways as mediating alerting effects of amphetamine. And, at a clinical level, the ability of amphetamine to increase the attentiveness of patients with MBD is a most striking finding. Perhaps both norepinephrine and dopamine ought to be implicated in MBD response to amphetamine. In the study of Arnold and coworkers,[2] although the two amphetamine isomers displayed similar potencies, the *d*- form was somewhat more effective than the *l*-isomer. This result is reminiscent of the slightly greater efficacy

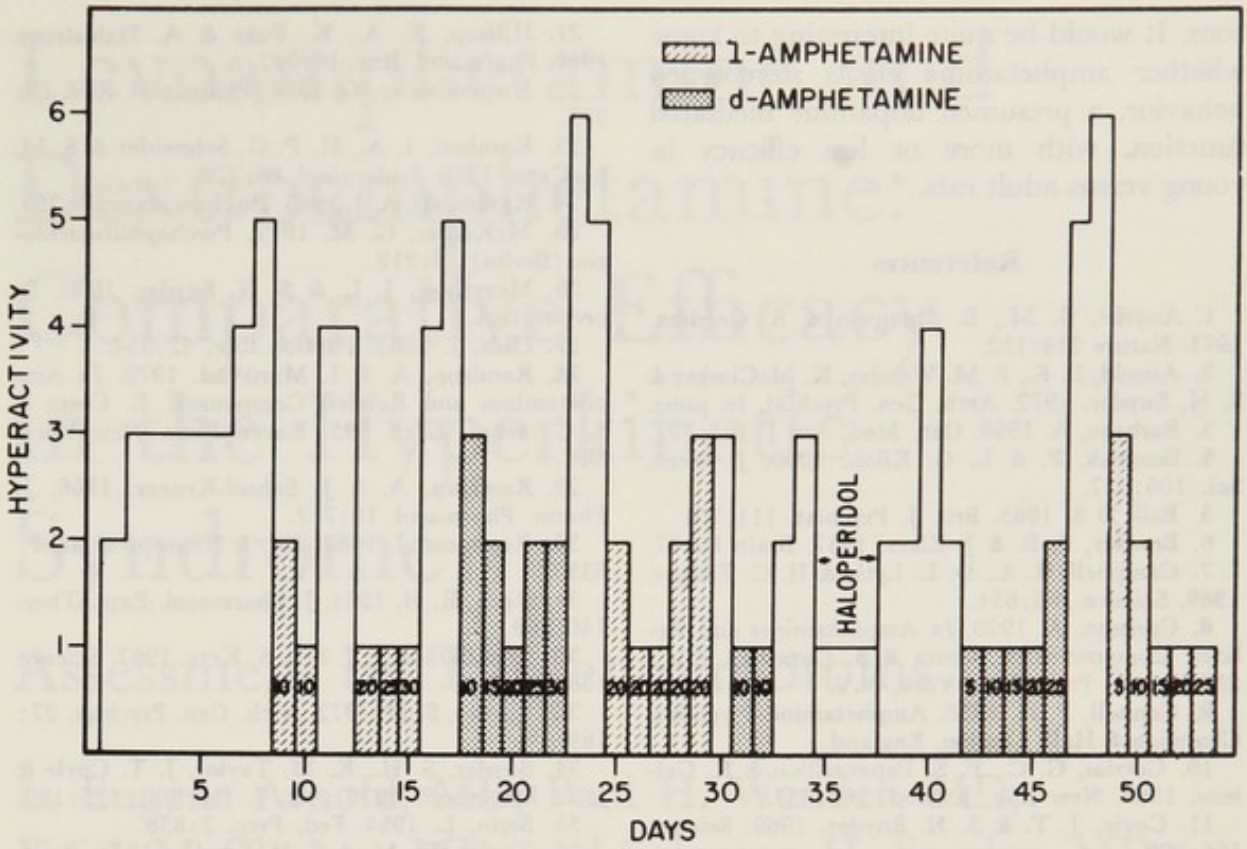

Figure 4. Effects of d- *and* l-*amphetamine on the hyperactivity of a patient with Gilles de la Tourette's disease and minimal brain dysfunction syndrome (hyperkinetic syndrome). Amphetamine dosage in milligrams of* d- *or* l-*amphetamine sulfate equivalents is indicated within the bars. Haloperidol dosage and the rating system for hyperactivity are described in the text.*

of *d*- than of *l*-amphetamine in eliciting stereotyped behavior in animals[36,37] and amphetamine psychosis in man.[1] In the latter two conditions, it was concluded that dopamine was the predominant catecholamine involved, and norepinephrine played some lesser role.

It should be noted that in all these speculations about differential roles of brain catecholamines, we have confined our discussion to catecholamines mediating the therapeutic actions of amphetamines and have not suggested that an abnormality of brain catecholamines is causally related to the symptoms of MBD. Drugs can exert marked therapeutic effects via mechanisms related only distantly to the pathophysiology of the disease, e.g., aspirin relieving the fever of pneumococcal pneumonia.

What of the paradoxical quieting effects of amphetamine in MBD? How might neurochemical or pharmacological analysis in animals help resolve this question? Since the paradoxical effect is observed in patients with MBD and not in normal children, one might claim that there cannot be any appropriate animal model. On the other hand, if it is assumed that the symptoms of MBD reflect a delayed maturation of certain brain systems, one might simply search for paradoxical responses to amphetamine in young animals. Unfortunately, behavioral studies of amphetamine in young animals are few. In one study,[7] young rats showed as much or more locomotor response to *d*-amphetamine as did adult rats. Presumably this response reflects the activity of central norepinephrine neu-

rons. It would be quite interesting to know whether amphetamine elicits stereotyped behavior, a presumed dopamine mediated function, with more or less efficacy in young versus adult rats.

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Levoamphetamine and Dextroamphetamine: Comparative Efficacy in the Hyperkinetic Syndrome

Assessment by Target Symptoms

L. Eugene Arnold, MD; Paul H. Wender, MD; Keith McCloskey, MD; and Solomon H. Snyder, MD

In a nine-week double-blind crossover comparison of dextroamphetamine, levoamphetamine (Cydril), and placebo with 11 hyperkinetic children, effects were assessed by an established teacher rating scale, a parent rating scale, and a new tool, weekly quantification of parent-selected target symptoms. Both active drugs were significantly more effective than placebo. Dextroamphetamine seemed consistently superior to levoamphetamine, though not to a significant degree (on this size sample). Levoamphetamine seemed "slower starting," requiring three weeks to show significant benefit on target symptoms, whereas dextroamphetamine showed nearly its maximum benefit the first week. Levoamphetamine seemed better for hyperactivity and aggressiveness than for inattentiveness, whereas dextroamphetamine seemed equally beneficial for all three. These data are consistent with the possibility that therapeutic effects of amphetamine on hyperkinetic children are mediated, at least in some, by dopaminergic systems.

It has been repeatedly stated in the literature[1,2] that, in the pharmacotherapy of hyperkinetic children, racemic (DL) amphetamine is sometimes more effective than the purified D-isomer (dextroamphetamine).

This curious phenomenon carries interesting theoretical as well as clinical implications. The general assumption seems to have been that levoamphetamine is almost an inert contaminant of racemic amphetamine in regard to central nervous system

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effects. This impression is confirmed not only by standard textbooks of pharmacology but also by the facts that the best-known brand of dextroamphetamine is manufactured in tablets half the size of racemic amphetamine tablets from the same manufacturer, and that levoamphetamine occupies a very small part of the amphetamine market in comparison to dextroamphetamine. It does seem well-established that levoamphetamine is a considerably weaker central stimulant than dextroamphetamine.[3] However, it is conceivable that, for some central effects, levoamphetamine may be similar in potency to its dextro-isomer. The observations that some hyperkinetic children respond better to racemic (DL) amphetamine than to dextroamphetamine in comparable doses suggests the possibility that the two isomers may have similar efficacy in treating this syndrome.

The term "comparable doses" may provide an explanation for the apparent superiority of racemic amphetamine in some cases. It is customarily prescribed in doses twice as large as dextroamphetamine. Bradley[1] recommended this two-to-one ratio, and Laufer and Denhoff [2] recommend racemic amphetamine in doses from 5 to 30 mg, compared to dextroamphetamine in doses from 2.5 to 20 mg. This ratio would give the child approximately the same amount of dextroamphetamine with either drug, but the child taking racemic amphetamine would, in addition, have an equal amount of levoamphetamine included in the racemic mixture. Could it be that these children are responding to the total dosage of amphetamine regardless of the isomer?

There is some precedent for the concept that the relative potency of the two amphetamine isomers may vary for different drug effects. Animal studies have indicated that for some behaviors elicited by amphetamine, such as locomotor stimulation, dextroamphetamine is ten times as potent as its L-isomer while for others, such as stereotyped gnawing behavior in rats, the two isomers have similar potencies.[4-5] In man, dextroamphetamine is considerably more potent as a central stimulant than levoamphetamine,[3] while the two isomers have similar potencies in producing "amphetamine psychosis" (Angrist, personal communication).

If the hyperkinetic children who respond better to racemic amphetamine than to dextroamphetamine are indeed responding to the total dose of amphetamine regardless of the isomer, perhaps they would respond as well to the same total dose in the form of pure levoamphetamine. This raises interesting possibilities, because the most troublesome side effects from amphetamine therapy of hyperkinetic children, anorexia and insomnia,[1] are more marked with the dextroamphetamine. If levoamphetamine were found to be an effective treatment for hyperkinesis, some children could either be treated with less side effects or perhaps treated more effectively with higher doses before the side effects became limiting.

Samples of levamfetamine succinate (Cydril) were administered to several hyperkinetic children in a pilot study with encouraging results. Therefore, a nine-week controlled double-blind crossover study was designed to compare dextroamphetamine, levoamphetamine, and placebo. (Such crossover studies are easier with amphetamine, which "washes out" within a day, than with phenothiazines, which may continue showing clinical effects months after discontinuing administration.)

Method and Design

The crossover design included three weeks for each child on each of the three drug conditions: placebo, dextroamphetamine, and levoamphetamine. Blind assessments of behavior were made weekly by

parents and teachers. Counting the clinician and child, this was thus actually a "quadruple-blind" study. (To promote the cooperation of all involved in the study, the teachers were given a stipend of $25 and the parents were reimbursed $2 for transportation each time they brought the child to the clinic. Of 14 children starting the study, 11 completed the nine weeks.)

Some of the apparently good responders from the pilot study were included in the controlled study. Since the hypothesis being tested was that some children respond as well to levoamphetamine as to dextroamphetamine, roughly equivalent to proving that "some swans are black," and postponing the determination of percentages to a later study, it was not felt necessary or even desirable to obtain a random sample. (If even one child responded as well to levoamphetamine as to dextroamphetamine, it would be a finding of immense theoretical and practical importance.)

The ten boys and one girl in the study were therefore selected with the following criteria in mind: (1) a stable enough family to offer hope of continued cooperation throughout the nine weeks of the study, (2) clinical impression of hyperkinesis diagnosed by a pediatrician or psychiatrist and supported by school reports of typical overactivity and inattentiveness, and (3) dissatisfaction with dextroamphetamine therapy for various reasons, usually side effects. The most common complaint was anorexia. In two cases the parents complained of insufficient benefit. One boy complained of a choking sensation on taking his morning dose of five dextroamphetamine tablets. Another complained of nausea and stomach cramps. One boy's mother complained the dextroamphetamine made him too somber and apathetic, not "boyish" enough. Two boys were resistant to taking amphetamine and were included in the study to demonstrate to them whether or not they actually benefited from the drug. The only girl in the sample had the best history for brain damage (postmeningitic) and had failed to respond to any medical management. The ages ranged from 5½ to 12. Intelligence ranged from borderline retarded to superior. Racially, there were two blacks and nine whites.

Each week the following data were obtained for each child: (1) The Teacher rating scale factor-analyzed and reported by Connors;[7] (2) a similar parent rating scale (both rating scales were checklists of symptoms to be rated from 1, not at all to 4, very much); (3) parents' evaluation of progress on target symptoms; (4) child's subjective impressions; (5) clinicians' impressions; (6) weight; (7) pulse; and (8) blood pressure.

The target symptoms deserve further explanation. At the beginning of the study the parents of each child were asked to list the four or five things about the child they found most worrisome. An attempt was made to quantify these, such as "bounces 40 times a day on the sofa." Each subsequent week the parent was asked about each of the points and asked to quantify the child's performance that week, eg, "bounced only about 20 times a day." At the end of the study these parental assessments of the target symptoms were typed out on separate cards, one for each week for each child, along with salient comments by the child, clinician, or teacher. Using each child as his own control, they formed the basis for a rank ordering of the nine weeks for each child from best to worst. The three independent raters were two child psychiatrists and a pediatrician with psychiatric training.

With a Latin square design and a double-blind procedure, all the children in the study were randomly assigned to each of the three drug conditions for three consecutive weeks, for a total of nine weeks. Each time a child started a new drug condition, he started with one tablet (equivalent to 5

Table 1. Average daily dose* and hemodynamic data

	Placebo	Dextro-amphetamine	Levo-amphetamine	Significant Difference
Av number tablets per day through three weeks of drug	7.13	6.09	5.98	Dextroamphetamine vs placebo $P < .05$
Tablets per day third week of drug	7.33	6.33	6.00	NS
Av pulse rate all three weeks of drug condition	88.6	93.4	93.1	Dextroamphetamine vs placebo $P < .05$
Pulse third week of drug	90.5	89.09	88.18	NS
Av systolic pressure all three weeks of drug	110.0	109.9	111.7	NS
Systolic pressure third week of drug	114.7	112.6	108.9	NS
Av diastolic pressure all three weeks of drug	73.9	71.1	71.1	NS
Diastolic pressure third week of drug	73.9	76.8	67.5	NS

* One tablet = 5 mg amphetamine sulfate.

mg amphetamine sulfate) a day and increased by one tablet per day. By the end of the first week he was taking three in the morning and three at noon, unless the dose was halted at a lower level because of side effects. After the first week the dose was adjusted individually for the optimum results. The dosage forms for the three drug conditions were, of course, identical in appearance.

The matched dosage forms were supplied by the Tutag Company which markets levoamphetamine (levamfetamine) under the trade name Cydril. In the interests of economy, the levoamphetamine used in the study was the company's stock 7-mg levoamphetamine succinate tablets. However, dextroamphetamine was available only as the sulfate. The assumption was made that doses of succinate and sulfate should have the same effect if the amount of amphetamine base is the same. Because of the difference in molecular weight and valence between succinate and sulfate,

Table 2. Average weekly weight (kg) and anorexia from parents' rating scale

	Placebo	Dextro-amphetamine	Levo-amphetamine	Significant Difference
				Dextroamphetamine vs placebo $P < .005$
Week 1 av weight	33.05	32.48	32.47	Levoamphetamine vs placebo $P < .005$
Week 2 av weight	33.29	32.51	32.72	Dextroamphetamine vs levoamphetamine NS (1-tailed paired *t*-test)
Week 3 av weight	33.50	32.20	32.40	
				Dextroamphetamine vs placebo $P < .05$
Week 1 av anorexia rating*	2.09	2.45	1.73	Levoamphetamine vs placebo NS
Week 2 av anorexia rating*	1.55	2.45	1.73	Dextroamphetamine vs levoamphetamine NS
Week 3 av anorexia rating*	1.36	2.27	1.73	

* 1, no anorexia; 4, very much anorexia.

7-mg amphetamine succinate tablets are equal in amphetamine base to 5-mg amphetamine sulfate tablets. Therefore, the dextroamphetamine sulfate tablets were made in a 5-mg size. All three "drugs" were treated clinically as if they contained 5 mg amphetamine sulfate.

Results

Though the clinicians were instructed to optimize the dose on each drug condition, the same doses in general were used for the two active drugs, approximately six tablets a day. The slight differences (Table 1) were not significant. There was, however, a tendency to use higher doses of placebo (over seven tablets per day), which probably reflected attempts to get a therapeutic result by higher doses.

As expected, the pulse and blood pressure data (Table 1) were in general not significantly different under the three conditions. In children receiving dextroamphetamine the pulse rate averaged over three weeks was higher than when receiving placebo at $P < .05$, but by the third week it actually dropped below placebo (not statistically significant).

Table 2 shows the rather surprising fact that weight loss with levoamphetamine was not significantly different from that with dextroamphetamine. The average weight at the end of the placebo period was 3% to 4% heavier than at the end of either of the active drug periods. The children's weight after receiving dextroamphetamine was slightly lower than after receiving levoamphetamine, as expected, and is reflected in more severe complaints of anorexia. Anorexia with dextroamphetamine was significantly worse than with placebo. Levoamphetamine was between placebo and dextroamphetamine and not significantly different from either in its anorexic effect.

Also nonsignificant were the differences between the two active drugs on the other side effects reported on the parents' questionnaire (Table 3). In fact, by the third

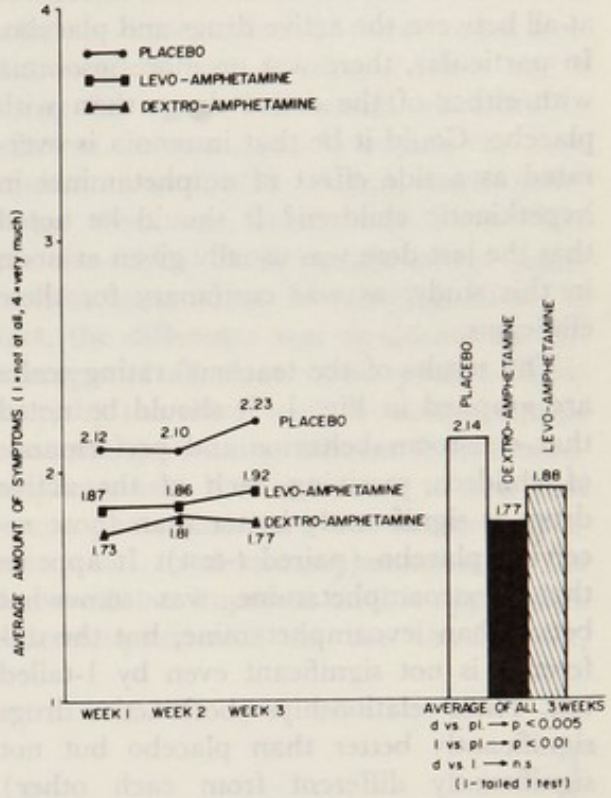

Figure 1. Average scores for each drug condition (placebo, dextroamphetamine, and levoamphetamine) on teacher's rating scale (1, no symptom; 4, most symptomatic).

Table 3. Average side effects (other than anorexia) from parents' rating scale*

	Placebo	Dextroamphetamine	Levoamphetamine
Week 1 av insomnia rating†	2.09	2.27	2.09
Week 2 av insomnia rating†	2.18	1.91	2.00
Week 3 av insomnia rating†	2.09	1.91	2.09
Av headaches all three weeks†	1.27	1.18	1.39
Av "nervous habits" all three weeks†	2.64	2.21	1.97
Av "tummy aches" all three weeks†	1.21	1.45	1.24
Av "side effects of medicine" †	1.48	1.94	1.73

* All differences nonsignificant. † 1, not at all; 4, very significant.

week there does not seem to be a difference at all between the active drugs and placebo. In particular, there was no more insomnia with either of the active drugs than with placebo. Could it be that insomnia is overrated as a side effect of amphetamines in hyperkinetic children? It should be noted that the last dose was usually given at noon in this study, as was customary for these clinicians.

The results of the teachers' rating scales are graphed in Fig. 1. It should be noted that classroom behavior and performance of children receiving each of the active drugs is significantly better than those receiving placebo (paired *t*-test). It appears that dextroamphetamine was somewhat better than levoamphetamine, but the difference is not significant even by 1-tailed test. These relationships (both active drugs significantly better than placebo but not significantly different from each other) hold up also (Fig. 2) in Connor's[7] factor I (aggressive conduct disorder) and factor IV (hyperactivity factor) in the third week. (Separate factors were not computed for the first two weeks of each condition.) On factor II (daydreaming and inattention), dextroamphetamine is significantly better than either placebo or levoamphetamine, and levoamphetamine just misses being significantly better than placebo.

Figure 3 shows the results of the parents' rating scales. Again, the placebo weeks are significantly worse than the weeks on either active drug. Dextroamphetamine again appears better than levoamphetamine, but not significantly so. Thus, the parents' ratings show the same general pattern as the teachers' ratings.

Because the parent rating scale included so many items (96) covering a wide gamut of symptoms, not all of which are believed to be related to the hyperkinetic syndrome, and because the number of subjects was insufficient for factor analysis, an "arm-

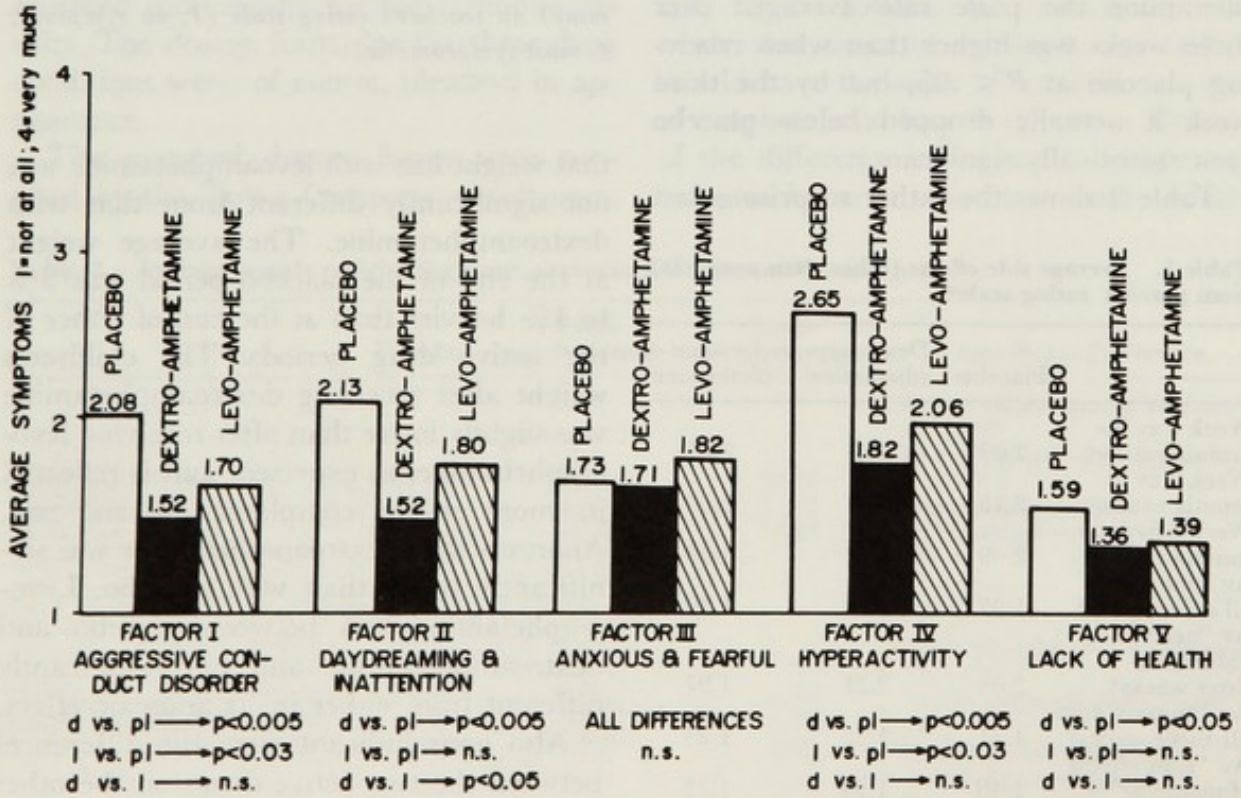

Figure 2. Third week averages on teacher rating scale by Connor's factors[7] (comparing placebo, dextroamphetamine, levoamphetamine).

chair factor" was preselected, consisting of the 11 items obviously relating to hyperactivity and inattention. The mean score on this factor for each drug condition is presented in Fig. 3. Here we again find much the same relationship as in the teachers' ratings, namely that both active drugs are significantly better than placebo but not significantly different from each other, though dextroamphetamine again appears slightly (not significantly) better. The same relationship is also found in a similarly preselected "bullying–aggressive factor" (Fig. 3).

Figure 4 shows the means of the rankings by three psychiatrists of each week for each child, based largely on the parents' weekly assessment of target symptoms, as explained under *Method and Design*. The nine weeks for each child were ranked from 1 through 9 with 1 being the best and 9 being the worst. The overall reliability coefficient (Ebel method [8]) among the three rankers was 0.8428. Again, both active drugs come out significantly better than placebo. Also, dextroamphetamine again looked better than levoamphetamine. In fact, the difference was significant for the averages of all three weeks pooled. However, by the third week levoamphetamine was not significantly different from dextroamphetamine. It is interesting to note that levoamphetamine starts out nearer to placebo than to dextroamphetamine in the first week but improves until it approaches dextroamphetamine in the third week,

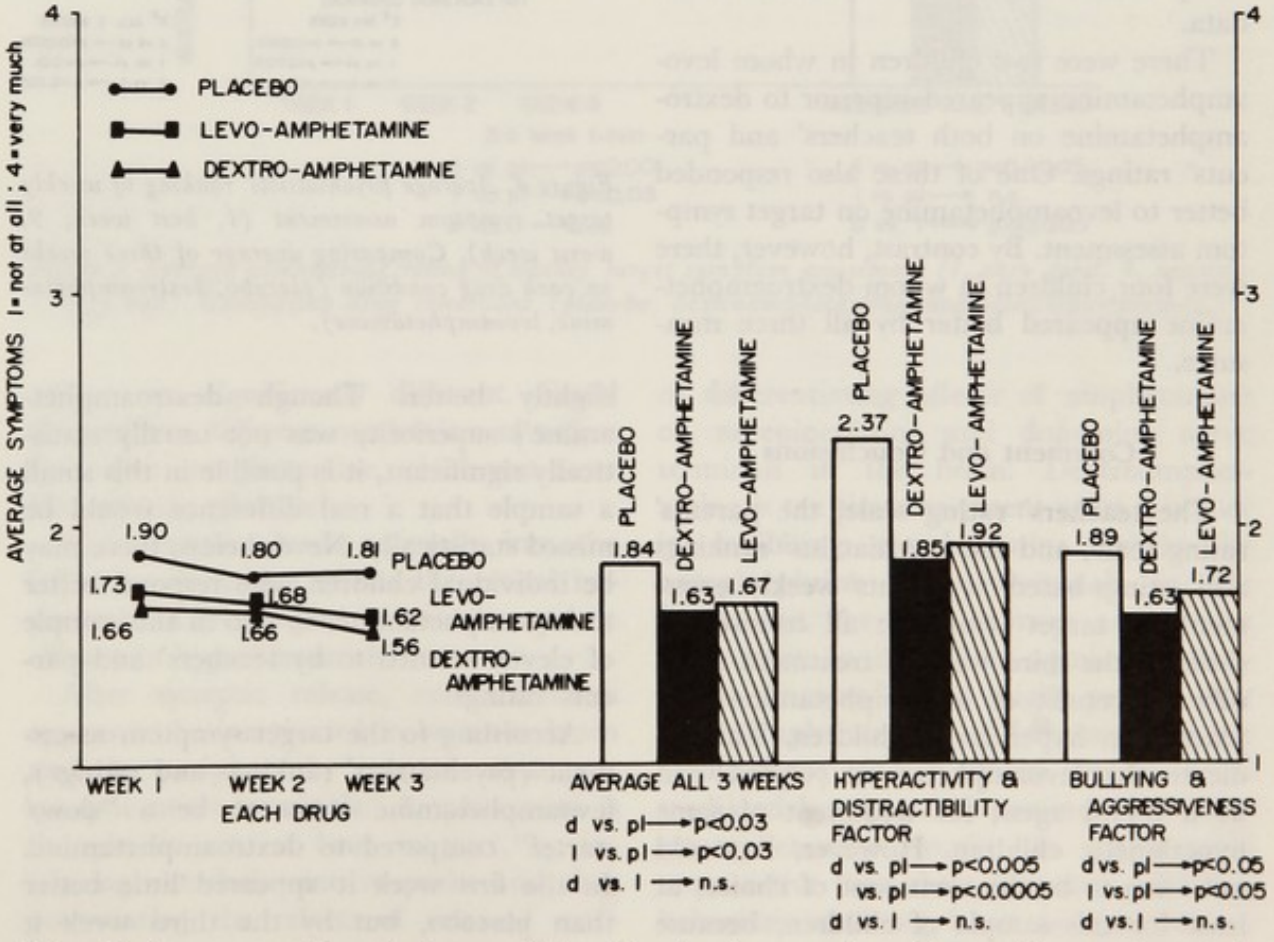

Figure 3. Average score for each drug condition (placebo, dextroamphetamine, and levoamphetamine) on parent's rating scale (1, no symptom; 4, most symptomatic).

whereas dextroamphetamine shows a more consistent effect through the three weeks.

The same pattern appeared (Fig. 5) when each week for each child was rated by the three psychiatrists on a 7-point absolute rating scale from very good (1) to very bad (7). The overall coefficient of reliability for the three raters was 0.7734 (Ebel [8]). Again we see dextroamphetamine significantly better than placebo with levoamphetamine between dextroamphetamine and placebo. In the first two weeks levoamphetamine was nearer placebo than to dextroamphetamine, but in the third week it veered away from placebo and approached dextroamphetamine in its effects. In this last week it was significantly better than placebo but not significantly different from dextroamphetamine, a pattern already consistently seen on the rest of the data.

There were two children in whom levoamphetamine appeared superior to dextroamphetamine on both teachers' and parents' ratings. One of these also responded better to levoamphetamine on target symptom assessment. By contrast, however, there were four children in whom dextroamphetamine appeared better by all three measures.

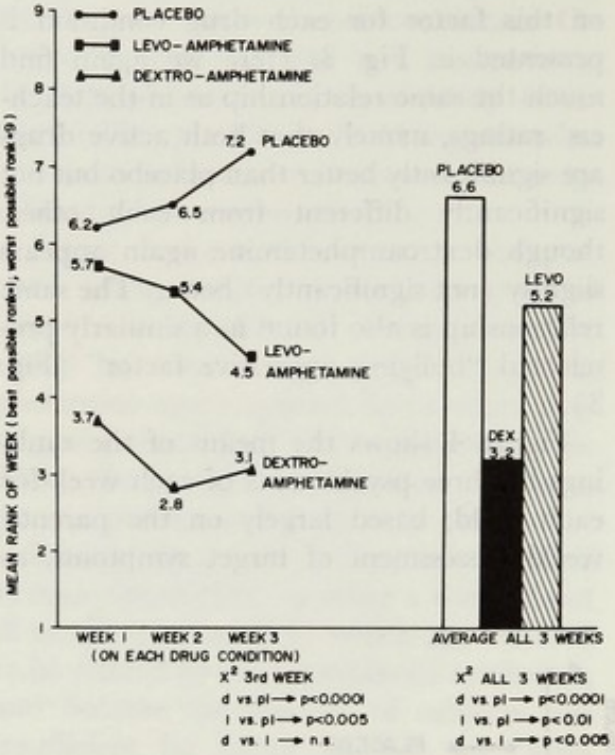

Figure 4. Average psychiatrists' ranking of weekly target symptom assessment (1, best week; 9, worst week). Comparing average of three weeks on each drug condition (placebo, dextroamphetamine, levoamphetamine).

Comment and Conclusions

The teachers' rating scale, the parents' rating scale, and the psychiatrists' rankings and ratings based on parents' weekly assessments of target symptoms all consistently show by the third week of treatment a significant benefit of levoamphetamine over placebo in hyperkinetic children. This indicates that levoamphetamine (Cydril) can be a useful agent for treatment of some hyperkinetic children. However, it would not seem to be the treatment of choice, at least for this sample of children, because dextroamphetamine generally appeared slightly better. Though dextroamphetamine's superiority was not usually statistically significant, it is possible in this small a sample that a real difference would be missed statistically. Nevertheless, there may be individual children who respond better to levoamphetamine, as two in this sample of eleven seemed to by teachers' and parents' ratings.

According to the target symptom assessment (psychiatrists' rankings and ratings), levoamphetamine seems to be a "slow/starter" compared to dextroamphetamine. In the first week it appeared little better than placebo, but by the third week it seemed almost as good as dextroamphet-

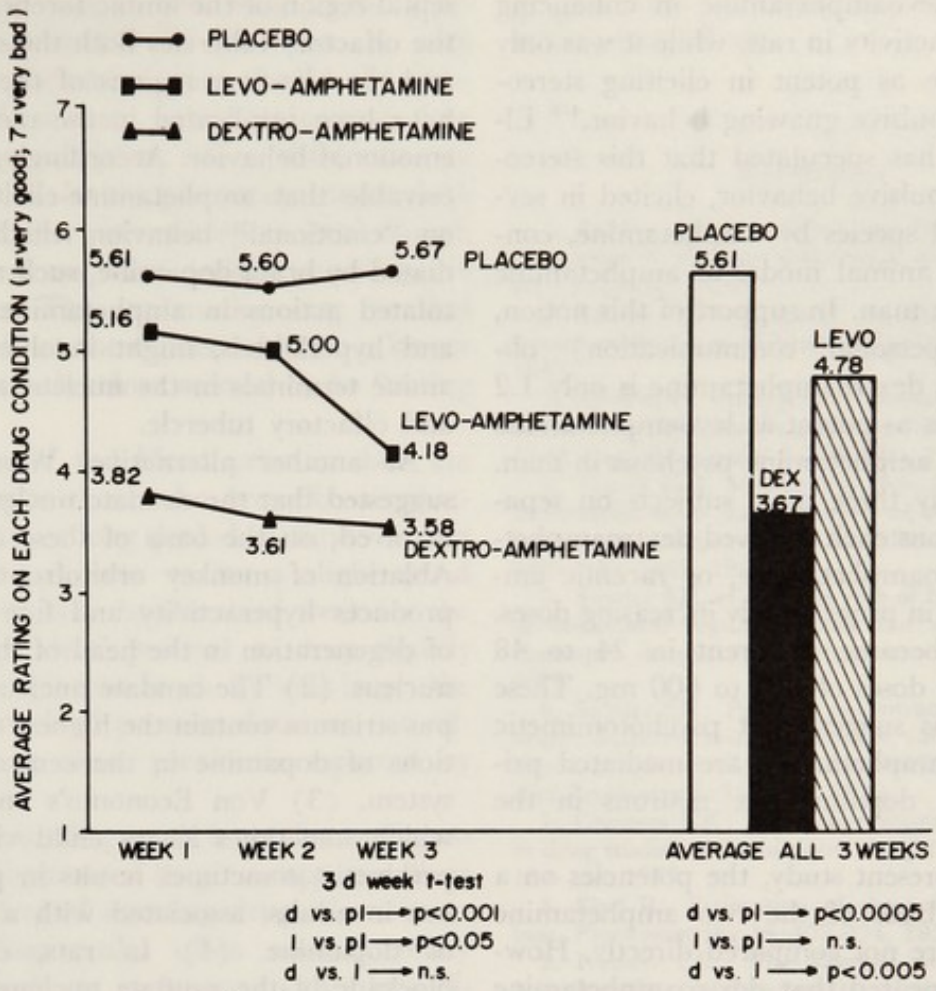

Figure 5. Average psychiatrists' rating of weekly target symptom assessment (1, very good; 4, neutral; 7, very bad). Comparing drug conditions (placebo, dextroamphetamine, and levoamphetamine).

amine, not significantly different. Could this imply a different mechanism of action from dextroamphetamine, which was more immediately effective?

This question leads naturally into the following discussion of the theoretical importance of levoamphetamine's therapeutic efficacy in hyperkinetic children.

After synaptic release, catecholamines appear to be inactivated in both the brain and the periphery by reuptake into presynaptic nerve terminals.[9] Amphetamine is thought to act, at least in part, by inhibiting catecholamine reuptake and thus potentiating the effects of released catecholamines. Recent studies suggest a means of differentiating effects of amphetamine on norepinephrine and dopamine nerve terminals in the brain. Dextroamphetamine is ten times as potent as its L-isomer in inhibiting catecholamine uptake by norepinephrine nerve terminals in the brain, but the two isomers are similar in potency in inhibiting uptake by dopamine neurons.[10] One might predict that dextroamphetamine and levoamphetamine would have similar effects on behaviors mediated by central dopamine while dextroamphetamine would be considerably more active than the L-isomer in affecting behaviors involving brain norepinephrine. Thus, dextroamphetamine was ten times as

potent as levoamphetamine in enhancing locomotor activity in rats, while it was only about twice as potent in eliciting stereotyped compulsive gnawing behavior.[4-6] Ellinwood[11] has speculated that this stereotyped compulsive behavior, elicited in several animal species by amphetamine, constitutes an animal model of amphetamine psychosis in man. In support of this notion, Angrist (personal communication) observed that dextroamphetamine is only 1.2 to 1.5 times as potent as levoamphetamine in eliciting amphetamine psychosis in man. In his study three male subjects on separate occasions each received dextroamphetamine, levoamphetamine, or racemic amphetamine in progressively increasing doses. Psychosis became apparent in 24 to 48 hours with doses of 300 to 600 mg. These observations suggest that psychotomimetic effects of amphetamine are mediated primarily via dopaminergic neurons in the brain.

In the present study, the potencies on a milligram basis of the two amphetamine isomers were not compared directly. However, it appeared that dextroamphetamine was only slightly more effective than levoamphetamine in ameliorating hyperkinetic symptoms. These results suggest that the beneficial effects of amphetamine on symptoms of the hyperkinetic syndrome might be mediated via brain dopamine.

There are several dopamine tracts in the brain.[12] The most prominent of these has cell bodies in the substantia nigra with terminals in the corpus striatum and appears to be degenerated in patients with Parkinson's disease. The nigrostriatal dopamine tract presumably is concerned primarily with motor coordination, but could be involved in a "dopaminergic" mode of amphetamine's therapeutic action on the hyperkinetic syndrome. Other major dopamine tracts take origin in the brain stem near the interpeduncular nucleus and have terminals in the nucleus accumbens in the septal region of the limbic forebrain and in the olfactory tubercle. Both the septal area and the olfactory regions of the forebrain have been implicated in the mediation of emotional behavior. Accordingly, it is conceivable that amphetamine-elicited effects on "emotional" behavior which are mediated by brain dopamine, such as the postulated actions in amphetamine psychosis and hyperkinesis, might involve the dopamine terminals in the nucleus accumbens and olfactory tubercle.

As another alternative, Wender[13] has suggested that the caudate nucleus may be involved, on the basis of these data: (1) Ablation of monkey orbitofrontal lobules produces hyperactivity and fine terminals of degeneration in the head of the caudate nucleus. (2) The caudate nucleus and corpus striatum contain the highest concentrations of dopamine in the central nervous system. (3) Von Economo's encephalitis, which sometimes leaves child victims hyperkinetic, sometimes results in parkinsonism in adults, associated with a depletion of dopamine. (4) In rats, cholinergic blockade of the caudate nucleus decreases conditioned avoidance and increases activity level. These data are only suggestive, but are compatible with the implications of the present study.

The quantitative assessment of side effects was somewhat surprising, since one of the reasons for the study was the suspicion that levoamphetamine might be as effective as dextroamphetamine while having fewer side effects. In actuality, the study seems to have demonstrated that side effects are not really an appreciable problem with either drug by the end of three weeks. In particular, insomnia was no more of a problem than with placebo, as long as the last dose of the day was not later than noon. There did seem to be some difference with anorexia, levoamphetamine causing less than dextroamphetamine, but more than placebo. It is interesting that the

amount of weight loss with levoamphetamine was practically the same as with dextroamphetamine, even though the complaints of anorexia were not as great. One interesting exception was a child who ate better with levoamphetamine than with placebo by her parents' report, even though she gained no more weight according to the scales. The explanation may be that she sat still at the dinner table for a longer period and therefore seemed to be "eating better."

The pulse and blood pressure data are reassuring to those who prescribe amphetamine over a long period of time. In fact there seemed even to be a slight trend (nonsignificant) by the third week for the pulse and blood pressure to drop slightly below the placebo level. By and large, the pulse and blood pressure data are not different from those previously reported by others.

One gratifying result from this study was the development of target symptom ratings as a method of assessing drug effect. Standard rating scales often contain many items which are irrelevant to the drug effect and thereby dilute the relevant findings. This seems to be what happened with the complete parents' rating scale employed in this study. The hyperactivity-distractibility factor was diluted by items irrelevant to most hyperkinetic children. Assessment of target symptoms selected by parents avoids this problem. The high reliabilities on both ranking and rating, and the consistency of these rankings and ratings with the other data available in the study, confirms the usefulness of such target symptom assessment as a means of evaluating drug effects.

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6. Alcoholism

Clinical Description

The distinction between a heavy social drinker and an alcoholic is arbitrary and subject to considerable dispute. The definitions of alcoholism in general stress (1) the use of alcohol in a habitual manner to relieve tension; (2) loss of control over the amount of alcohol consumed; and (3) alcohol consumption to an extent that interferes with the drinker's health (physical or psychological), interpersonal relations, or economic functioning.

Early warning signs of alcoholism include drinking alone, drinking early in the day, the need to drink in anticipation of certain situations, an increase in the amount usually consumed, absenteeism due to hangovers, drinking sprees, blackouts, and preoccupation with thoughts about alcohol. Several different patterns of alcoholism have been described, including the skid row type, which constitutes from 5% to 8% of the alcoholic population. The remaining large majority of alcoholics retain some degree of integration with their families and communities.

Debates exist as to whether alcoholism should be considered a specific disease or a symptom of some more fundamental problem. An attempt has been made to differentiate between primary and secondary alcoholics. Persons diagnosed as having a psychiatric disorder that precedes the appearance of alcoholism are called secondary alcoholics. Those alcoholics having no such previous psychiatric history are primary alcoholics.

For us to understand the nature of alcoholism, two fundamental questions must be answered: How do people who will become alcoholic differ from people who will not? How specific is ethyl alcohol to this difference? Perhaps the most popular view, which may state the problem too simply, is that alcoholism is due to a specific need for alcohol, that is, without available alcohol there would be no such thing as alcoholism. A more inclusive view, proposed by some, is that the basic problem in alcoholism may be a personality configuration involving diminished ability to cope with stress and a tendency toward addictive (drug-seeking) behavior. Therefore, it is suggested that the preferential use of alcohol by certain individuals results from its easy access. There is some support for this argument in the findings that people who indulge heavily in psychoactive drug-taking also use large quantities of alcohol, and in the observation that persons who are alcoholic

frequently develop dependencies upon other agents, such as sedatives and minor tranquilizers. All of these agents may have common effects on individuals with particular personality predispositions.

Although physiological, biochemical, and psychosocial factors in alcoholism have been the subjects of vigorous research, at present little is known about the causes of alcoholism. Some recent studies have attempted to determine the manner in which genetic and environmental factors interact in the etiology of alcoholism.

Among the factors that have been invoked to explain alcoholism are moral weakness, cultural pressures, and influences within the family. It has been generally accepted that alcoholism is related more to environmental than to genetic factors. First, the very wide differences in the incidence of alcoholism among various groups are not easily explained by genetic factors alone. For example, the incidence of alcoholism among Irish-Americans is relatively high, but much higher than that of the Irish in Ireland. The rapid increase in the incidence of alcoholism in second- and third-generation Americans of certain ethnic groups, those of Italian and Jewish ancestry, for example, cannot be attributed to genetic factors alone. Several sociological factors appear to correlate with the low incidence of alcoholism in the original ethnic group. These include the use of alcohol within the family as a food, usually in a diluted form, the absence of stigma attached either to the use or refusal of alcohol, the absence of any association between the consumption of alcohol and ideas of manhood or virility, and the fact that excessive drinking is not socially acceptable. The increase in the incidence of alcoholism among Italian-Americans and Jews with assimilation into the broader American culture might in part be due to a dilution of the factors mentioned above.[88]

However, the existence of environmental influences in alcoholism does not necessarily minimize the contribution of genetic factors. Several recent lines of work point to important genetic differences in the physiological effects and metabolism of alcohol, as well as in the occurrence of alcoholism.

One study[89] has shown that the rate of metabolism of ethyl alcohol in persons appears to be largely under genetic influence. Fourteen pairs of twins, seven identical and seven fraternal pairs, were studied to ascertain the rate of alcohol metabolism after acute ingestion. All subjects abstained from alcohol and other drugs in the month prior to study. There was a wide variation in the rate of alcohol metabolism in the group as a whole. However, the rates of metabolism were almost identical in pairs of monozygotic twins and less similar in dizygotic pairs. The contribution of heredity to individual differences in the rate of ethanol metabolism was estimated to be 0.98, 1.00 indicating complete genetic control over the variability. It is possible that the individual differences in the rate of alcohol metabolism may be related to predisposition for alcoholism.

Another method by which biological predisposition to alcoholism has been studied is reported by Wolff,[90] who investigated the vascular flush response to the ingestion of alcohol in Oriental and Caucasian adults and infants. Differences in the flush response to alcohol between Oriental and Caucasian adults have been confirmed.[91] Wolff offers the intriguing speculation that the vascular response to alcohol and the unpleasant somatic symptoms that frequently accompany the ingestion of alcohol in Orientals might represent one mechanism by which a genetic factor could decrease the likelihood that alcoholism will develop in a given individual.

One group of researchers compared the incidence of alcoholism in half-siblings of alcoholics.[92] Each half-sibling shared one biologic parent with an alcoholic proband. The

half-siblings who had no alcoholic biological parent shared with the alcoholic probands only the experience of being raised in a home with an alcoholic parent. A high concordance with respect to alcoholism was found to exist only between half-siblings and their biological parents. Thus, it appears that being raised in a family with an alcoholic stepparent is not in itself sufficient to increase the likelihood that a child will become alcoholic. However, the authors point to several nongenetic factors that may contribute to their findings. For example, knowing that one's biological parent is alcoholic may influence subsequent drinking behavior. Similarly, the nonalcoholic parent may expect that the biological offspring of an alcoholic are destined to become alcoholics. These expectations may bring about "alcohologenic" changes in the parent-child relationship.

In another study the prevalence of alcoholism was compared between two groups of sons of alcoholic parents. One group of sons were adopted away as infants; the other group, their brothers, remained at home and were raised by their alcoholic parents.[93] High rates of alcoholism were found in both the adopted and nonadopted sons (25% and 17%, respectively). While length of exposure to the alcoholic parent was not associated with the development of alcoholism, the severity of the parent's alcoholism was. The results suggested that there is an important genetic contribution to the development of alcoholism in the sons of alcoholics.

Treatment

Several modalities are used in the treatment of alcoholism. Persons who are in acute stages of alcohol withdrawal may develop seizures or delirium tremens (DTs), a medical emergency that may be fatal if untreated. Treatment of DTs usually requires hospitalization, medication with minor tranquilizers such as chlordiazepam or chlordiazepoxide (Valium®, Librium®), and careful management of fluids and electrolytes.

Patients with chronic alcoholism have been helped by individual, family, and group psychotherapy, and by self-help programs such as Alcoholics Anonymous. The motivation of the alcoholic to abstain from drinking is crucial to the success of these interventions. Frequently all the important figures in the alcoholic person's world, including family, employer, coworkers, and friends, must be involved in establishing a life situation that will be conducive to diminished reliance on alcohol.

Medications that have been used in the treatment of the chronic alcoholic include disulfuram (Antabuse®), minor tranquilizers such as Valium® and Librium®, and, in selected patients, tricyclic antidepressants. Antidepressants may be useful if drinking occurs in the wake of a depressive episode and alcohol is used in an attempt to self-medicate.

Disulfuram can be an effective deterrent to alcohol ingestion. Following disulfuram, alcohol, even in small amounts, produces an unpleasant reaction that consists of flushing, apprehension, labored breathing, hypotension, nausea, and vomiting. Some physicians purposely induce a mild disulfuram-alcohol reaction in their patients to give them a preview of what to expect if they should drink while taking the drug. Although disulfuram is effective in promoting abstinence when regularly used, many alcoholics stop taking the drug, especially in the absence of external pressures. It is difficult to obtain patients' compliance to use the drug for prolonged periods of time. Alcoholics are more likely to stay with the medications in certain situations: Traffic courts may require habitually drunken drivers to appear each day for their medication in lieu of going to jail, and some military institutions have required alcoholic servicemen to report for medication to their com-

manding officer each morning. Clearly, in these situations the external contingencies provide considerable reinforcement for compliance.

The minor tranquilizers have been used to treat the anxiety that alcoholic patients claim leads them to drink. Indeed, many alcoholics enjoy taking these drugs and will request them from the physician, and it has been suggested that dependence on the minor tranquilizers differs little from dependence on alcohol. However, properly used, they can be useful temporary adjuncts to treatment, allowing patients to more easily give up their reliance on alcohol.

About 60% to 80% of alcoholics can benefit substantially with treatment, in that they have fewer episodes of drinking, miss fewer days at work, are better able to fulfill obligations to their families, and have an improved sense of well-being.

Reading Selection

The article *Alcohol Problems in Adoptees Raised Apart From Alcoholic Biological Parents* by Goodwin and coworkers describes a study that makes use of the "crossfostering" design in which infants removed from their biological parents for adoption are studied as adults. This procedure avoids possible confounding introduced by knowledge that a biological parent is alcoholic. Explicit definitions were used for the diagnosis of alcoholism and for different categories of drinking behavior in the probands. "Heavy drinkers" were defined as those who "for at least one year drank daily and had six or more drinks at least two or three times a month; or drank six or more drinks at least one time a week for over one year, but reported no problems." "Problem drinkers" had to meet the criteria for heavy drinkers, and, in addition, have some alcohol-related problems, but insufficient in number to meet the criteria for alcoholism. The diagnosis of alcoholism required the subject to meet all the criteria for the heavy drinker and meet other criteria, involving marital, occupational, legal, and medical problems related to alcohol use. The drinking patterns of 55 subjects with a biological alcoholic parent were compared with those of 78 subjects without alcoholic biological parents. The incidence of alcoholism in children of alcoholic biological parents was significantly greater than in the children of nonalcoholic parents. It is noteworthy, however, that heavy drinking and problem drinking were not very different in the two groups; only alcoholism as specifically defined in the report distinguishes these groups of offspring. The results seem to indicate that environmental and social factors account for drinking patterns other than alcoholism, while genetic factors contribute to the etiology of alcoholism as defined in this study.

Alcohol Problems in Adoptees Raised Apart from Alcoholic Biological Parents

Donald W. Goodwin, MD; Fini Schulsinger, MD; Leif Hermansen, MD; Samuel B. Guze, MD; and George Winokur, MD

Drinking practices and problems, plus a wide range of other life experiences, were studied in a group of 55 men who had been separated from their biological parents early in life where one parent had a hospital diagnosis of alcoholism. Compared to a matched control group of adoptees, significantly more of them had a history of drinking problems and psychiatric treatment. The two groups did not differ with regard to other forms of psychopathology, such as depression or character disorders.

Children of alcoholics had three times the divorce rate of the controls. Apart from alcohol problems and divorce, the two groups did not differ significantly with regard to any other variable studied. The adoptive parents of index and control subjects were of similar socioeconomic class and had similar rates of alcoholism and other psychiatric disorders. These findings suggest that genetic factors may play a role in the development of alcohol problems.

For years, studies have indicated that alcoholism is a familial disorder. By most estimates, at least one quarter of the fathers and brothers of alcoholics are likewise alcoholic.[1-5] The lifelong expectancy rate for alcoholism among men in the general population is believed to be about 3% to 5%.[6-10]

"Familial" is not synonymous with "genetic." Usually the biological parents of individuals are also important persons in their environment. One approach to separating "nature" from "nurture" is to study individuals separated from their biological relatives soon after birth and raised by nonrelative foster parents. Adoption studies, however, pose many problems. Obtaining access to adoption agency records may be difficult. Most agencies have little information about the drinking habits of parents

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whose children are placed for adoption. Among highly mobile people such as Americans, locating subjects is a formidable undertaking.

For these reasons a collaborative adoption study has been conducted in Denmark, a country where few of these difficulties exist. There is little immigration in or out of the country, and centralized national registries about adoptions, psychiatric hospitalizations, and criminal records can be made available for scientific purposes on sound discretionary conditions. The purpose of this study was to determine whether men raised apart from their biological parents were more likely to have drinking problems or other psychiatric difficulties if one of their biological parents was alcoholic than if there was no recorded alcoholism among their biological parents.

Method

The sample was obtained from a pool of 5,483 nonfamily adoption cases, namely, all such cases which took place in the city and county of Copenhagen, from 1924 through 1947. This pool of adoption cases was originally established as part of a family study of schizophrenia.[11] As part of the same study, all available psychiatric records from the adoptees and their biological and adoptive parents were screened. The sample consisted of an index group of probands who had a biological parent who had been hospitalized primarily for alcoholism. Having such a parent was a cardinal criterion for inclusion in the study as a proband. In addition, the proband group consisted entirely of males who had been separated from their biological parents before the first six weeks of life, were adopted by nonrelatives, and had no known subsequent contact with their biological relatives. By applying these criteria, 67 proband adoptees were selected for study. Only male adoptees were studied, since men are known to be at higher risk for alcoholism than are women.[1–10] Eighty-five percent of the alcoholic parents were fathers.

In choosing a control group of adoptees, the above criteria were all applied with one exception: none of the controls had a biological parent with a hospital record indicating alcoholism or alcohol abuse. Otherwise, they were matched with the probands by age, sex, and time of adoption. Two control groups were established. In one group, none of the controls had a biological parent with a record of psychiatric hospitalization. In the second control group, the adoptees had a biological parent at one time hospitalized for a psychiatric condition *other* than alcoholism. In this manner, 70 controls were chosen for the first group and 37 for the second. The controls consisted of adoptees closest in age to the probands who met the other selection criteria. The first control group was somewhat larger than the proband group in anticipation of possible deaths and other reasons for inability to study the individuals. Of the 37 controls who had a biological parent hospitalized for a psychiatric condition other than alcoholism, most had a diagnosis of depression or character disorder; schizophrenics were excluded.

A psychiatrist interviewed the subjects with no knowledge of whether they were probands or controls except in four instances where he correctly guessed the category because of knowledge that four controls were being added at the end of the study. The interviews were in Danish but recorded in English. They lasted two to four hours and followed a lengthy schedule eliciting information about demographic factors, the adoptive parents, psychopathology in the adoptees, drinking practices and problems, and a wide range of other life experiences. The study was not identified as an "adoption" study and subjects rarely volunteered information about their biological parents; no subject mentioned that

he had a biological parent with a drinking problem. Law enforcement records also were reviewed for information about the adoptees and their biological parents.

The interviews and records were sent to Washington University in St. Louis where coding, card punching, and computer analysis was performed, again without knowledge of the subjects' category. The study was "blind" from beginning to end.

Statistical tests were χ^2 (two-tailed, Yates correction) and "Student's" t for uncorrelated means (two-tailed).

Results

From the original sample of 174 men compiled from adoption records, 41 subjects were not located or refused to be interviewed. Of these, 14 were probands and 27 were controls. The proportion of unlocatable individuals and refusals was essentially the same in the proband and two control groups. One other subject was dropped from the study because it was impossible to establish which of two possible biological fathers was the real one. This left 133 subjects who were located and cooperated fully in the study. They consisted of 55 adoptees with an alcoholic biological parent (the proband group), 50 control adoptees with no recorded psychiatric hospitalizations among their biological parents, and 28 controls who had a biological parent psychiatrically hospitalized with a diagnosis other than alcoholism.

Analysis of the data revealed no significant differences between the two control groups. Therefore, the two groups were combined to provide a total control group of 78.

Table 1 compares demographic variables in the proband and control groups. As noted above, all subjects were men. The mean age in both groups was 30 with a range of 23–45 years at time of interview.

Table 1. Demographic characteristics of adoptees (%)

	Probands* (N = 55)	Controls† (N = 78)
Age 20–24	9‡	10
25–29	51	53
30–34	14	19
35–39	14	10
> 40	11	8
Marital history		
Ever married (never divorced)	62	74
Ever divorced §	27	9
Never married	11	17
Academic education		
< 9 yr	67	69
9–11 yr	24	23
12–15 yr	7	8
> 15 yr	2	0
Socioeconomic class		
Low	53	46
High	47	54
Served in military	67	72

* Refers in this and other tables to adoptees of alcoholic parentage. † Refers to adoptees of presumed nonalcoholic parentage. ‡ Figures rounded off to nearest whole number for ease of perusal. Sums may therefore not equal 100%. § $P < .02$.

Divorce was the only demographic variable that distinguished the two groups. The probands had a divorce rate three times greater than that of the control group ($P < .02$).

The data pertaining to education can be misleading, given the educational system in Denmark. "Academic" schooling is often followed by various forms of "vocational" or other training which are equivalent to high school or college education in the United States. The data presented conforms closely to academic education levels in the population from which the sample was drawn. Social class estimates were based on a rating scale adapted from Svalastoga[12] used in other Danish adoption studies.

Table 2 presents information about the adoptive parents. The home was "intact" when the subject lived with both adoptive parents from adoption until at least 16. Estimates of psychopathology in the adoptive parents were based on information provided by their adopted children and cannot be considered definitive. In general,

Table 2. Foster home experience (%)

Adoptive Home Characteristics	Probands (N = 55)	Controls (N = 78)
Home intact	87	86
Parental economic status		
Below average	15	19
Average	58	55
Above average	27	26
Parental psychopathology, any	42	50
Father* "depressed"		
Possible	2	8
Definite	7	4
Father "alcoholic"		
Possible	5	10
Definite	7	12
Father "antisocial"		
Possible	0	3
Definite	0	0
Father, any psychopathology	24	36
Mother "depressed"		
Possible	4	5
Definite	16	9
Mother, any psychopathology	29	28

* "Diagnoses" are based on the adoptees' observations and do not represent first-hand psychiatric observations.

the parents were considered depressed, alcoholic, or suffering from some form of psychopathology when they reportedly sought medical treatment for the condition.

In general, the two groups of adoptive parents were very similar. The adoptive parents of the probands tended to have somewhat more depression than did the adoptive parents of the controls, but the differences were not significant. The presumptive alcoholism rate actually was higher in the adoptive parents of the control group, but the difference again was not significant.

Table 3 compares psychopathology, exclusive of alcoholism, in the adoptees themselves. Diagnoses of anxiety neuroses, depression, and sociopathy were based on the criteria of Feighner et al.[13] The controls had somewhat more anxiety neurosis and depression than did the probands, but the differences were not significant. Nor were they significant with regard to sociopathy and drug abuse. Various character diagnoses commonly used in Denmark are combined under the heading of "personality disturbance." Total psychopathology rates, exclusive of alcoholism, were almost identical in both groups.

With regard, however, to psychiatric treatment and hospitalization, the two groups differed significantly. (Psychiatric treatment refers to any type of treatment—verbal or pharmacological—administered by any health professional for a mental or emotional problem.) Nearly half of the probands had received psychiatric treatment as compared to one quarter of the controls. The probands had five times the rate of psychiatric hospitalization compared to the controls. Of the eight probands who had been hospitalized, six were alcoholic by criteria presented in Table 5. Of the two controls who had been hospitalized, neither was alcoholic.

Four of the six hospitalized alcoholics were definitely, according to their hospital records, admitted for alcohol-related problems; records were not available for the other two. Thus, alcoholism, as defined in Table 5, contributed to the disproportionately high rate of hospitalization in the

Table 3. Psychopathology in adoptees (%)

	Probands (N = 55)	Controls (N = 78)
Anxiety neurosis		
Possible	16	18
Definite	2	10
Depression		
Possible	13	17
Definite	2	3
Sociopathy		
Possible	0	3
Definite	5	3
Drug abuse		
Possible	4	1
Definite	5	1
Personality disturbances, other (excluding above)*	51	53
Psychopathology, any (excluding alcoholism)	56	53
Psychiatric treatment, any†	40	24
Psychiatric hospitalization‡	15	3

* Refers to a variety of character diagnoses commonly used in Denmark, eg, anti-aggressive personality, compulsive personality, sensitive-insecure personality. Most of these are not synonymous with "psychiatric illness" as term is commonly used.
† $P < .01$. ‡ $P < .05$.

proband group. This also may be true with regard to psychiatric treatment in general. Of the 55 probands, 22 had received psychiatric treatment, nine of whom were alcoholic by these criteria. In the control group 19 had received psychiatric treatment, two of whom were alcoholic. The difference between the alcoholics in the two groups who received treatment was significant at the .02 level.

Since outpatient records were not available, it was impossible to determine how many of the alcoholics who received outpatient treatment were treated primarily for alcohol-related problems. Nevertheless, the strong correlation of alcoholism and psychiatric treatment suggests the two may be related.

Table 4 lists problems associated with drinking reported by the adoptees. Almost without exception, the proband group had more drinking problems than did the control group. With regard to five variables, the differences between the two groups were statistically significant. "Hallucinations" in Table 4 refers to auditory or visual perceptual distortions associated with withdrawal from alcohol. "Lost control" refers to the experience of wanting to stop drinking on a particular drinking occasion but being unable to do so. "Morning drinking" refers to repeated morning drinking, not just one or two before-breakfast drinking experiences.

The proband group had an average of 2.05 alcohol-related problems. The control group had an average of 1.23 alcohol-related problems. Subjects in both groups were ranked according to number of alcohol symptoms reported. The difference between the two groups was significant at the .02 level ($t = 2.49$).

Table 4 also compares the two groups with regard to how many subjects in each received treatment specifically for alcoholism and how many were hospitalized with a known diagnosis of alcoholism or alcohol abuse. Five probands reported receiving treatment for a drinking problem; all received disulfiram (Antabuse). This compared to one subject in the control group who had received treatment for a drinking problem; he had never received disulfiram. Four probands had been hospitalized for a problem known to be alcoholic in nature; as noted above, two other probands may have been hospitalized for this reason, but records were not available. No subject in the control group had been hospitalized for an alcohol problem.

Table 4. Comparison of drinking problems and patterns in two adoptive groups (%)

	Probands (N = 55)	Controls (N = 78)
Hallucinations*	6	0
Lost control†	35	17
Amnesia	53	41
Tremor	24	22
Morning drinking†	29	11
Delirium tremens	6	1
Rum fits	2	0
Social disapproval	6	8
Marital trouble	18	9
Job trouble	7	3
Drunken driving arrests	7	4
Police trouble, other	15	8
Treated for drinking, any*	9	1
Hospitalized for drinking	7	0
Drinking pattern		
Moderate drinker	51	45
Heavy drinker, ever	22	36
Problem drinker, ever	9	14
Alcoholic,ever†	18	5

* $P < .05$. † $P < .02$.

The last item in Table 4 represents a composite picture of drinking patterns based on quantity and frequency of drinking as well as problems associated with drinking. Criteria for the four drinking categories are shown in Table 5. Using these criteria, ten of the 55 probands were described as "alcoholic" as compared to four of the controls. In other words, the probands had nearly four times the alcoholism rate as did the control group. Comparing alcoholics with other drinkers results in a statistical difference between the two groups at the .02 level ($\chi^2 = 5.835$).

Table 5. Criteria for drinking categories

Moderate drinker	neither a teetotaler nor heavy drinker.
Heavy drinker	for at least one year drank daily and had six or more drinks at least two or three times a month; or drank six or more drinks at least one time a week for over one year, but reported no problems.
Problem drinker	(a) Meets criteria for heavy drinker.
	(b) Had problems from drinking but insufficient in number to meet alcoholism criteria.
Alcoholic	(a) Meets criteria for heavy drinker.
	(b) Must have had alcohol problems in at least three of the following four groups:
	GROUP 1: Social disapproval of drinking by friends, parents
	Marital problem from drinking
	GROUP 2: Job trouble from drinking
	Traffic arrests from drinking
	Other police trouble from drinking
	GROUP 3: Frequent blackouts
	Tremor
	Withdrawal hallucinations
	Withdrawal convulsions
	Delirium tremens
	GROUP 4: Loss of control
	Morning drinking

No one in the study was a teetotaler. Heavy and problem drinking, as defined in Table 5, occurred somewhat more frequently in the control group than in the proband group but the differences were not significant. Only alcoholism, as defined in Table 5, significantly distinguished the two groups. The mean age of subjects in all four drinking categories was the same—about 30.

To be categorized as "heavy drinker," "problem drinker," or "alcoholic," the subject must have drunk in a manner to meet the criteria for at least a year's period *at some time in his life*. Information was also obtained to determine whether the period of maximal drinking was "current" or had occurred at least a year prior to the interview. Eight of the probands and three of the controls were currently alcoholic, as defined in Table 5. The difference between the two groups was significant at the .05 level ($\chi^2 = 4.8671$).

In addition to the criteria for alcoholism presented in Table 5, the Danish psychiatrist (L.H.) who performed the interviews ranked the subjects on a 4-point scale ranging from the mildest drinkers with the fewest problems to the heaviest with the most. (The heaviest group comprised individuals who, according to the *World Health Organizational International Classification of Diseases*, ed 8, would be diagnosed in a group of alcoholic psychoses together with cases of excessive, episodical drinking [303.], excessive habitual drinking [303.1], and alcohol addiction [303.2].) Using this scale, the proband group had twice the number of "heaviest" drinkers than did the control group. By rejecting cases where there was disagreement between the diagnosis based on criteria presented in Table 5 and the "heaviest" drinker category, there were eight subjects in the proband group having the most severe form of alcohol problem, compared to three in the control group. The difference was significant at the .05 level ($\chi^2 = 4.8670$). Where specific "problems" were the basis for diagnosis, therefore, there was no disagreement and the difference between the proband and control group was statistically significant, with the proband group having a disproportionately higher number of alcoholics.

Table 6 presents variables that could be construed as reflecting "orality" as well as judgments by the interviewer regarding whether the subjects were unusually creative, interested in philosophy and religion, was sports minded, or had severe "self-esteem" problems. Only one comparison was significant. The controls tended to be somewhat more "artistic-creative" than did the probands. There was no evidence of greater "orality" in either group.

The two groups were also compared with regard to whether they had *any* form of psychopathology, including alcoholism, var-

Table 6. Comparison of two adoptive groups, miscellaneous (%)

	Probands (N = 55)	Controls (N = 78)
Heavy smoker	49	37
Marked oral traits, global	11	22
"Great" liking for food	20	23
Artistic-creative*	66	82
Religious-philosophical	15	18
Sports-minded	53	46
Marked self-esteem problems	4	3
Psychopathology by diagnosis, any (including alcoholism)	22	18
Psychopathology by diagnosis† and/or impression; any (including alcoholism)	62	69

* $P < .05$. † For explanation of high figures, refer to Table 3. In other Danish adoption studies, control samples have also demonstrated a rather high prevalence of psychopathology. Information about rates of psychopathology in a comparable group of nonadoptees is currently being obtained.

ious character diagnoses, and those psychiatric conditions defined by specific criteria referred to above.[13] In the proband group, 62% had some form of psychopathology, based either on specific diagnostic criteria or implicit criteria based on the judgment of the interviewer. This compared with 69% in the control group. Limiting the term "psychopathology" to conditions where specific criteria were used, 22% of the probands and 18% of the controls were suffering from one or more of these psychiatric conditions. In short, differences between the two groups with regard to total psychopathology were negligible. Only alcoholism, particularly when defined by criteria based on problems from drinking, significantly distinguished the two groups.

Since four controls received a diagnosis of alcoholism, conceivably one or more might have had an alcoholic biological parent who had not been hospitalized and therefore had no medical record of alcoholism. Police files also were available. None had a parent with a police record.

Sixteen of the 55 biological parents of probands had been arrested for alcohol intoxication, compared to ten of the 78 control parents ($\chi^2 = 4.441$, $P < .02$). This provided additional evidence of the validity of the hospital diagnosis of alcoholism in the parents of the probands.

Law enforcement records also were screened to learn how many of the adoptees had a police record. In both groups, 44% had some police record, almost always for minor offenses. Twenty percent of probands had been arrested for intoxication compared to 10% in the control group. The difference, however, was not statistically significant. The only significant difference between the two groups pertained to subjects who received "treatment" instead of being jailed or fined for their offense. Eleven percent of the probands had received treatment compared to 1% of the controls, a difference at the .01 level. What "treatment" consisted of, or how often it may have directly or indirectly been related to alcohol abuse, could not be determined from the records.

As shown in Table 2, about 13% of the probands had an adoptive father designated by the interviewed adoptee as a "possible" or "definite" alcoholic, compared to about 22% in the control group. Of the ten alcoholic probands, two had an adoptive parent considered alcoholic. Among the four alcoholic controls, one had an alcoholic adoptive father. There was no significant correlation between the drinking pattern of the adoptees and the presence or absence of alcoholism in the adoptive parents.

Comment

The data indicate that children of alcoholics are more likely to have alcohol problems than are children of nonalcoholics, despite being separated from their alcoholic parents early in life. All individuals in the study were separated from their biological parents before the first six weeks of life and raised by nonrelatives without known subsequent contact with their natural parents. Nevertheless, by their late 20's or earlier,

offspring of alcoholics had nearly two times the number of alcohol problems as did children of individuals without a record of hospitalization for alcoholism.

Judgment regarding the presence or absence of a "problem" was made by a trained psychiatrist with no knowledge of the parentage of the subjects being interviewed. This "blindness" was rigidly maintained from the beginning of the study until data analysis was completed.

The primary focus of the study was on alcohol problems and not on "alcoholism." The latter term lends itself to such a divergent range of definitions that whatever definition is used can be challenged by those who disagree with it. It should be emphasized, therefore, that "alcoholism" as used in this paper involves applying criteria which are arbitrary; a certain minimum number of problems are required before the diagnosis is made and no single problem is considered diagnostic. Nor is the diagnosis based on quantity and frequency of drinking, although generally problems are directly correlated with amount of alcohol consumed.

However, the criteria used in this study have been used in previous studies and been validated against official records indicating a serious drinking problem.[14,15] In any case, alcoholism, as defined here, did distinguish the two groups, with the offspring of alcoholics receiving the diagnosis nearly four times more often than the offspring of presumed nonalcoholics. (Presumed means there was no hospital record of alcoholism among the biological parents of the control group; it is possible that some of the parents of the controls were alcoholic but had not been hospitalized.)

Perhaps the most objective measure of increased alcohol problems in the proband group was the extent of psychiatric treatment in the group. Eight of the 55 probands had been psychiatrically hospitalized as compared to two of the 78 controls. Moreover, six of the eight probands hospitalized were diagnosed as alcoholic by criteria in Table 5. None of the four controls with a diagnosis of alcoholism had been hospitalized. Nine of the ten alcoholic probands had received psychiatric treatment, compared to one of the four alcoholic controls. Finally, when *current* alcoholism was the dependent variable, the probands were significantly more likely to be considered current alcoholics than were the controls, suggesting their problems were possibly more severe and intractable.

In ranking the subjects on a 4-point scale, there were some discrepancies between the judgment of the interviewing psychiatrist, where quantity of alcohol consumed was a factor, and the diagnosis based on purely problem-type criteria. Even so, the probands were significantly more alcoholic than the controls when the comparison was restricted to those cases where there was agreement between the two approaches.

Apart from alcoholism, the two groups were virtually indistinguishable with regard to other types of psychiatric illness and life experiences, with one exception: divorce. The probands were three times more likely to be divorced than were the controls. Drinking did not appear to be related to the higher divorce rate. Moderate drinkers in the proband group were as likely to be divorced as heavy drinkers and alcoholics. Divorce and alcoholism have often been associated, but the former has generally been attributed to disruptive effects of the latter. Our data suggest that divorce and alcoholism may perhaps be co-variants of a single or related genetic predisposition.

Concerning both alcoholism and divorce, it is important to note that most of the subjects have by no means transversed the age of risk for either of these problems. More than 60% of the subjects were still in their 20's at time of interview. It might have been expected that the alcoholics in the

present study would have been older on the average than the nonalcoholics. Subjects, however, had a mean age of 30 regardless of their drinking history. Studies by Amark[1] and others indicate that the age of risk for alcoholism is roughly from 20 through 45. Therefore, it is possible that the alcoholism rates, as well as divorce rates, will continue to increase over the next two decades, although whether the difference between the proband and control groups will continue to widen cannot be predicted.

The finding that, apart from divorce, *only* alcoholism significantly distinguished the two groups suggests there may be a specificity in the transmission of the disorder heretofore underestimated. The rates of diagnosable depression, anxiety neurosis, sociopathy, and drug addiction were fairly low in both groups and neither group had a significantly higher rate of one of these conditions than did the other. Also, it is interesting that heavy and even problem drinking, as defined in this paper, fail to distinguish the two groups. If anything, there was somewhat more heavy and problem drinking in the control group than in the proband group, although the differences were not significant. This suggests that severe forms of alcohol abuse may have a genetic predisposition but that heavy drinking itself, even when responsible for occasional problems, reflects predominantly nongenetic factors.

It should be emphasized that "genetic predisposition" remains more probable than proven, and certainly may not apply to *all* alcoholics. The adoptees, after all, as a rule spent the first few weeks of life in the care of at least their biological mothers. Wives of alcoholics may well differ from wives of nonalcoholics and conceivably the mothers of the probands in some cases were themselves alcoholic or had other forms of psychopathology, leading to neglect or other kinds of pathogenetic influence on their children. Although this possibility cannot be ruled out, it would seem somewhat farfetched with regard to explaining the findings as a whole.

Another nongenetic factor that may have biased the results was selectivity in the process of adoption. Possibly, those infants having a known alcoholic parent at time of adoption may have been matched with less "desirable" parents than were children of presumed normal parentage. Adoption practices in Denmark 20 to 50 years ago are difficult to assess. From an adoption study of criminality also conducted in Denmark, it appears that a bias did occur in the adoption process, but only at the extreme ends of the social spectrum. In other words, upper-class adoptive parents tended to receive upper class biological children, and low-class adoptive parents received low-class adoptive children. However, in the very large medium group there was no evidence of bias. Moreover, since the adoptive parents of the two groups did not differ with respect to economic status or other demographic variables, including divorce, it would appear that a selective bias in adoption was minimal at most.

Other evidence for and against a genetic predisposition to alcoholism was recently reviewed by Goodwin.[16] The nature-nurture problem in alcoholism has been approached in various ways, but two studies are particularly relevant to the present one. In the early 1940's Roe and Burks[17] obtained information about 49 foster children in the 20 to 40 year age group, 22 of normal parentage and 27 with a biological parent described as a "heavy drinker." Among children with heavy drinking parents, 70% were users of alcohol, compared to 64% in the control parentage group. In adolescence, two children of "alcohol-parentage" got into trouble because of drinking too much as compared to one in the "normal-parentage" group. The authors found that adopted children of heavy drinkers had

more adjustment problems in adolescence and adulthood than did adopted children of nonalcoholics, but the differences were not significant, and neither group had adult drinking problems. They concluded there was no evidence of hereditary influences on drinking.

This conclusion, however, can be questioned on several grounds. First, the sample was small. There were only 21 men of "alcoholic" parentage and 11 of normal parentage. Since women, particularly at the time of the study, were at very low risk for alcoholism, discovering they had no problem with alcohol was not unexpected. Second, although the biological parents of the proband group were described as "heavy drinkers," it is unclear how many would justify a diagnosis of alcoholism. Most had a history of antisocial behavior and apparently none had been treated for a drinking problem. By contrast all of the biological parents of the proband group in the present study received a hospital diagnosis of alcoholism, and at a time when this diagnosis was rarely employed in the country where the study took place.

Probands in the Roe and Burks study also differed from controls in other respects. They were older at time of placement and a much higher percentage was placed in rural areas or small towns where alcoholism rates are considerably lower than in urban areas.[18] In view of the finding in the present study of a high divorce rate among the children of alcoholics, it is interesting that Roe and Burks report that 35% of their probands were "unhappily married" compared to 20% of the controls. The difference was not significant, however, and further study is needed to confirm our findings.

More recently, Schuckit et al[19] also studied a group of individuals reared apart from their biological parents where either a biological parent or a "surrogate" parent had a drinking problem. The subjects were significantly more likely to have a drinking problem if their biological parent was considered alcoholic than if their surrogate parent was alcoholic. Studying 32 alcoholics and 132 nonalcoholics, most of whom came from broken homes, it was found that 62% of the alcoholics had an alcoholic biological parent compared to 20% of the nonalcoholics. This association occurred irrespective of personal contact with the alcoholic biological parent. Simply living with an alcoholic parent appeared to have no relationship to the development of alcoholism. Although the sample was relatively small, the results were significant at the .0005 level, and tend to support the findings of the present study.

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7. Psychoendocrinology

Neuroendocrine Function

The secretion of endocrine hormones is controlled through a multilevel system, each level regulated by those above it and responsive to feedback from those below. Information about environmental stress, hormonal feedback, and other factors may influence the neuroendocrine system, in part through noradrenergic, serotonergic, and dopaminergic systems in the hypothalamus.

These biogenic amine systems of the hypothalamus appear to contribute to the regulation of secretion of hypothalamic hormones, polypeptides manufactured in hypothalamic cells. The polypeptides vasopressin and oxytocin and the larger molecule neurophysin are synthesized in the cell bodies of the supraoptic and paraventricular nuclei of the hypothalamus and pass down axons to the posterior pituitary where they are released into the general circulation by a process termed neurosecretion.

Other hypothalamic hormones are not themselves released into the general circulation but are transported down axons and stored in nerve terminals near the median eminence of the hypothalamus. Here they are released into a capillary portal system that bathes the cells of the anterior pituitary; the anterior pituitary cells contain tropic hormones whose release into the general circulation is regulated by the hypothalamic hormones. At least nine hypothalamic regulatory factors have been demonstrated, six of them promoting and three inhibiting the release of anterior pituitary hormones. The six hypothalamic releasing hormones (RH) or releasing factors (RF) are thyrotropin releasing factor (TRF) luteinizing hormone or follicle stimulating hormone releasing factor (LH-RF/FSH-RF), growth hormone releasing factor (GH-RF), corticotropin (CR or ACTH) releasing factor (CRF), melanocyte stimulating hormone releasing factor (MSH-RF), and prolactin releasing factor (PRF). Release inhibiting factors have been demonstrated for growth hormone (GH-RIF, also known as somatostatin), melanocyte stimulating hormone (MSH-RIF), and prolactin (PRIF) (see Besser[94,95] for review). Although the present discussion is limited to the effects of the hypothalamic hormones on the anterior pituitary, it should be recognized that a good deal of research is currently addressed to the extrahypothalamic distribution and extraendocrine functions of these substances.[96,97]

The hypothalamic hormones regulate the secretion of the anterior pituitary hormones: corticotropin (CR or ACTH), thyroid stimulating hormone (TSH), growth hormone (GH), prolactin, luteinizing or follicle stimulating hormone (LH or FSH), and melanocyte stimulating hormone (MSH). Each hypothalamic hormone may influence more than one anterior pituitary hormone. For example, TRF stimulates prolactin release as well as TSH and FSH release; GH-RIF not only inhibits the release of GH; but also inhibits the release of TSH and FSH.

The anterior pituitary hormones control the secretion of such hormones as cortisol, thyroid, estrogen, and testosterone. Under normal conditions each of these hormones has a negative feedback effect that suppresses the release of the respective pituitary hormone.

The regulation of the peripheral endocrine system by the hypothalamus has been called "cascading amplification" since a few nanograms of hypothalamic releasing factor (10^{-9} gm) present in the median eminence can result in the release of much larger quantities of the pituitary hormones. The anterior pituitary hormones, in turn, stimulate their target organs to produce even greater amounts of endocrine hormones.[94]

Clinical Research

A variety of methods are available to identify and quantify hormones and their metabolites in various body fluids. These methods include gas chromatography and radioimmunoassay, techniques that permit the measurement of very small amounts of these substances. It has been possible to obtain small samples of serum from patients and normal subjects at frequent intervals by use of small-bore indwelling intravenous catheters, thus avoiding the stresses of repeated venipuncture. Studies in which serum samples have been drawn every 20 minutes around the clock have revealed that such hormones as cortisol are secreted in discrete pulses that follow a circadian rhythm. It should be recognized therefore that the value of single determinations of such hormones is limited.

While base-line measurements of naturally occurring hormones provide useful information about endocrine function, additional information can be obtained from stimulation and suppression tests. Stimulation tests are used to provoke hormone output at a particular level of the endocrine system. For example, ACTH can be administered to test the extent to which the adrenal cortex can secrete cortisol in patients with suspected Addison's disease (hypoadrenalism). In contrast, suppression tests are used to determine the responsiveness of a particular level of the endocrine system to feedback inhibition of its secretory activities; for example, dexamethasone, a synthetic corticoid hormone, will normally suppress ACTH secretion and is often administered in suspected cases of Cushing's syndrome (hyperadrenalism) to determine if ACTH release is less responsive than normal to suppression by serum corticoids (dexamethasone suppression test).

A number of stimulation tests are relatively specific for certain of these hormones and are relevant to current psychoendocrine research. The administration of insulin produces hypoglycemia, which in turn provokes the secretion of GH and ACTH (the latter hormone monitored in most clinical investigations by measurement of cortisol). The administration of L-DOPA provokes GH secretion and inhibits the release of prolactin. Some evidence suggests that noradrenergic and serotonergic hypothalamic neurons influence the regulation of ACTH, noradrenergic hypothalamic neurons influence GH, and dop-

aminergic hypothalamic neurons influence prolactin secretion. Therefore, it has been suggested that the response of these hormones to the different stimulation tests provides an index of the functioning of these biogenic amine systems in the hypothalamus.

Reading Selection

Current advances have made possible the formation of new hypotheses that link research on neuroendocrine function, brain biogenic amines, and psychiatric disorders. Some of this work is reviewed in the article by Sachar entitled *Hormonal Changes in Stress and Illness*. Many studies have shown that levels of adrenal corticosteroid, thyroid, estrogen, testosterone, aldosterone, insulin, and growth hormone can all be altered by psychological stress.[98] Indeed, considerable evidence supports the view that most hormonal aberrations observed in depression and schizophrenia are secondary to anxiety. For example, in schizophrenia elevated levels of cortisol accompany anxiety associated with acute psychotic episodes. Cortisol levels fall when the anxiety abates, irrespective of whether the other psychotic symptoms disappear or persist.[99] Also, while cortisol secretion is elevated in anxious depressed patients, it is usually not elevated in apathetic depressed persons. However, as discussed in Sachar's article, further work has suggested that neuroendocrine changes in at least some patients with depressive disorders are not solely stress-related.[100–102]

The pituitary-thyroid axis has also been implicated in the pathogenesis of depression, and TRF has been investigated for possible antidepressant properties. Although several laboratories report antidepressive effects for TRF,[103,104] these findings have not been replicated by others.[105–107] Thyroid hormone may speed the action of tricyclic antidepressants in the treatment of some clinical depressions but, the mechanism(s) through which this effect takes place and the significance of this finding, if any, for the pathogenesis of depressive disorders have not been elucidated.[108,109]

In spite of the preliminary nature of many of the results described above and the methodological problems that make interpretation of the data difficult, converging evidence suggests that the neuroendocrine system may be involved in the pathogenesis of some forms of depression. The role of neuroendocrine abnormalities in the etiology of such psychiatric disorders as schizophrenia[110,111] and anorexia nervosa[112–114] are also currently under investigation.

Hormonal Changes in Stress and Mental Illness

Edward J. Sachar, MD

The adrenal response to stress is well known, but many other hormonal systems normally are also highly sensitive to stress. In mental illness it is thus critical to separate out the nonspecific endocrine responses to the emotional distress accompanying serious psychotic processes. This difficult task is being facilitated by improved hormone assays, which reveal striking differences between depressed and normal subjects.

It is probably for historical reasons that when we think of the effects of stress on the endocrine system we tend to think first of epinephrine and corticosteroid secretion. Almost 50 years ago, Cannon demonstrated the epinephrine response to stress, and made it the basis of his hypothesis that the hormone mobilized the organism for "fight or flight" by acting on such physiologic functions as heart and respiratory rate, blood pressure, and fat and carbohydrate metabolism. Some years later, Selye called attention to the adrenocortical hormone response to stress. His General Adaptation Syndrome was mainly concerned with responses to physical stress, but his observation that psychologic stress could also stimulate adrenocorticotropic hormone (ACTH) and corticosteroid secretion stimulated a great deal of subsequent research.

In early studies on the effects of psychologic stress on ACTH and cortisol secretion, a major question was whether the hormonal responses really were a result of psychologic stimuli or were evoked by admixtures of physiologic stresses. Great pains were taken to design experiments that would eliminate any physical trauma. A classic example of purely psychologic stress is seen in rats that have become adapted to a particular cage. If they are then moved to a new, strange cage, their output of corticosteroids increases markedly. Another example is the conditioned emotional and endocrine response of monkeys to a red light paired previously with an electric shock. Even when they have learned to avoid all shocks by pressing a lever after the light signal, the monkeys still have a

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substantial increase in their cortisol secretion levels at the sight of the red light.

These and similar experiments proved that psychologic stress alone is a powerful stimulant of corticosteroid secretion, and attention soon turned to its effects in humans. Corticosteroid excretion patterns have been measured in normal subjects exposed to experimental psychologic stressors, as well as in people whose real-life situations involve severe emotional stress (e.g., parents of children dying of leukemia, soldiers undergoing basic training, and patients awaiting surgery).

In general, the adrenal response to stress in humans is not nearly as dramatic as in animals. It is apparent that human beings differ from animals in that they are very adept at finding ways to cope with stress. The stress response is present, but it is "damped down" by the system of psychologic defenses and coping devices through which we minimize our emotional reactions to threatening stimuli.

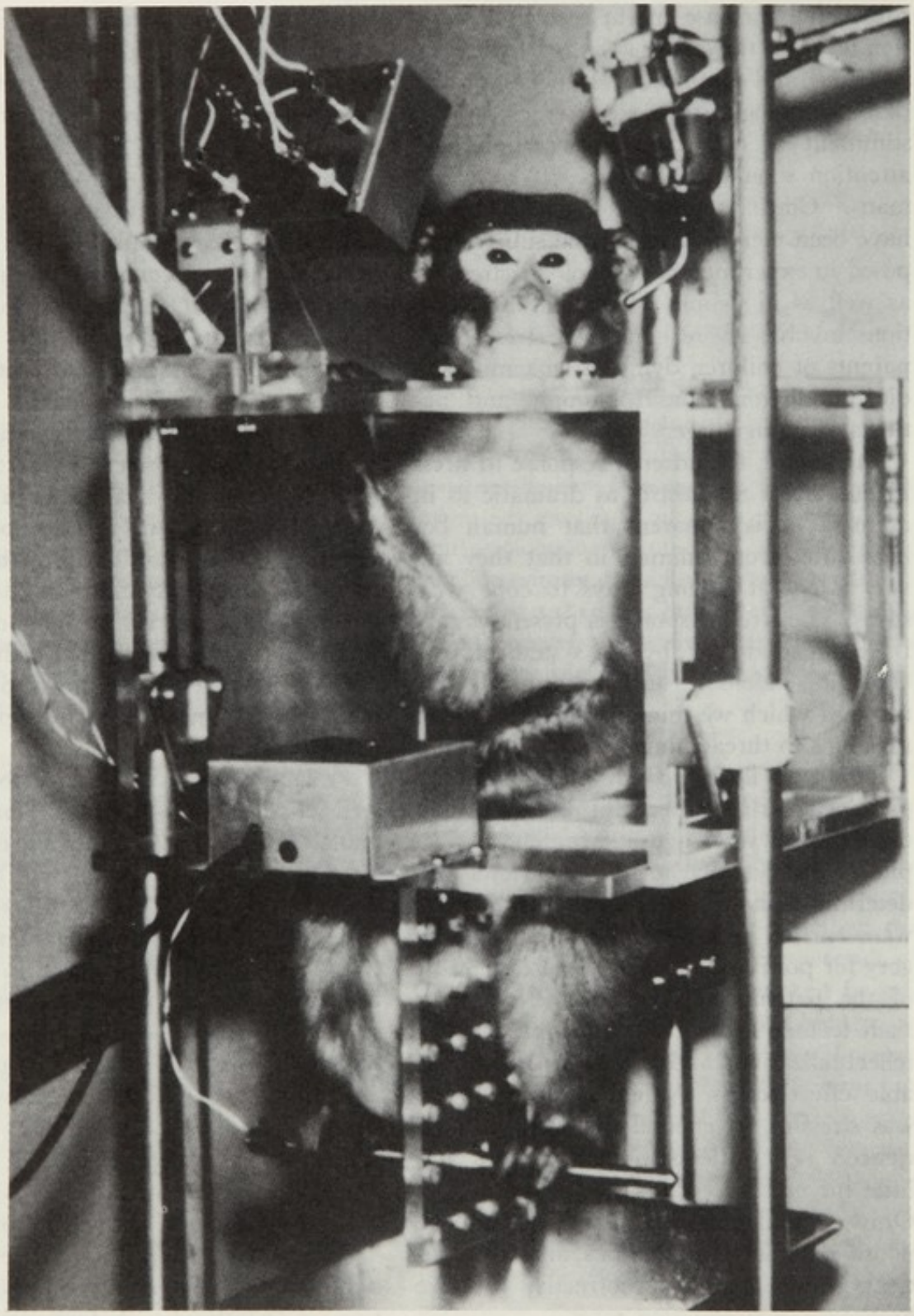
This was illustrated in a study of the psychoendocrine aspects of breast cancer done several years ago at Montefiore Hospital, in which psychologic interviews and determination of cortisol production rates were carried out in women awaiting surgery for possible cancer of the breast. Most of the patients coped with the stress by such techniques as denial, prayer, and intellectualization, and did so with remarkable effectiveness. Although the situation was stressful, in general the women experienced very little emotional distress and little increase in corticosteroid production. Only a small minority were judged to be poorly defended and anxious, and these patients were predicted, correctly, to have high cortisol production rates.

Interestingly, the most dramatic corticosteroid stress responses are seen in acutely psychotic patients whose defenses have broken down completely, for example acute schizophrenic patients who are in states of panic. The two- to threefold elevations in corticosteroid excretion that occur in these patients are similar to those found in stress studies conducted in laboratory animals.

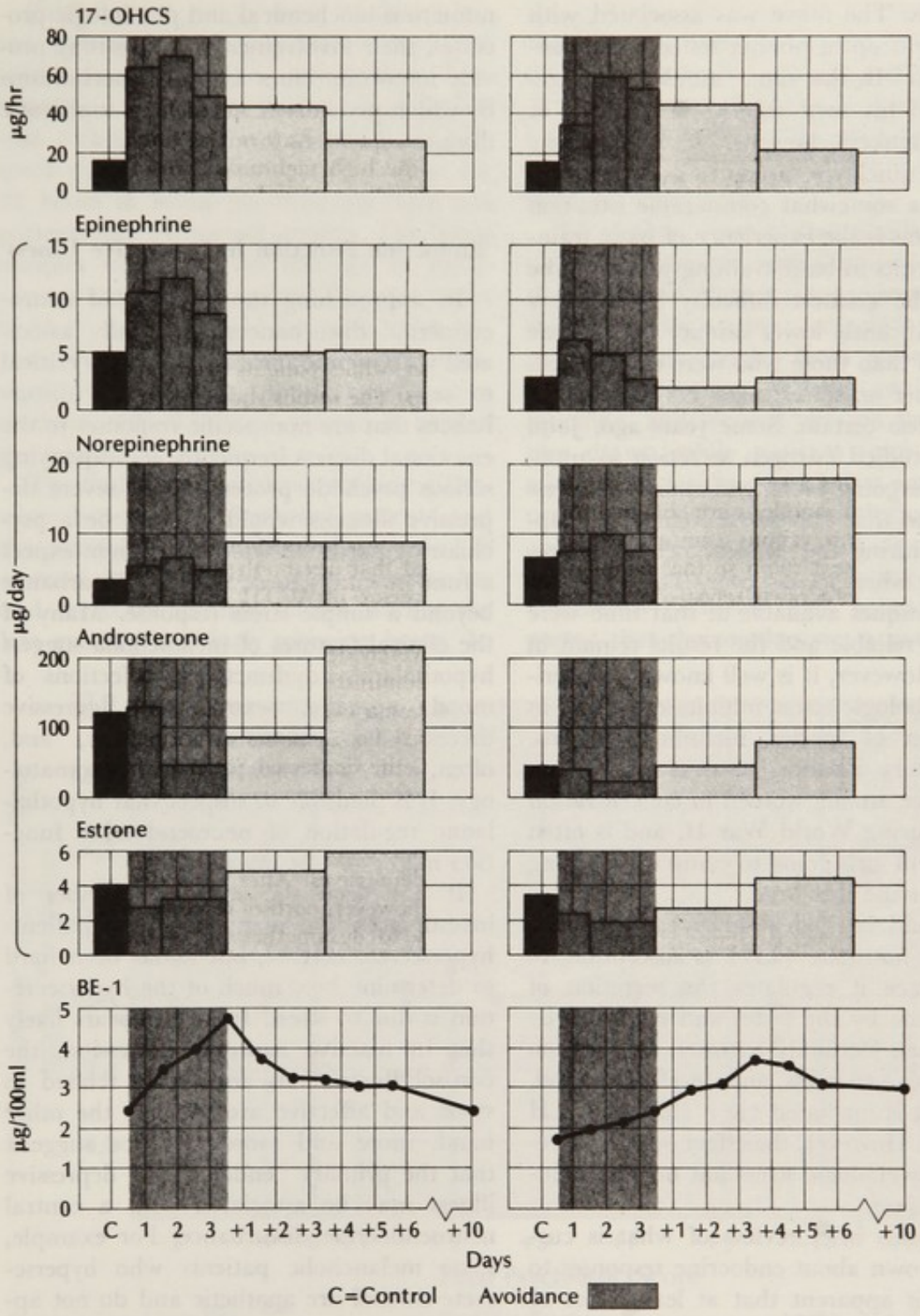
Improvements in hormone assay techniques in the last decade have led to a realization that many hormonal systems other than the adrenal are exquisitely sensitive to stress. It is apparent, for instance, that anxiety is a potent stimulus to growth hormone (GH) secretion in both animals and people. It is often apparent in routine tests for growth hormone secretion. If the patient is apprehensive, the mere anticipation of the insulin or arginine injection required for the test will cause a spurt of GH secretion. In fact, to do a growth hormone test, it is frequently necessary to put the patient at bed rest for an hour or so prior to the test to make sure that his growth hormone level has come down to base line, which in the normal fasting person approaches zero.

Prolactin also is responsive to stress, as well as to other psychologic stimuli. Normally, prolactin secretion increases during sleep and gradually declines to basal level after awakening. It is also markedly stimulated by nursing or nipple stimulation in women. A prolactin response to stress has been shown in animal studies and also in studies of people undergoing surgery or diagnostic procedures such as gastroscopy and proctoscopy. Recently, the results of a study done by Andrew Frantz and colleagues in paratroopers revealed a tremendous elevation in prolactin levels associated with jumping from great heights.

Another hormone that appears to be stress responsive, but in the opposite direction, is testosterone. A fascinating experiment demonstrating the testosterone response to stress involved taking a dominant male monkey from his own colony and introducing him to a strange colony where he



Experimental situation above was designed to evoke purely psychologic stress. After period of adaptation to restraining chair, monkey can avoid getting a mild electric shock from the footrest by pressing hand lever when a red light comes on. Yet the psychologic stress of the red light affects hormone secretion. Results in two monkeys (data from Dr. John W. Mason, Walter Reed Army Institute of Research) are graphed



above. There was a rise in urinary levels of corticosteroids (17-OHCS), epinephrine, and plasma BE-1, an index of thyroid hormone. Urinary androgen (androsterone) and estrogen (estrone) excretion appeared to be suppressed during stress, with rebound increases afterward.

lost status. The move was associated with a striking drop in plasma testosterone concentration. If the same monkey was returned to his own colony and harem of female monkeys, however, his testosterone secretion quickly returned to normal levels. Perhaps a somewhat comparable situation for humans is the experience of basic training. Recruits in basic training judged to be having the greatest difficulty in adapting had significantly lower urinary testosterone excretion than those who were coping well.

Whether or not estrogen is responsive to stress is less certain. Some years ago, John Mason studied estrogen secretion in monkeys undergoing prolonged avoidance stress and found that estrogen secretion was suppressed during the stressful period but rebounded when it was over. The biochemical techniques available at that time were not very reliable and the results remain in doubt. However, it is well known that serious psychologic stress inhibits ovulation in a number of species, including humans. Anovulatory amenorrhea was a common occurrence among women in concentration camps during World War II, and is often reported in girls going to camp or boarding school for the first time.

It would be logical to assume that luteinizing hormone (LH) is susceptible to stress, since it regulates the secretion of testosterone by the testes and estrogens by the ovaries. Certainly testosterone secretion is responsive to stress, and, in all likelihood, the effect is mediated via a change in LH secretion. However, the effect on LH secretion of psychologic stress has not been elucidated as yet.

From this brief review of what is currently known about endocrine responses to stress it is apparent that at least three of the pituitary hormones—ACTH, prolactin, and growth hormone—and at least two target gland hormones—testosterone and cortisol—are highly sensitive to stress. Since these hormones have widespread effects on numerous biochemical and physiologic processes, their involvement in stress may provide important clues as to the mechanisms by which psychologic stress leads to somatic diseases of various kinds.

Endocrine Function in Depressive Illness

In approaching the question of neuroendocrine disturbances specifically associated with mental illnesses, then, it is critical to separate out those endocrine disturbances that are nonspecific responses to the emotional distress frequently accompanying serious psychotic processes. The severe depressive illnesses would seem to be a psychiatric disorder in which one might expect a fundamental neuroendocrine disturbance beyond a simple stress response. Many of the clinical features of melancholia suggest hypothalamic dysfunctions, affections of mood, appetite, sexual and aggressive drives, sleep, autonomic activity, and, often, a diurnal variation in symptomatology. It is plausible to suspect that hypothalamic regulation of neuroendocrine function might also be involved.

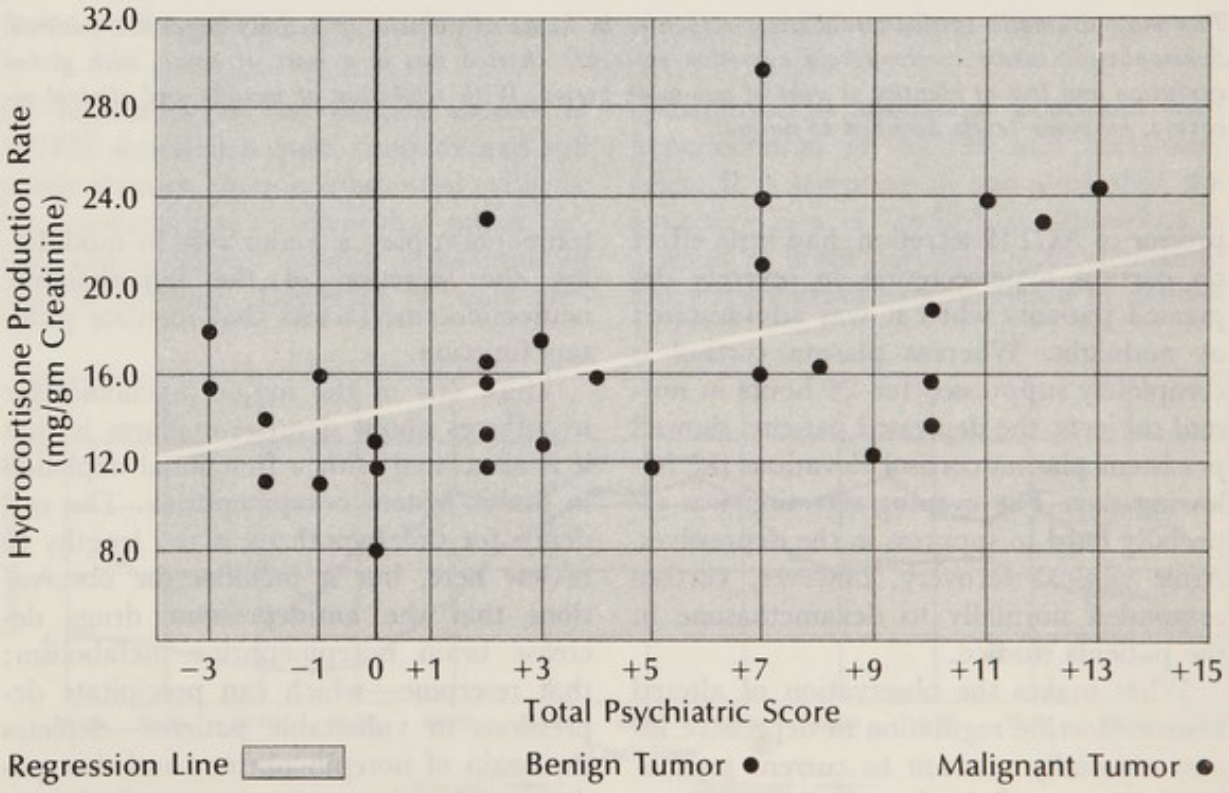
It has been shown by a number of investigators that many depressed patients hypersecrete cortisol, but it has been hard to determine how much of the hypersecretion is due to stress. It now appears likely that in reactive neurotic depression, the cortisol fluctuations are closely related to stress and affective arousal. On the other hand, more and more evidence suggests that the primary "endogenous" depressive illness may be associated with a central neuroendocrine disturbance. For example, some melancholic patients who hypersecrete cortisol are apathetic and do not appear affectively aroused. They do not show the signs of anxiety, fright, extreme grief or sorrow we ordinarily regard as hallmarks of distress, yet cortisol secretion is often markedly increased.

Furthermore, the 24-hour cortisol secretory pattern in such patients is distorted in ways that are hard to explain by a stress hypothesis. In studies done in conjunction with colleagues at Albert Einstein, we analyzed plasma cortisol every 20 minutes for 24 hours in seven psychotically depressed patients and 54 normal persons. The blood samples were obtained through an intravenous cannula strung into the next room so that samples could be withdrawn repeatedly without inconvenience to the patient. With the new techniques of microanalysis, only 0.1 cc of plasma is needed per analysis.

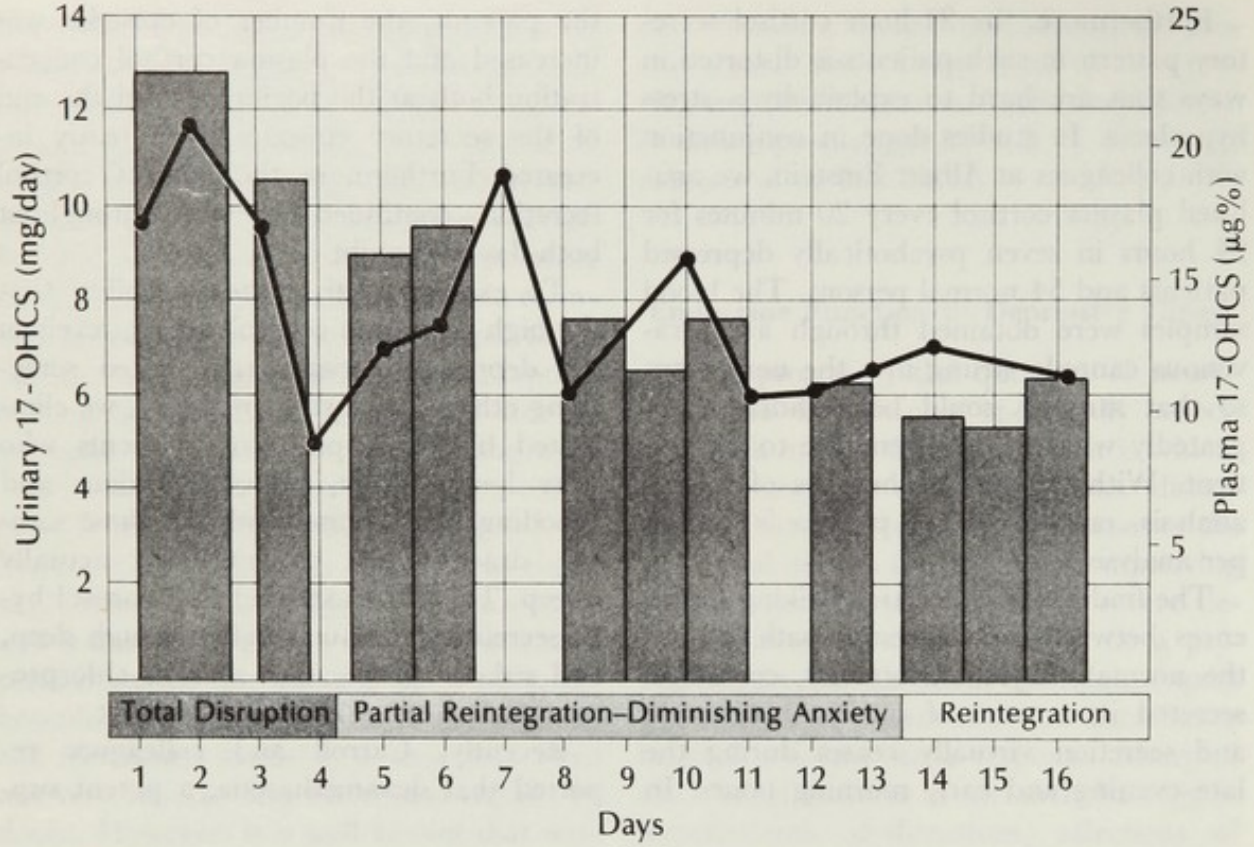
The findings revealed two striking differences between the depressed patients and the normal subjects. Normally, cortisol is secreted in a series of pulses or episodes, and secretion virtually ceases during the late evening and early morning hours. In the patients, the number of episodes was increased and the plasma cortisol concentration both at the beginning and the end of the secretory episodes was greatly increased. Furthermore, the patients' cortisol secretion continued actively throughout both day and night.

To explore further the possibility that the high nighttime cortisol plasma levels in the depressed patients represented something other than a stress response, we eliminated blood samples from patients who were lying awake, perhaps anxious and brooding, and focused only on those samples drawn while patients were actually asleep. The results showed that cortisol hypersecretion continued right through sleep, and sedative medication such as chlorpromazine had no effect in reducing it.

Recently, Carroll and colleagues reported that dexamethasone, a potent sup-



The adequacy of psychologic defenses against the threat of breast cancer was evaluated in 30 women awaiting biopsy for breast tumors and their corticosteroid secretion rate measured concomitantly. In general, those with highest psychiatric scores, i.e., whose psychologic defenses were failing, also had highest hydrocortisone production rates.

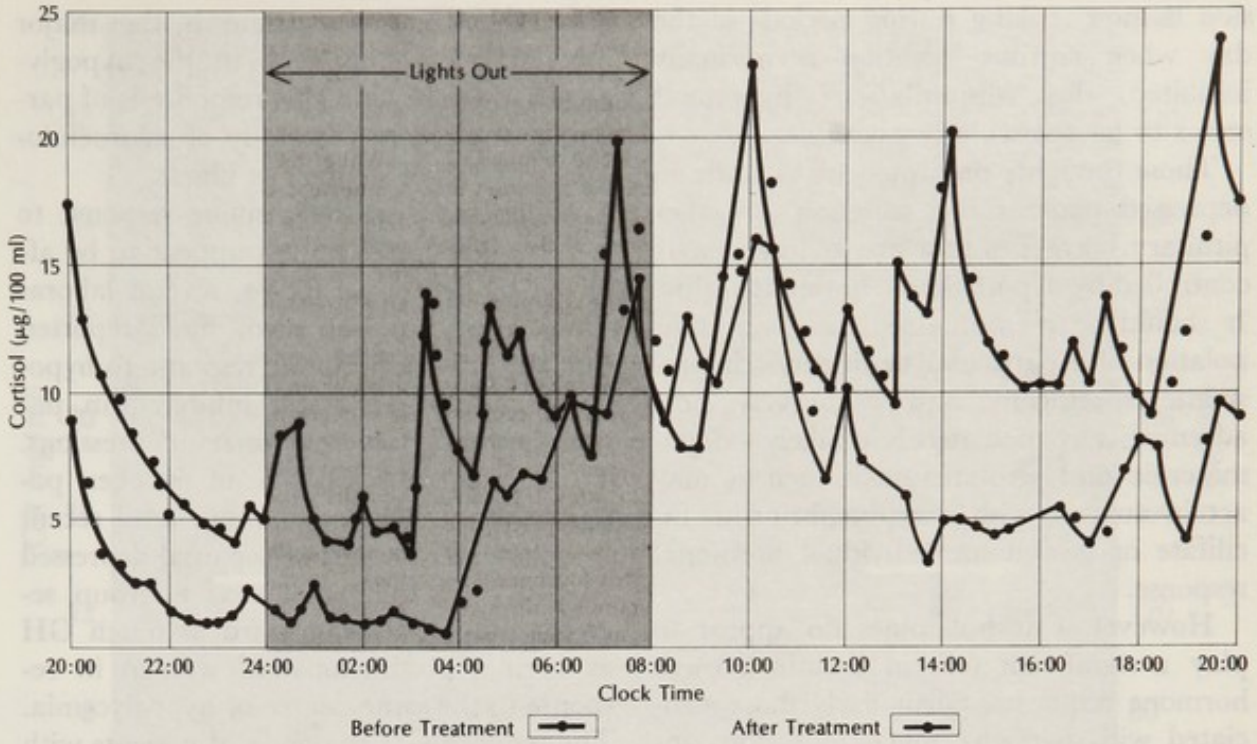


The most dramatic corticosteroid-stress responses in humans are seen in acutely psychotic patients. Schizophrenic whose corticosteroid excretion rates are charted was in a state of panic, with global confusion and loss of identity at start of two-week period. With resolution of anxiety and clinical recovery, hormone levels declined to normal.

pressor of ACTH secretion, had little effect on cortisol hypersecretion in severely depressed patients when it was administered at midnight. Whereas plasma cortisol is completely suppressed for 24 hours in normal subjects, the depressed patients showed persistent plasma cortisol elevations the following day. The evening secretion was especially hard to suppress in the depressives. After clinical recovery, however, cortisol responded normally to dexamethasone in the patients studied.

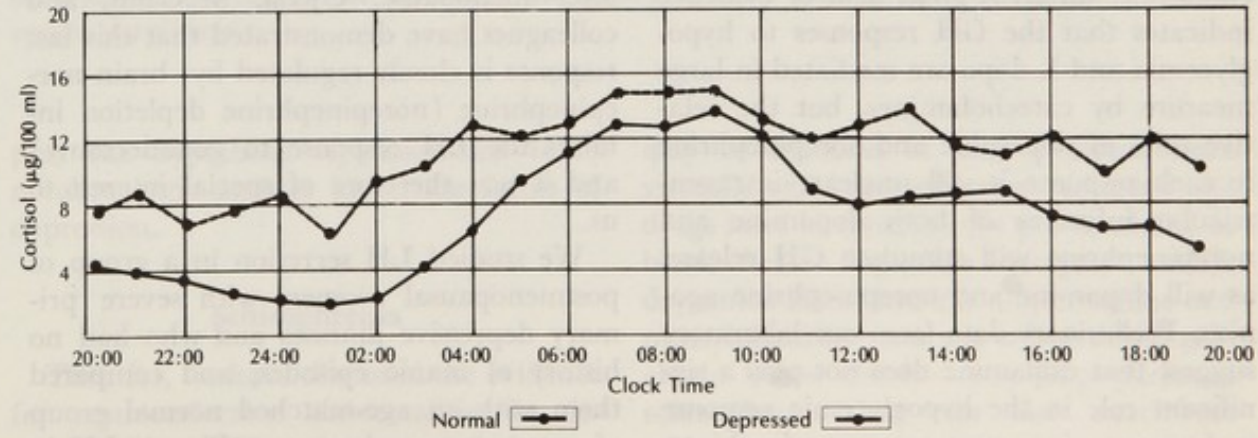
What makes the observation of altered neuroendocrine regulation in depressive illness especially relevant to current psychobiologic research is that the same neurotransmitters that have been implicated in the chemical pathology of affective disorders—norepinephrine, dopamine, and serotonin—also play a major role in modulating the secretion of the hypothalamic neuroendocrine factors that regulate pituitary function.

Thus, one of the major psychobiologic hypotheses about depressive illness is that it is associated with a functional depletion in limbic system norepinephrine. The evidence for this hypothesis is too lengthy to review here, but it includes the observations that the antidepressant drugs decrease brain norepinephrine metabolism; that reserpine—which can precipitate depressions in vulnerable patients—depletes the brain of norepinephrine; and that patients with primary "endogenous" depressions excrete less of the brain norepinephrine metabolite, methoxyhydroxyphenylglycol, in their urine. While the neurotransmit-



In a 62-year-old postmenopausal woman with severe primary depression, plasma cortisol levels (sampled every 20 minutes over 24 hours) were substantially elevated and secretion was abnormally active during evening and early morning hours.

ter regulation of the various aspects of ACTH secretion is quite complex and still partly obscure, there is substantial evidence for a noradrenergic system that under certain circumstances *inhibits* stress-induced ACTH secretion. Depletion of brain norepinephrine in animals is associated with hypersecretion of ACTH and corticosteroids. It is tempting to speculate that the hypersecretion of cortisol in depressives is a result of brain norepinephrine depletion. Since the cortisol hypersecretion in depres-



Plasma cortisol levels measured in seven depressed patients over a 24-hour period were distinctly elevated in comparison with levels obtained from 54 normal individuals. In addition, cortisol levels in the depressives did not show pronounced circadian variation characteristics of normals, in whom cortisol secretion markedly decreased late at night and early morning.

sion is most striking during periods of the day when cortisol secretion is normally inhibited, this "disinhibition" hypothesis seems to be particularly plausible.

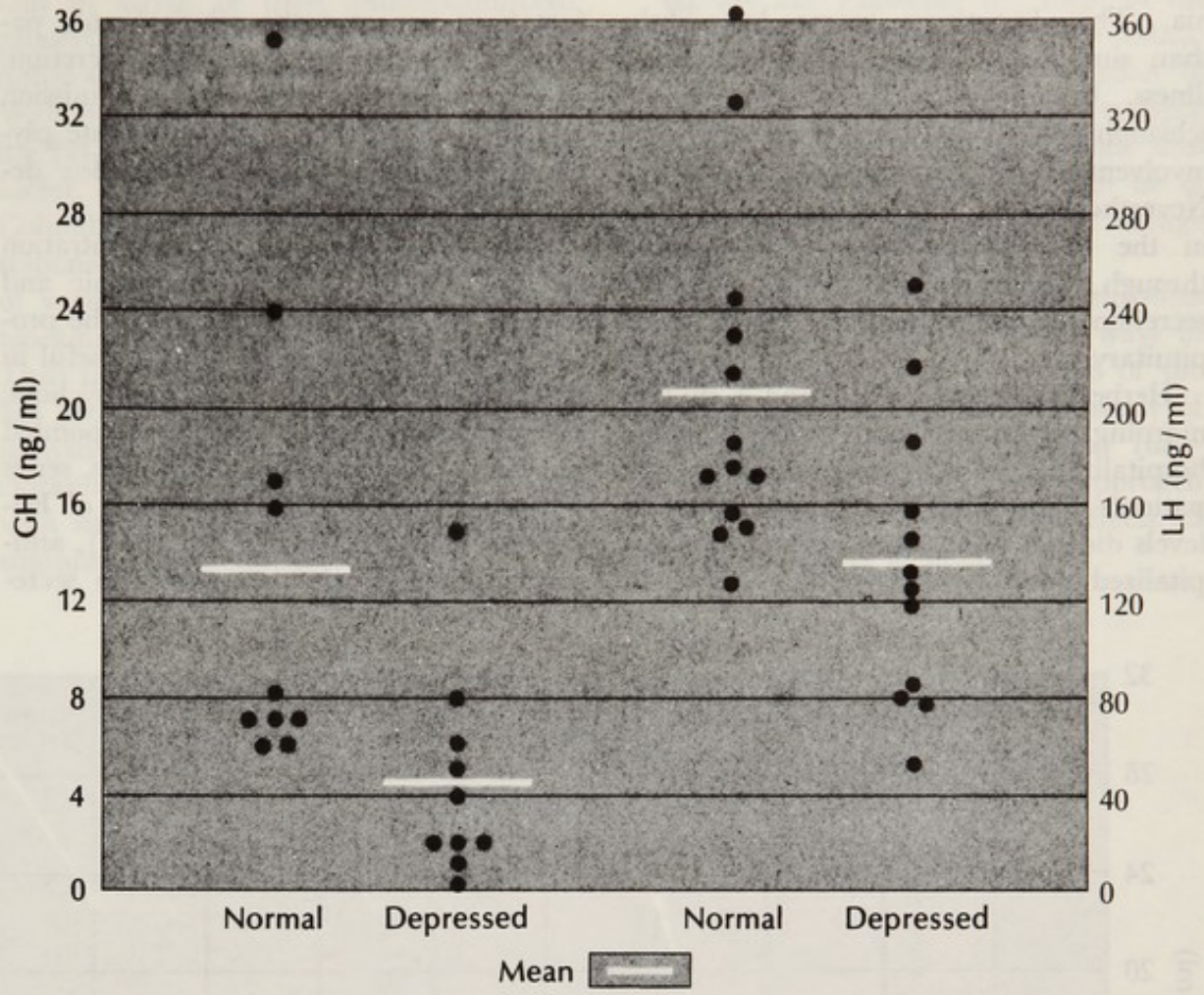
These thoughts prompted us to study in depressed patients the secretion of other pituitary hormones that are at least partly controlled by hypothalamic norepinephrine. It should be reemphasized, however, that isolation of a particular neuroendocrine response specifically and exclusively noradrenergically mediated is unlikely—dopaminergic and serotonergic influences may act in concert with norepinephrine to facilitate or inhibit an individual hormonal response.

However, catecholamines do appear to play a significant role in certain growth hormone responses, particularly those associated with hypoglycemia and L-dopa ingestion. GH secretion appears to be controlled by both releasing and inhibiting hypothalamic factors, and it occurs in response to a variety of stimuli—not only hypoglycemia and L-dopa ingestion but also slow-wave sleep, exercise, anxiety, and administration of arginine. All these responses are potentiated by estrogens. The neurotransmitters that mediate the responses to each of these stimuli may be different, or at least the balance of their influences may differ. A great deal of evidence indicates that the GH responses to hypoglycemia and L-dopa are mediated in large measure by catecholamines, but the relative roles of dopamine and norepinephrine in each response is still unclear; intraventricular infusions of both dopamine and norepinephrine will stimulate GH release, as will dopamine and norepinephrine agonists. Preliminary data from our laboratory suggest that dopamine does not play a significant role in the hypoglycemic response in humans, since pretreatment of subjects with pimozide, a specific dopamine receptor blocker, does not reduce the magnitude of the growth hormone response. Presumably, then, norepinephrine is the major mediating catecholamine in the hypoglycemia response, and this response is of particular interest in the study of neuroendocrine aspects of depressive illness.

While the growth hormone response to L-dopa ingestion does not appear to be affected by depressive illness, several laboratories, including our own, have reported that the growth hormone response to hypoglycemia is significantly inhibited in patients suffering severe primary depressions. To eliminate the variable of estrogen potentiation of GH secretion, our most recent study focused on postmenopausal depressed women, and the patients as a group secreted only about one third as much GH as normal postmenopausal women in response to the same degree of hypoglycemia. The reduced GH responses of patients with primary depressive illness might then be regarded as support for the hypothesis that reduced brain noradrenergic activity is implicated in these cases.

Another hormone in whose secretion catecholamines play a significant role is LH. Once again, there is a variety of LH responses to consider—including the rise at puberty, the spurt at ovulation, the fall in response to estrogens, and the rise when estrogens are removed by gonadectomy or after menopause. Ojeda, McCann, and colleagues have demonstrated that this last response is closely regulated by brain norepinephrine (norepinephrine depletion inhibits the LH response to gonadectomy) and it was therefore of special interest to us.

We studied LH secretion in a group of postmenopausal women with severe primary depressive illnesses and who had no history of manic episodes, and compared them with an age-matched normal group of postmenopausal women. Plasma LH in the depressed patients was significantly lower than in the normal subjects. Again, this observation—if replicated—could sup-



Growth hormone (GH) response to insulin hypoglycemia in postmenopausal women with severe primary depression was significantly inhibited compared to the response in normal postmenopausal women, as were values for luteinizing hormone (LH). Since norepinephrine is believed to be the major catecholamine mediating both GH response to hypoglycemia and LH response to menopause, these observations support the hypothesis that diminished brain noradrenergic activity has a role in certain depressions.

port the hypothesis of diminished brain noradrenergic activity in certain forms of depression.

Schizophrenia

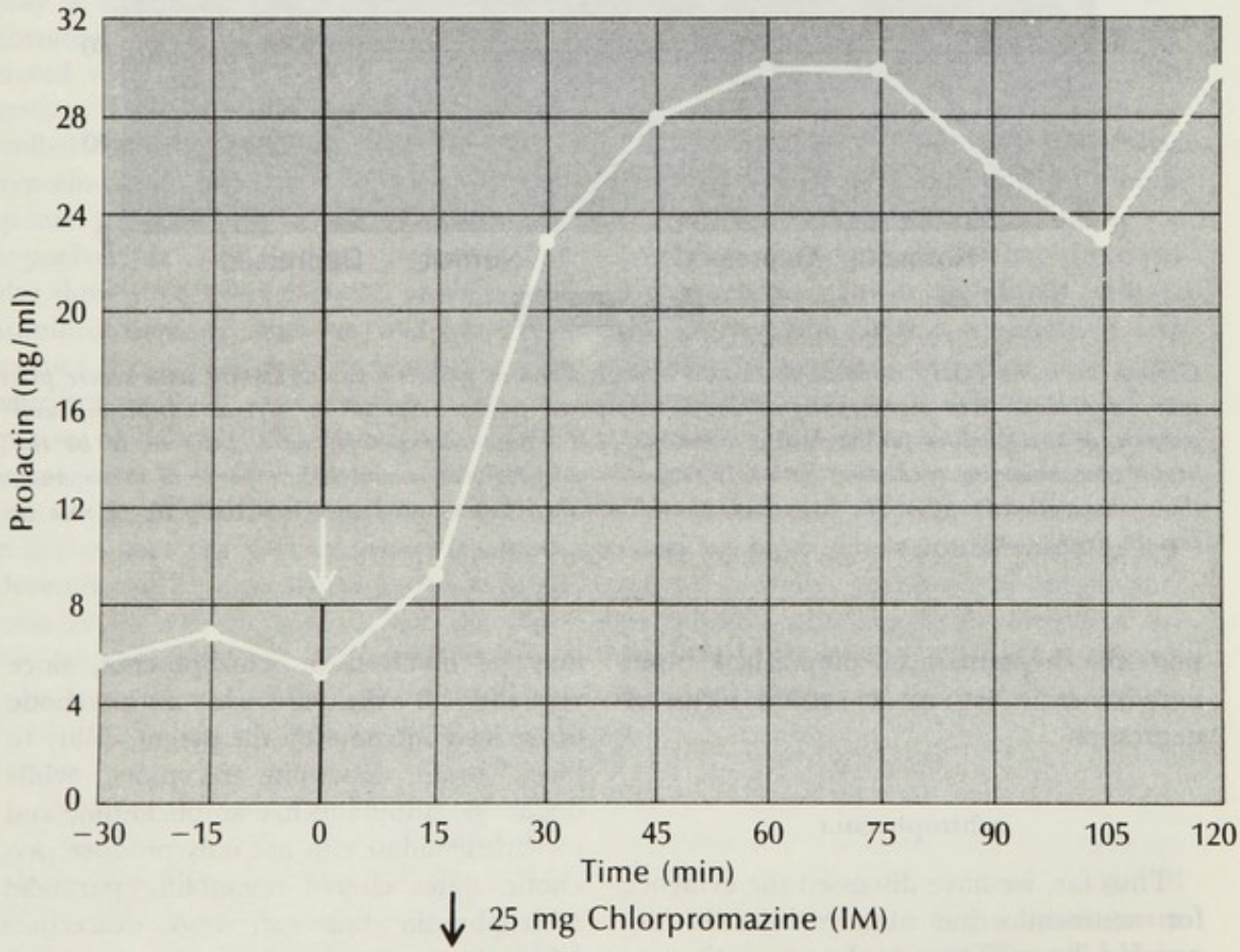
Thus far, we have discussed the evidence for neuroendocrine abnormalities in depressive illness. There is also currently considerable psychobiologic interest in the schizophrenic illnesses. Recent research has suggested that a brain dopamine system may be involved in schizophrenia, since virtually all the effective antipsychotic drugs have in common the potent ability to block brain dopamine receptors, while dopamine stimulants like amphetamine and methylphenidate can not only produce psychotic states closely resembling paranoid schizophrenia but can also exacerbate schizophrenic psychoses.

These observations raise the possibility that endocrine systems regulated by brain dopamine might be affected in schizophre-

nia. This hypothesis seems less likely than similar hypotheses about depressive illness, because the clinical features of schizophrenia do not suggest as clearly an involvement of hypothalamic functions. Nevertheless, a brain dopamine system in the tuberoinfundibular tact controls, through varying degrees of inhibition, the secretion of prolactin from the anterior pituitary.

Herbert Meltzer, Frantz, and I studied morning serum prolactin levels in newly hospitalized, unmedicated schizophrenic patients and found that their prolactin levels did not differ from normal, nonhospitalized control subjects. One might in fact have expected the schizophrenic patients to have elevated prolactin secretion, in view of the stress of hospital admission and the anxiety associated with acute psychotic decompensation. This paradox deserves further investigation.

While base line prolactin concentration did not differ between schizophrenic and normal subjects, measurements of the prolactin response appear to be most useful in the study of the effects of antipsychotic drugs in man. As L. A. Frohman pointed out in a previous article in this series ("Neurotransmitters as Regulators of Endocrine Function," HP, April 1975), antipsychotic drugs stimulate prolactin secre-



Plasma prolactin rose sharply in a 25-year-old schizophrenic male in response to 25 mg of chlorpromazine. Since dopamine inhibits prolactin secretion, and antipsychotic drugs have antidopaminergic properties, the prolactin response may prove to be a useful test of a drug's effectiveness in blocking brain dopamine receptors.

tion by virtue of their antidopaminergic properties. Indeed, galactorrhea is an occasional side effect of phenothiazine therapy. With colleagues at Albert Einstein, including Peter Gruen, Norman Altman, Marvin Liefer, and Frieda Halpern, and Frantz of Columbia, we have evaluated the prolactin response as a screening test for the efficacy of various classes of neuroleptic drugs in blocking brain dopamine receptors in man. Thus far, every potent antipsychotic agent has proved to be a prolactin stimulant in humans (with the possible exception of clozapine). Conversely, ineffective drugs with similar chemical structures have not stimulated prolactin secretion.

We are also exploring the value of the prolactin test as a semiquantitative indicator of the completeness and duration of dopamine blockade in patients receiving antipsychotic medication. Our results thus far suggest that this approach can be of value in regulating the therapeutic dosage of drugs in psychotic patients.

In summary, neuroendocrine measures appear to be of value in several ways in psychiatric research: as reflections of the stress response, as avenues to the study of hypothalamic and neurotransmitter function in mental illnesses, and as an approach to the assessment of the brain effects of psychotropic drugs in man.

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9. Glossary

ABNORMAL SPIKING. A type of atypical electrical activity identified in the electroencephalogram and associated with epilepsy and other central nervous system disorders.

ACTH. (Adrenocorticotropic hormone or adrenocorticotropin). A hormone secreted from the anterior pituitary (adenohypophysis) that stimulates secretion of adrenal corticol hormones.

AGE OF RISK. Age interval during which a particular disease is most likely to occur.

AGGLUTININ. A common form of antibody which interacts with the antigenic substance to produce an aggregating complex. For example, some bacterial agglutinins interact with bacterial antigens to produce clumps of the antigenic complex. *See also* antibody, antigen.

ALIQUOT. Sample portion removed from a large homogeneous quantity of material. Experimental analyses are performed on the sample (aliquot) in order to obtain information regarding the characteristics of the source from which it is taken.

ALPHA-METHYLMETATYROSINE. Compound which is metabolized to metaraminol in norepinephrine neurons. Metaraminol is believed to displace norepinephrine from its storage sites and is subsequently released by neural activity. Thus administration of alpha-methylmetatyrosine leads to the production of a false neurotransmitter substance.

AMENORRHEA. Absence of the menses.

AMITRIPTYLINE. A tricyclic antidepressant drug. *See also* tricyclic antidepressants.

AMYGDALA. One of the structures forming the temporal lobe of the brain. The amygdala is a part of the limbic system. *See also* limbic system.

AMYOTROPHIC LATERAL SCLEROSIS. A chronic progressive neurological disease of unknown cause characterized by muscle weakness and atrophy.

ANHEDONIA. Inability to experience pleasure.

ANOMALY. Abnormality.

ANOREXIA NERVOSA. A medical condition characterized by self-imposed severe diet and occasionally self-induced vomiting, usually resulting in marked and sometimes life-threatening malnutrition.

ANTIBODY. A type of protein which is produced in response to antigenic stimulation. In general antibodies play an important role in maintaining the functional integrity of the organism. *See* antigens.

ANTIGENS. Various foreign materials such as bacteria or toxins which are capable of stimu-

lating the production of antibodies. *See* antibody.

ANTIGLOBULIN. Antibody to a globulin protein.

ANTIRABBIT HETEROPHILE HEMOLYSIN. Substance which lyses (that is, disintegrates) rabbit and human red blood cells.

ANTISOCIAL PERSONALITY. Personality type characterized by behavior which repeatedly brings the individual into conflict with the law.

APHONIA. Loss of voice.

ARGENTAFFINOMA. *See* carcinoid tumor.

ASTHENIC PERSONALITY. *See* psychasthenic personality.

AUTISM, INFANTILE. A psychosis of early childhood characterized by lack of interest in people, social withdrawal, and odd mannerisms such as rocking and spinning.

BALANCED POLYMORPHISM. Preservation of equilibrium in genetic variability of a population by various natural selective processes. *See also* polymorphism.

BASAL GANGLIA. Region of the telecephalon consisting of the caudate, putamen, globus pallidus, and amygdaloid nuclei. Dysfunction of the basal ganglia has been associated with disturbances of posture and movement.

BLOOD-BRAIN BARRIER. The physiological barrier that limits the accessibility of many substances from blood to neural tissue. Molecular size and other physicochemical properties are important in determining the extent to which a particular substance will cross the blood-brain barrier.

BRUXISM. Grinding of the teeth.

CARBOXYL GROUP (—COOH). Characteristic chemical constituent of organic acids.

CARCINOID TUMOR. Type of malignant tumor characterized by asthma, diarrhea, flushing of the skin, and heart disease. The production of serotonin by the tumor cells is thought to be largely responsible for these symptoms. Also called argentaffinoma.

CARDIAC DECOMPENSATION. Heart failure.

CATALEPSY. Pathological condition characterized by waxy flexibility of the body so that the patient maintains postures for prolonged periods of time. Catalepsy is characteristic of catatonic schizophrenia and certain organic brain syndromes.

CATHEXIS. Emotional feelings which are invested in a particular person, object, or idea.

CEREBROVASCULAR DISEASE. Damage to brain tissue and impairment of mental function which results from deterioration of blood vessels supplying the brain.

CHEMICAL SYMPATHECTOMY. Chemical disruption of the sympathetic nervous pathways. For example, reserpine produces a chemical sympathectomy by depleting the transmitter substance, norepinephrine, from sympathetic neurons.

CHOLINERGIC. Refers either to those neurons which have acetylcholine as their transmitter substance (that is, cholinergic neurons) or to the function of acetylcholine-containing neurons (that is, cholinergic effect).

CHROMATOGRAPHY. Method of chemical analysis used to separate and identify the various substances in a mixture.

CIRCADIAN CYCLES. Rhythmic cycles with a period of about 24 hours. Common in the biochemistry, metabolism, and physiology of many life processes.

CLOZAPINE. A potent nonphenothiazine antipsychotic drug that is devoid of extrapyramidal side effects.

CONCORDANCE. Phenotypic similarity for a given trait or characteristic.

CORTICAL EVOKED RESPONSE. Record of the electrical potential of cortical cells generated in response to a given stimulus. An example would be the record of electrical activity in the visual cortex in response to a light flash.

CORTICOSTEROID. Steroid hormone synthesized and secreted by the adrenal cortex.

CORTICOTROPIN RELEASING FACTOR. A hypothalamic polypeptide whose secretion into the pituitary portal system stimulates the secretion of corticotropin by the anterior pituitary.

CYCLOPHRENIC. Personality type characterized by alternation in mood between elation and depression. The mood swings are not as great as in manic-depressive illness. Also called cyclothymic.

CYCLOTHYMIC. *See* cyclophrenic.

DECARBOXYLATION. Removal of the carbon dioxide residue from a molecule. Decarboxylation is frequently accomplished by enzymatic action. *See* carboxyl group.

DÉJÀ VU. Sensation that an experience which is occurring for the first time has taken place at some time in the past.

DEMOGRAPHY. Evaluation of factors such as age, education, and related characteristics of a population under study.

DEPERSONALIZATION. Feeling of unreality or estrangement in regard to one's sense of personal identity.

DEXAMETHASONE. A synthetic steroid compound used in clinical tests of seroid secretion. Administration of this compound usually suppresses the production of endogenous steroids.

DIZYGOTIC TWINS. Twins which develop from separate fertilized eggs in a common uterine environment.

DOUBLE-BLIND. Experimental design in which neither the patient nor the investigator is aware of the medication given to the patient until after completion of the clinical trial. A given medication may be one of several active drugs, or it may be inert (placebo). The double-blind design helps to control for the confounding influence of experimenter's and subject's expectations on treatment effect.

DYSKINESIA. Involuntary movements frequently resulting from dysfunction in the extrapyramidal system of the brain. The dyskinesias constitute one group of extrapyramidal side effects which can occur with long-term phenothiazine administration.

DYSPNEA. Difficulty in breathing.

ECTOMORPHY. Slender body build.

ED_{50}. Dose of a drug which produces a specified effect in 50% of the population under study.

ELECTROENCEPHALOGRAM. Recording of the electrical potentials of the brain. In humans, the measurement is usually obtained from electrodes placed on the scalp.

ENDOGENOUS. Originating from within the organism.

EPIDEMIOLOGY. Science dealing with the factors which determine the incidence and distribution of a disease in a population.

ESTRADIOL. An estrogenic steroid synthesized and secreted by the ovaries.

ETIOLOGY. The cause or causes of a disease state.

EXCORIATIVE DERMATITIS. Superficial inflammation of the skin which is often the result of excessive scratching.

EXOGENOUS. Originating from outside the organism.

FAMILIAL. Occurring in or affecting different members of the same family.

FIBRINOGEN. Blood plasma protein which is necessary for the formation of clots.

FIRST-DEGREE RELATIVE. Parents, siblings, or children of an index case. *See* proband.

FREE-FLOATING ANXIETY. Feeling of dread, anxious expectation, or panic which cannot be readily attributed to a specific cause.

GALVANIC SKIN RESISTANCE. Recording of resistance to the passage of electrical current through the skin. This measurement is used as an index of psychophysiological states.

GENERAL ADAPTATION SYNDROME. A concept proposed by Dr. Hans Selye for the response of the organism to major stress. Included are

the phases of alarm reaction, resistance, and exhaustion.

GENETIC MARKER. A behavioral or physical trait whose mode of inheritance is well understood.

GENOTYPE. Genetic constitution of an organism.

GLOBULINS. Family of proteins in the blood which include the immunoglobulins. *See also* antibody.

HALF-SIBLING. Siblings who share only one biological parent.

HAPTOGLOBIN. Globulin substance in the blood that binds free hemoglobin.

HARTNUP'S DISEASE. Inherited metabolic disorder characterized by defective kidney absorption of certain amino acids, defective intestinal absorption of tryptophan, and behavioral abnormalities.

HEMOGLOBIN. Oxygen-carrying protein of red blood cells.

HIPPOCAMPUS. Portion of the temporal lobe of the brain. *See also* limbic system.

HISTAMINE. An amine (beta-imidazolyethylamine) found in most mammalian tissues, including the brain. Allergic reactions are frequently associated with a release of histamine from cellular storage sites.

HISTAMINOLYTIC. Antihistaminic effect.

HISTRIONIC PERSONALITY. *See* hysterical personality.

HUNTINGTON'S CHOREA. Inherited neurological disorder with characteristic degenerative changes in the cerebral cortex and basal ganglia. Symptoms include involuntary movement of the extremities, inarticulate speech, and general deterioration of intellectual function. Psychosis can be an early symptom.

17-HYDROXYCORTICOSTEROIDS. Metabolites of adrenocorticosteroids.

HYDROXYLATION. Incorporation of oxygen into a compound to form a hydroxyl group (—OH).

HYPERAMNESIS. Unusual clarity of memory with vivid recollection of fine details.

HYPERTENSION. High blood pressure.

HYPERVENTILATION. Increase in the rate and depth of breathing. The resulting imbalance in blood chemistry often causes dizziness and a tingling sensation around the mouth and in the extremities. Hyperventilation frequently accompanies anxiety states.

HYPOKINESIA. Abnormally decreased motor activity.

HYPOTHALAMUS. A region in the diencephalon of the brain. Involved in the regulation of many physiological functions including sleep, blood pressure, respiration, hunger, temperature, endocrine balance, and as a component of the limbic system in the control of emotional expression. *See also* limbic system.

HYSTERICAL PERSONALITY. Personality type characterized primarily by theatrical exhibitionism, emotional shallowness, vanity, immaturity, and impulsive behavior. Also called histrionic personality.

IDEATION. Mental representation of objects and events.

IMMUNOGLOBULINS. Globulin proteins which function primarily as antibodies. *See also* antibody.

IN SITU. Refers to a process which takes place within its natural site.

INSULIN COMA THERAPY. Therapeutic technique in which a patient is rendered unconscious by the administration of insulin. Insulin coma therapy was frequently used in the treatment of schizophrenia prior to the introduction of phenothiazines.

INTRADERMAL. Within the skin.

IN VITRO. Outside the living organism.

IN VIVO. Within the living organism.

KRAEPELINIAN CLASSIFICATION. Emil Kraepelin differentiated dementia praecox from manic-depressive psychosis. He delineated three subtypes of dementia praecox: paranoid,

catatonic, and hebephrenic. Eugen Bleuler later introduced the term schizophrenia to replace dementia praecox.

LABELED COMPOUND. Compound which has one or more specific atoms replaced by a radioactive isotope. Labeled compounds are frequently used as markers to study chemical reactions or the distribution of a substance in the body.

LESCH-NYHAN SYNDROME. Inherited metabolic disorder characterized by deficiency in the enzyme hypoxanthine-guanine phosphoribosyl transferase. This disorder occurs only in males, and the primary abnormalities are irregular movements of the extremities, self-mutilation, mental retardation, and high serum uric acid.

LIMBIC SYSTEM. Consists of septum, hypothalamus, mammillary bodies, amygdala, thalamus, cingulate gyrus, hippocampus, and some midbrain areas. These structures, along with connecting pathways, have been suggested to play an important role in the experience and expression of emotion.

LUTEINIZING HORMONE. A hormone secreted by the anterior pituitary gland that stimulates development of the corpora lutea in ovaries, and the secretion of testosterone by the interstitial cells of the testes.

MASS SPECTROMETER. An instrument used for analyzing mixtures which contain stable isotopes.

MESENCEPHALON. *See* midbrain.

MESOMORPHY. Muscular athletic build.

MIDBRAIN. Area of the brain which develops from the middle of the three primary divisions of the embryonic brain. Also called mesencephalon.

MITOCHONDRIA. Mitochondria are particles found in the cytoplasm of all cells. These organelles contain a multitude of enzymes including those involved in providing energy for the cell and the enzyme monoamine oxidase which metabolizes norepinephrine, dopamine, and serotonin.

MITRAL STENOSIS. Narrowing of the valve on the left side of the heart (mitral valve). Mitral stenosis is frequently the result of rheumatic heart disease.

MK485. A drug used to inhibit decarboxylation. Since MK485 does not readily pass the blood-brain barrier, its effect is limited primarily to the periphery. MK485 has been administered clinically in conjunction with L-DOPA and 5-hydroxytryptophan in order to prevent the conversion of these substances to active amines before they reach the blood-brain barrier.

MONOAMINES. Class of compounds characterized by a single amine group. Includes norepinephrine, dopamine, serotonin, and acetylcholine.

MONOZYGOTIC TWINS. Genetically identical twins which develop from the division of a single fertilized egg within a common uterine environment.

MORBIDITY RISK. The risk of becoming afflicted with a particular disorder. Morbidity risk is frequently expressed as the ratio of affected to unaffected individuals in a given population.

NARCOLEPSY. Disorder characterized by sudden and irresistible attacks of sleep which usually last less than 15 minutes. The cause of this disorder is unknown.

NICOTINAMIDE. Physiological active derivative of nicotinic acid. Nicotinamide, like nicotinic acid, is effective in the prevention and treatment of pellagra. *See* pellagra.

NICOTINIC ACID. B-complex vitamin effective in the prophylaxis and treatment of pellagra.

NOSOLOGY. Science of classification of disease states.

ORALITY. Tendencies to reduce tension and drives through modes involving the mouth, such as biting, sucking, chewing, drinking, kissing, and talking.

PALMAR SKIN POTENTIAL. Record of the electrical potential across the skin of the palm, used in the study of psychophysiological states.

PARASITOSIS. In the context of amphetamine psychosis, the sensation that one is infested with parasites.

PARENCHYMA. Characteristic tissue of an organ (eg, neurons in the central nervous system).

PARESTHESIA. Abnormal sensations such as burning or prickling. Paresthesia occurs in a wide variety of medical and psychiatric disorders.

PARKINSON'S DISEASE. Disturbance of motor function characterized chiefly by slowing and weakening of voluntary movement, muscular rigidity, and tremor. Parkinson's disease is thought to result from the destruction of specific dopamine-containing neurons in the brain.

PATHOPHYSIOLOGY. Physiological mechanisms leading to a disordered function.

PELLAGRA. Multiple vitamin deficiency disorder characterized by diarrhea, skin rash, and psychiatric symptoms such as anxiety, confusion, depression, and apathy.

PENETRANCE. The extent to which a gene produces a phenotype.

PENTYLENETETRAZOL SHOCK THERAPY. Treatment for psychiatric disorders in which convulsions are produced by the intravenous administration of pentylenetetrazol (Metrazol). This form of therapy has been largely replaced by electroconvulsive therapy.

PERIPHERY. Outside the central nervous system.

PERNICIOUS ANEMIA. Red blood cell deficiency disease (anemia) due to vitamin B_{12} deficiency. The primary clinical features are weakness, sore tongue, numbness, tingling, and confusion.

PHENOMENOLOGY. Description of clinical phenomena associated with disease states.

PHENOTHIAZINES. Class of drugs (eg, chlorpromazine) effective in the treatment of various psychotic disorders, particularly the schizophrenias.

PHENOTYPE. Physical and behavioral attributes of an organism. Phenotypic expression is a function of both genetic and environmental factors.

PHENYLKETONURIA (PKU). Inherited disorder in which deficiency of the enzyme phenylalanine hydroxylase results in defective metabolism of the amino acid phenylalanine. Symptoms include mental deficiency and epileptic seizures.

PILOERECTION. Erection of the hair.

PLACEBO. Inert substance which is given in lieu of active medication. *See also* double-blind.

PLASMINOGEN. Chemical precursor of the substance plasmin. Plasmin is an enzyme which dissolves blood clots.

PLATELET. A cellular constituent of the blood which plays an important role in the coagulation process. The platelet appears to have certain physicochemical properties in common with synaptosomes.

PLEIOTROPISM. The multiple effects of a single gene.

POLYGENIC. Involving more than one gene for a given phenotypic effect.

POLYMORPHISM. Literally, having more than one form. For example, there are numerous differences between members of the same species.

PRECURSOR. A substance which is converted to an end product through a chemical reaction or a series of chemical reactions.

PRELUDIN. A sympathomimetic drug with pharmacological and physiological actions similar to amphetamine.

PREMORBID. State or characteristic preceding the onset of a disease.

PRIMARY PROCESS THINKING. Cognitive process associated with dreaming, early childhood, and the psychoanalytic concept of the unconscious. Primary process thinking is characterized by equating wishes with reality, using one object to symbolize another,

and failure to distinguish the parts of an object from the whole.

PROBAND. The person in a family initially identified as demonstrating the physical or psychological trait under study.

PROLACTIN. An anterior pituitary hormone that is capable of initiating and sustaining lactation.

PSYCHASTHENIC PERSONALITY. Behavior pattern characterized by easy fatiguability and lack of energy with an oversensitivity to physical and emotional stress. Also called asthenic personality.

PSYCHOGENIC. Psychological or experiential in origin.

PSYCHOPATHIC PERSONALITY. *See* antisocial personality.

PSYCHOTOGENIC DRUG. *See* psychotomimetic drug.

PSYCHOTOMIMETIC DRUG. Drug capable of inducing a behavioral state which resembles a naturally occurring psychosis.

RABBIT HEMAGGLUTININ. Antibody which agglutinates rabbit red blood cells.

RADIOIMMUNOASSAY. Method for measuring a minute amount of a chemical substance that combines radioisotope labeling with immunological techniques.

RAPHE NUCLEI. Area in the core of the brainstem which contains a high density of serotonergic cell bodies.

RESERPINE. A drug that depletes monoamines from storage sites in neurons. Used clinically in the treatment of high blood pressure and rarely in psychiatric disturbances.

SLOW WAVE SLEEP. Deep state of sleep in which vivid dreaming rarely occurs.

SOCIOPATHIC PERSONALITY. *See* antisocial personality.

SOCIOPATHY. A personality disorder characterized by antisocial and criminal behavior.

SOMATOSTATIN. A hypothalamic hormone that inhibits the release of growth hormone by the anterior pituitary.

SPERMIDINE. Polyamine found in brain and other tissues.

STEREOISOMERS. Molecules such as *d*- and *l*-amphetamine which have the same number and type of atom groupings, but with different spatial configurations, and as a consequence potentially different properties.

SUBSTANTIA NIGRA. Pigmented area in the midbrain that contains dopaminergic cell bodies which project to the corpus striatum. Damage to this area produces Parkinson's disease.

SYMPATHOMIMETIC DRUGS. Category of drugs (eg, amphetamine) with effects similar to those observed during sympathetic nervous system activation.

TACHYPHYLAXIS. Rapid development of tolerance associated with depletion of a response mechanism.

TELENCEPHALON. A region of the brain consisting of the cerebral cortex, basal ganglia, and rhinencephalon, which includes many limbic structures. *See also* basal ganglia and limbic system.

TITER. A measurement of the relative concentration of a substance. For example, high titers of serum antibody indicate that the serum can be very dilute and still produce a measurable antigen-antibody interaction.

TOLERANCE. A decrement in drug effects with repeated or continuous administration.

TOXIC PSYCHOSIS. Chemically induced psychosis.

TRICYCLIC ANTIDEPRESSANTS. Class of compounds effective in the treatment of depression. Tricyclic refers to the three organic ring structure which chemically characterizes this group of medications.

TURNOVER RATE. The rate at which a specific endogenous substance is replaced. The turn-

over rate for a neurotransmitter substance such as norepinephrine is frequently used as an index of the functional state of norepinephrine neurons.

WHEAL. Circumscribed area of swelling due to fluid accumulation beneath the skin's surface; usually caused by a local allergic reaction.

WILSON'S DISEASE. Hereditary defect in copper metabolism manifested by abnormal movements, liver disease, and psychological disturbances.

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