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Psychological and biochemical mechanisms of schizoprenia

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THE PSYCHOLOGICAL AND BIOCHEMICAL
MECHANISMS OF SCHIZOPHRENIA

Submitted in partial fulfillment of
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It is difficult for a person not suffering from schizophrenia to imagine the terror, the feelings of unreality, the dismay of the afflicted person. In personal interviews patients have described to me some of the fantastic phenomena which they had experienced, events amazing, if not horrifying to the point of disbelief, were it not for the deadly serious expressions upon their faces. Their concept of the world, their Weltanschauung, is turned inside out so that the earth, the sun, the stars, in short, the entire universe, revolve around them. They are at once hopelessly isolated from the external world and yet intimately involved with every radio broadcast, the object of every laugh, the subject of every discussion. One patient envisioned himself as walking down a long, dark corridor, completely alone, with no end in sight. A second patient lamented:

What's the sense of living? My arms and legs are gone and my head is detached from my body. Electric shock is the only thing that can snap me out of this now. Isn't this a terrible curse to be stricken with?

This particular patient, who often suffered long periods of depersonalization and disturbances of body perception during which he could not feel his limbs or else they appeared enlarged or detached from his body, was extremely aware of his plight and frequently demonstrated marked insight into his condition. A third patient, who had been extremely aggressive only a few weeks before, but was now enjoying a brief period of remission, remarked in a group therapy session which I attended:

I've had feelings when I wanted to strike
out at others for no reason. Have you ever wanted to break all your teeth out or burn out your eyes with a cigarette? I have. I tried to strangle my mother who I love very much. Now isn't that ridiculous?

Other partially remitted patients admitted that they, too, had once had similar aggressive feelings. The lesson to be drawn from these examples is that within the confines of every mental hospital dwells a human tragedy of unequaled proportions. Although afflicted with a disease (a word which is used advisedly) of crippling effect, incurring psychological death, these beings will live as long as the people outside the hospital walls who despise and condemn them, when they consider them at all. Within the normally developed body of the sick person, however, a mysteriously elusive poison has warped the images formed in the brain, leaving the ambulatory patient accursed, spending a pitiable, anxious existence pacing the long, poorly-lit corridor of a locked ward, head lowered, a cigarette burning unfelt etchings upon his fingers. This is the plague of millions--schizophrenia.

This disease has played its tragic role in the literary history of all ages, from the Greeks, through Shakespeare, to our present age. According to the book of Mark one of Jesus's great miracles was freeing the deranged from the devils which possessed them. Mark vividly describes the afflicted person in one passage.

"...there met him out of the tombs a man with an unclean spirit, who had his dwelling among the tombs; and no man could bind him, no, not with chains: because that he had been often bound with fetters and chains, and the chains had been plucked asunder by him, and the fetters broken in pieces:"
neither could any man tame him. And always, 
night and day, he was in the mountains, and 
in the tombs, crying, and cutting himself 
with stones.

Mark 5:2-5

In medieval times the mentally ill were burned at stakes 
to exorcise the demons afflicting the possessed. The satanic 
association of these "witches" must have been deeply impressed 
upon the people when, for a few moments, a haggard old woman 
chuckled and sang while flames lapped at her throat. Often 
in schizophrenia the patient has little feeling in the extremities. 
One case has been reported in which a patient had been badly 
burned over her entire body. The poor woman lay on the floor 
carrying on a normal conversation and complaining occasion-
ally of a pain between her shoulders, the only part of her body 
left unscathed. Within a few moments she had died (10).

As recently as the seventeenth century the noble residents 
of Salem, Massachusetts, carried on witch trials and made short 
work of those who carried the curse. Even today, although 
intellectually we subscribe to the humanitarian ideals of 
therapeutic community, we react with emotional spit for the 
mentally ill and the families which carry this stigma.

The social problem connected with mental illness is of 
no less intensity than the moral problem involved. In today's 
hospitals one out of every four beds is occupied by a mental 
patient, and yet, until quite recently, the money allocated 
to psychiatric research was less than five million dollars per 
amnum in comparison to approximately thirty million dollars 
for tuberculosis, cancer, and infantile paralysis respectively 
(24). In terms of research funds per patient, the patient
with polio receives $28.20, with cancer $27.70, with tuberculosis $26.50, but with schizophrenia $4.15 (10).

In 1951 there were an estimated 1.5 million persons suffering from mental illness and another 7.5 million cases of personality disturbances. In addition, it was estimated that there were 1.5 million mentally deficient people. Of the 1.5 million persons afflicted with mental illness, roughly 21% are diagnosed as schizophrenics (24). In terms of patient population in mental hospitals, schizophrenics occupy about 60% of the total group. Yet, hospital conditions for the care of mental patients are generally poor. This is reflected in the observation that not a single state hospital met the personnel requirements of the American Psychiatric Association as late as 1957 (10). On a broader scale, the national standard-setting organization, the Joint Commission on Accreditation of Hospitals, had approved only 30% of the state mental hospitals as compared with 100% of the nationwide Veteran's Administration Hospitals in 1951 (24).

In some states, the average per day upkeep of mental patients is significantly less than the comparable amount of money spent for the maintenance of criminals in penal institutions. In New York State, for example, $4.40 per day is spent for criminal maintenance, $7.70 per day for the care of the mentally ill. And with every passing year the number of patients in mental hospitals grows larger. The best hospitals claim 75-85% remission. The worst, however, obtain only 40-50% remission and these figures do not include the number of relapses that frequently occur (10).

Three great names stand out in the early attempts to draw
mental illness into the realm of scientific investigation. These are Kraepelin, Bleuler, and Freud. Ironically, these outstanding contributors to psychiatric research were all born within a span of two years, Kraepelin in 1856 and Bleuler and Freud in 1856. Kraepelin's main contribution to this field consisted of classifying schizophrenia into definitive categories under a single heading. Today, although this classification has been disputed by some workers, it is believed that there are enough common factors to each subgroup to warrant the use of a single, collective term (41). Kraepelin gave the misleading name "dementia praecox" [lit. dementia--madness; praecox--to ripen beforehand] to the disorder, the second term indicating his observation that the disease often has an early age of onset.

In 1911 Eugen Bleuler published his magnificent work, Dementia Praecox or the Group of Schizophrenias, which attempted to classify the symptoms of dementia praecox with respect to the criteria of necessity, i.e. primary and secondary symptoms, onset, and prognosis. Bleuler coined the equally inadequate term "schizophrenia" [Gk. schizo--split; phrenia--mind] which is in common usage today, but is often confused with the Jekyll and Hyde concept of multiple personality (9).

Freud, of course, introduced the radical concepts of consciousness and unconsciousness, drives, and the influence of environmental forces in shaping the personality, which have taken an immovable place in the psychiatric literature of the past four decades. It is of historical interest to note that all of these workers were convinced that eventually a physical
cause for schizophrenia and the other mental diseases would be elicited.

During that period of the nineteenth and early twentieth centuries, when bacteriology was making rapid progress in determining the causes of several previously mysterious diseases, hope was aroused that a distinct physiological basis for schizophrenia might be discovered. Indeed, such a hope found a concrete basis when, in 1913, two bacteriologists, Hideyo Noguchi and J.W. Moore, working at the Rockefeller Institute, demonstrated the connection between the mental disease, paresis, and syphilis. These workers elicited the presence of the syphilitic spirochetes in the brains of deceased paretic patients (24). But alas, though the search intensified, no definite evidence was brought forth, and temporarily environmental theories dominated the field.

Some workers, however, clung tenaciously to the physical concept of mental illness and consequently became known as "organicists". Several forms of treatment were advocated by these men, including lobotomy, electroconvulsive shock (ECT), Sakel's insulin therapy, hydrotherapy, and, more recently, drug therapy. These forms of treatment were all empirically derived and found functionally useful. None were developed from the tenets of a definite hypothesis. Although a great deal of work has centered around explaining the mechanisms by which these treatments exert their beneficial effects, definite explanations for their usefulness are sadly lacking despite the fact that these treatments have been employed as therapeutic tools, in some cases, for more than thirty years.

As specific research techniques have become more refined,
a wide variety of data has accumulated concerning psychiatric disorders. As one scans the literature, however, there is an increasing dismay at the numerous conflicts that exist in the data and at the lack of correlation of the numerous independent studies. Indeed, one of the few valid generalizations that can be drawn from a literature survey pertaining to schizophrenia is that patients exhibit far more physical variation than normals in the studies which have been made.

Since 1950 several interesting theories have been proposed regarding the physical cause of schizophrenia by groups in this and other countries. Although these theories will be examined at length in a later chapter, one study should be cited as basic to most of these explanations, namely the genetic investigations conducted by Kallman concerning heredity in mental disorders. Kallman, utilizing a large number of twin studies, concluded that schizophrenia is inherited and that environmental factors served to inhibit potential schizophrenia in some cases in contrast to the environmental theories which attribute schizophrenia to unfavorable environmental conditions. This conclusion was based on the observation that both monozygotic twins developed schizophrenia with a far greater frequency than corresponding dizygotic twins, who developed the disorder with approximately the same frequency as siblings, whenever the genetic factor for schizophrenia was presumably present as indicated by family background. In the few cases in which only one of a pair of identical twins developed schizophrenia, environmental support apparently prevented the onset of the disorder in the non-schizophrenic (but always schizoid) twin (20). Numerous explanations and criticisms of this work have been compiled and these will be considered in the appropriate context.
these will be considered in the appropriate context. On the basis of Kallman's work, however, research has centered around the specific factors in the body chemistry which result from genetic abnormality presumed to initiate the disease. When the mechanisms of genetic transmission were elicited a short time ago, new prospects emerged for the isolation of factor X in schizophrenia, and research with this goal in mind is continuing today.

The object of this paper is to correlate, insofar as possible, the numerous detailed studies which have been reported. Implicit in this object is the expectation that the various hypotheses that have been proposed can be validated or invalidated on the basis of how accurately the data is explained by the hypothesis in question.

A great deal of attention has been devoted to psychology in the paper. At present psychology seems to offer the only reliable methods with which to deal directly with the schizophrenic process with any degree of success. Therefore, psychological mechanisms will be elaborated with the tentative aim of explaining these mechanisms on the basis of physiological data. This hope is justified to some extent, as is the entire range of psychiatric research, by the simply-stated observation of Ralph W. Gerard: "There is no twisted thought without a twisted molecule"(69). To be sure the body and the mind are so infinitely complex that, in a real sense, many of the psychological concepts will extend beyond the limits of physiology and biochemistry. However, many of psychology's basic assumptions do find application in the biochemistry laboratory and should be considered as manifestations of biochemical processes.
The plan of the paper is as follows. The first section deals with psychology in its application to schizophrenia. In this section the concept of the normal personality will be developed and, in turn, applied to the mechanisms of schizophrenia and neurosis. A chapter dealing with psychotherapy is included to recognize the central contribution which psychology has made to research and therapy in this field and to consider the mechanism of remission brought about by psychotherapeutic methods. The final chapter in this section considers the use of statistical techniques in experimental research and is applicable not only to research designed with psychological theory in mind, but also to the theories of biochemistry and physiology. Indeed, most of the biochemical data that has accumulated is based upon the statistical differentiation between schizophrenic and control groups.

The second section of the paper deals with the biochemical aspects of the problem. The first chapter is concerned with the rise of drug therapy to prominence in the clinical field and the types of drugs employed in practice. Chapter two deals with the psychotomimetic drugs, briefly considering the historical background of the interesting substances, then introducing the suggestive concept of the "model psychosis" and its place in psychiatric research. Finally, the last two chapters examine the biochemical abnormalities observed in schizophrenia and the theories which attempt to explain these divergences from the normal. Incorporated into these chapters will be the criticisms to which the data has been subjected, the author's comments upon the significance of the various studies, and the conclusions concerning treatments past and present which can
be derived from the biochemical theories.

Humphrey Osmond has distinguished clearly the empirical, systematic, and scientific methods of investigation from genuine creativity when dealing with the unknown (106). It is to this creativity that I give special recognition.
Chapter One
THE CONCEPT OF THE NORMAL PERSONALITY

No body of theories has had a more profound effect on psychology than those of Sigmund Freud. Although many of his theories have since been disputed, his original, creative thinking into problems which had hitherto remained unexplained, indeed regarded as taboo in the shades of post-Victorian Europe, places him among the great minds of the modern Western world. The effects of Freudian literature have spread to all walks of life, constituting a mainstay in the thinking of businessmen, educators, authors, and philosophers, to mention only a few. This chapter is devoted to a brief review of Freud's ideas and their manifestations in present-day psychodynamic thought, as incorporated into the concept of personality development.

Freud conceived the adult personality, when fully developed, as divided into three realms—the ego, the superego, and the id. The ego is the conscious self, perhaps the resultant of the other forces, and that portion of the personality, developing from birth, which is acted upon by the overt influences of the environment. At the unconscious level of the mind dwells the id, which contains the primitive, animal-like impulses of the body. These impulses show their most obvious influence during early childhood, when censoring forces are for the most part undeveloped. Thirdly, then, is the censoring force, the superego, which develops, in time, as the moral standards of the individual as governed by the values of parents and society (13). Therefore, beneath the surface actions and thoughts of
the ego is a constant interplay of forces; one "a cauldron of seething excitement" (6), the other an austere judge; one the source of aggression, the other the source of censorship.

As has been indicated, Freud divides the mind grossly into consciousness and unconsciousness, in the sense that certain forces remain segregated from the conscious mind. There are, however, important manifestations of the unconscious forces in the actions of the conscious self. In dreams, Freud felt that inner censorship was relaxed partially, which allowed primal desires to be evidenced in symbolic form, governed by the "pleasure principle". He taught by example that dreams are primarily instruments of wish and fulfillment. In children these wish fulfillments are often portrayed without censorship or distortion. As the superego develops, however, and the latent content of the dream deals more with socially unacceptable behavior, dreams become extremely distorted to the point where their meaning can only be ascertained by interpreting the symbols employed in the manifest dream. This result is caused by the still-present influence of the superego, creating defense mechanisms, inhibiting sexual and narcissistic drives, nevertheless unsuccessful in destroying the dream as such or in erasing the anxiety and guilt felt through the dreamer's unconscious (13).

Because sexual drive plays such a large part in personality as Freud saw it, he separated the stages of sexual development into three periods: the oral, anal, and phallic. He suggests that a person can become fixated at any one of these stages with the corresponding development of personality traits associated with each stage. Two major points should be made here.
First, it is in these stages of sexual development that one of the basic ideas of psychological theory is encountered. This is the premise that the experiences of childhood are of great significance in determining the personality make-up of the adult.

White illustrates the use of these stages of development in examining the personalities of his three normal subjects. For example, with reference to Joseph Kidd, the author points out that his need for support from his environment can be understood if consideration is given to the early gratification of oral pleasures which he experienced, followed by an experience of great frustration when this gratification was withdrawn. It is interesting to note that as long as Kidd's demands are met, his oral tendencies are not clearly evident. But in his post-adolescent years, when this support is substantially withdrawn, Kidd reverts back to an earlier period and the oral fixation which he developed at that time (40,41).

The stages of object-finding might be defined as the periods through which an individual passes during which time an awareness of the self in relation to the environment is developed and, in Freudian terms, with psychosexual urges serving as the primary driving force. Freud separates these stages into several periods of which the narcissistic period is the earliest. This period is primarily involved with self-gratification and the individual thus makes heavy demands on the environment, autonomous from the social barriers which will later be encountered. The second stage, the Oedipus period, is one in which the parent of the opposite sex becomes the love-object.
A person fixated at this point of development forms the Oedipus complex in which the parent of the same sex is rivalled by the child for the affection of the second parent. During the period of latency, the third stage, the girl associates with her clique, the boy with his gang. Fixation at this point makes relearning at puberty difficult and causes the potential development of homosexual characteristics. Finally, at puberty the sexual urge bursts forth powerfully and boys and girls are attracted to each other in general and development is complete, although usually one of this group is selected as husband or wife (6).

A final point in Freud's theories should be made, involving the concept of sublimation. This concept is utilized to explain the constructive enterprises of man and asserts that the libidinal energy which the ego must subvert from direct, aggressive outlet, is able to be deflected into acceptable, creative channels (13). The concept of sublimation has been criticized on two grounds. Although libidinal energy may be a driving force in the individual, sublimation of these energies would not result in a displacement of, for example, sexual craving, just as thirst can only be satisfied by the act of drinking (5). Secondly, in some cases Freidians would trace certain vocational interests, again as an example, to a fixation period. If drawn to such a conclusion, however, it becomes difficult to understand the meaning to be extracted from such an interpretation (40). Allport's theory of functional autonomy will be considered later in this chapter as an alternative mechanism by which interests can be explained.
Because of the difficulty which later psychologists encountered in accepting a great deal of Freudian doctrine in regard to personality development, the ideas of Freud have been considerably revised and extended by later workers. Freudian theory has been sharply criticized on the basis that it rests upon a small number of atypical cases which Freud encountered during his lifetime. In later theories emphasis is laid upon the normal personality itself and its use as a baseline in comprehending abnormal mechanisms. Although the import of early learning and childhood experiences is still considered basic to development, the historical significance of personality traits, notably interests, has been seriously questioned by later authors (3, 40, 41). Finally, the concepts of the id, ego, and superego have been subjected to criticism on the basis that these terms, as strict entities, are not necessarily the only concepts which enter into development. Rather that presenting random criticisms, however, a brief examination of modern dynamic psychology will be made.

Initially, personality may be considered as developing from an interplay of environmental and genetic forces. Inherited traits form the framework within which personality will later be built, however, environmental forces are equally important in development and in adjusting personality to ever situations. Allport uses the following equation to diagram this concept: \[ \text{Personality} = r(\text{heritage}) \times \text{environment} \] (3, p. 106).

The infant may be considered a totally integrated being in the sense that he initially demonstrates a total response to stimuli. Movement, for instance, is undifferentiated and only later does the child gradually develop the differentiated
motor skills. With the processes of maturation and learning acting upon him, however, the infant inhibits the gross reactions of his childhood, replacing them with individual, selective reactions.

The process of differentiation described above, also pertains to the development of interests and emotions, as well as motor processes, and would seem to be antagonistic to a theory of integration of personality. Both, however, are important concepts in personality theory. The following diagram (Figure 1) illustrates schematically the integrated personality and is seen to be hierarchial in nature. Early learning is supplied through conditioning. These conditioned reflexes are integrated into habits, the habits into traits, and the traits into the various "selves" that compose the individual. The diagram makes allowance for the totally integrated personality, indicated by point D, although whether this point is attained is speculative. Along the baseline are all the events in a life. Some of these result in an alteration of habits or traits, while others exert but a small influence on the personality. Entered below the baseline are some events which require a particularly difficult adjustment. These periods are very likely to result in new habits, some lasting for only a short time, while others continue a lifetime. The length of the baseline is a measure of new learning situations which arise. Also considered in the diagram is the minor integration A which, although not usually present, represents a self-sustaining system apart from the major portion of the integrated personality. Points B and B' indicate the possibility of a fixated
Fig. 1 A Schematic Representation of Integration
(3, p.141)
point of adjustment, i.e. a means of adjustment found so satisfactory in the early years that the personality does not progress beyond this point to the normal stage of development (B'). Finally, points C and C' attempt to include the possibility of the "dual"personality, in which there are two or more independent "selves". This type of personality is not to be confused with schizophrenia, which may briefly be described as a fragmentation or perhaps a compartmentalization of personality traits. Beyond the age of adolescence the personality does not vary a great deal. Although the individual retains the capacity for flexibility, it is more likely that older methods of adjustment will be employed to adjust to new situations (3).

The doctrine of maturation has been the subject of considerable controversy in the study of personality development and is closely related to genetic concepts. It is evident that many inherited traits take time to come to full potency. This fact is particularly noticeable in the maturation of the endocrine glands and the motor processes. However, just as personality may be considered as formed by an interplay of heredity and the environment, so the influence of maturation must be considered tempered by the process of learning, each contributing its influence to the process of growth. The manner in which the individual makes use of inherited traits is the basis for flexibility in personality. Learning processes, then, become equally important as the process of maturation in personality development. Initially conditioning may be the most important form of learning, however, after a short period of
time other forms gain equal status. Imitation of others, either consciously or unconsciously, may be considered another early means of learning. A third form of learning, of course, is the rational treatment of various situations, giving consideration to whatever intellectual processes enter into mastery of the environment.

One of the most important mechanisms of adjustment is the development of the self-concepts (40). In order to adjust to many situations it is necessary to understand one's abilities, characteristics, and tendencies as others will react to them. The pianist whose ability is well-accepted feels comfortable when playing before a new audience. A second pianist of unrecognized ability will feel uncomfortable before a similar audience, for his ability is measured by the audience's reaction to it. Generalizing from this example, self-esteem is dependent upon the reactions of society to the individual and may be raised by perfecting the abilities in which the individual excels. More generally, the concept which the individual has of himself is in large measure based upon the reactions of society to the various components which form the personality.

Another concept markedly influencing personality development is that of inferiority and compensation, originally developed by Alfred Adler in the context of neurotic compensation. White cites an example of inferiority compensation in the case of Pearson Frack, World War II bombardier, who, after a narrow escape from death, developed fainting spells above an altitude of ten thousand feet. Frack, however, denied any fear of flying and attributed his fainting spells to physical injuries incurred
during his escape, despite the fact that doctors insisted that
he had fully recovered. Fear represented failure to Brack,
who, as a child, had been constantly reprimanded by his grand-
father for resembling the child's irresponsible father. Thus,
Brack made an artificial, brittle adjustment to responsibility
and, when failure threatened his position, he fainted rather
than admit that he was afraid (41). Brack's adjustment to his
conflict constitutes a form of neurotic compensation. Normally
defense mechanisms of a sort, or substitution for inferiority
feelings are encountered as means by which the anxiety generated
by these feelings can be allayed.

The importance of the Freudian concepts already reviewed
can not be underestimated. The concepts of the ego, id, and
superego, libidinal drives, sublimation, fixation, etc., are
useful in understanding personality if considered in the light
of other important factors noted in this chapter. However,
Freudian theory seems to overemphasize the role of sex in per-
sonality, which, although important because of the special re-
strictions which are placed upon this urge, can not explain the
complex mechanisms of human drives. Allport, in dealing with
this problem, has suggested the theory of functional autonomy
as a partial explanation for drives. He defines functional
autonomy thusly:

... [Functional autonomy] regards adult
motives as infinitely varied, and as self-
sustaining, contemporary systems, growing
out of antecedent systems, but functionally
independent of them. (3, p.194)

Allport emphasizes here the necessity to stress the
significance of events existing in the present time and has
expanded the theory of Woodworth that mechanisms can be turned
into drives, thus that interests, originally derived from early conditioning, ability, or fixated stages of development, shed their historical nature and become drives in and of themselves. In answer to the criticism that simple motor tasks should with continual exercise aquire an increasingly powerful driving force, Allport states, "Only skills in the process of perfecting serve as drives" (3, p.205). This theory, then, complements, rather than displaces, the other factors involved in personality growth.

In summary, personality as a dynamic theory, is today portrayed as being influenced directly from birth by the environment as well as heredity. The processes of differentiation and integration emerge as complementary systems, the former encouraging selective response and the latter grouping these responses into a unified hierarchy. Maturation and learning provide the means and the method by which personalities adjust to life's situations. Included in these adjustments are the development of self-consciousness, compensation for inferiority feelings, and the transformation of interests into drives.

Finally, in the adult personality, an integrating philosophy of life represented by point D (Figure 1) is developed. A large variety of interests are acquired, drawn from abilities and traits. Lastly, the individual becomes capable of objectively evaluating his own position in the hierarchy of society with respect to the other individuals in the society with whom he has contact.
Chapter Two
THE ABNORMAL PERSONALITY

The concept of the normal personality has been discussed with respect to the present theories of psychodynamics. The central problem of this paper, however, is the abnormal personality, specifically schizophrenia. In this chapter a few general considerations concerning the abnormal personality will be made and then a more specific discussion concerning the psychodynamic theory of schizophrenia will be outlined.

It was the purpose of studying the neurotic and psychotic states comprehensibly that caused the development of personality theory by various workers in psychology, especially Freud. Hence the theories of Freud, as indicated, tend to be pervaded by the direct influence of abnormal, rather than normal cases. Freud's observations concerning neurosis, unlike his concepts of normal personality, are still strongly entrenched in that part of psychological theory dealing with neurotic mechanisms. It will, then, be of functional, as well as historical, interest to examine his thoughts in this regard.

Freud and Breuer, working with psychosomatic patients, noted peculiar physical disabilities occurring which were unable to be explained by a physiological standard. In the past histories of several patients were noted strong emotional experiences loosely connected to the disability. Under the influence of hypnosis, one patient became completely remitted after undergoing a rather violent emotional episode concerning a past experience during which she had temporarily suppressed her feelings. Freud and Breuer, investigating this phenomena, concluded
that the reliving of such experiences under controlled condi-
tions was therapeutically beneficial. This theory became known
as the concept of abreaction (6,13). Abreaction, then, con-
sists of producing a normal response to emotional experiences
involved with emotional maladjustment, and offers the first
opportunity to bring abnormal mechanisms into the realm of
scientific investigation.

Freud later found that the hypnotic state, which had pre-
viously been considered essential to this treatment, thus limit-
ing the number of patients which could be aided, was in fact,
superfluous to the phenomena. Instead, hypnosis merely pro-
vided a means by which the subject's defenses could be lowered
and the repressed experience recalled. Freud proceeded to de-
velop a technique by which any patient could be treated, namely
the process of free association. It is assumed that a patient
will attempt to repress his thought at first and that the
therapeutic process will be slow. As treatment proceeds, how-
ever, defense mechanisms are shattered and thoughts will be
concerned primarily with the existing conflict. The latter
assumption is based upon the conviction that the patient is
dominated by the therapeutic situation and consequently is
primarily concerned with thought content appropriate to his
anxiety (13, 41).

In answer to the question concerning what thought could
be so repugnant as to be shunted into the unconscious, yet
exert such a powerful effect, Freud argued that sexual striv-
ings, present since early childhood, represented such thoughts.
As he became more familiar with the content of patient's
thoughts, he became progressively aware of the importance
of the sexual urge in maladjustment. He noticed these strivings in the acting out which patients exhibited in transferring the emotions of earlier relationships to the doctor. He recognized too the sexual connotations in errors, fantasies, and dreams recounted by patients. Freud concluded, then, that unconscious anxieties exerted a powerful influence in normal and abnormal personalities (13). In general anxiety and defense occupy a central place in neurosis and other psychological disorders, as well as in normal behavior. However, it is the employment of unsuitable and often bizarre defense mechanisms which reflect emotional disorder (40).

The process of development involves two separate tendencies, each interacting on the other, namely differentiation and integration. Factors encouraging differentiation are parental influence, reward and punishment, and innate aptitude, to mention only a few. Normally a hierarchy of values is set up and interests are integrated into a workable system of life. In the abnormal personality, however, certain interests are extremely disproportionate to others, particularly those involving a social role. Because the self-concept is partially dependent upon the regard which others hold for us, and this concept is a primary unifying mechanism in personality development, distortion of the social role impairs the ego-development (3,41). In this connection mention should be made of Sheldon's somatotype theory. Sheldon et al. have found a high correlation between temperamental make-up and physical type. Sheldon classifies body type into three general categories, those with softly-rounded features, endomorphs, those with
distinctly athletic features, mesomorphs, and those characteristically slim and wiry, the ectomorphs. To each group he assigned such personality traits as sociability, aggressiveness, and sensitivity respectively. Physical build, then, and the reactions of others to appearance are involved in the development of the self-concept (20,41).

The social role is also facilitated by group membership and identification of one's role in the group. This factor encourages adjustment and acceptance, and therefore encourages the interaction of differential tendencies into the hierarchy of values. If group membership is discouraged, the learning process derived from the social role is again impaired.

Schizophrenia represents the most marked departure from the tendencies mentioned above. The subgroups of schizophrenia will now be considered to note the kind of adjustment that can alternatively be made to impaired developmental processes.

1) Simplex--This subgroup represents the least noticeable departure from the normal and probably has the most favorable prognosis. The onset of schizophrenia simplex is insidious and is characterized by an initial lack of interest in the surroundings and increased isolation from friends and relatives. Although violence is seldom present beyond the usual limits of irritability, the characteristics become increasingly noticeable with passing time. Affectivity in the later stages is liable to become shallow.

2) Paranoid--The paranoid group characteristically involves the rich development of a delusional system, usually
associated with auditory and sometimes visual, hallucinations. Again, in common with the other subgroups, lack of interest is apparent. Eventually confusion, general disintegration of personality, and loss of contact with reality becomes apparent. White's case study of L. Percy King demonstrates these characteristics. King had become increasingly aware of changes taking place within himself, especially the presence of threatening voices. Exaggerated feelings of self-reference became marked and a proportionate withdrawal from his normal contacts ensued. King explained these changes by creating an elaborately organized delusional system, attributing his effeminate urges to an external source in the process which White terms projection. This then was a solution to a serious inner conflict. On one hand King felt inadequate concerning his sexual urges, on the other he could not allow his homosexual tendencies to be admitted into consciousness without an intolerable blow to self-esteem. King transfers responsibility for these urges to the external source and thus can consciously recognize them (41).

3) Catatonia—A second answer to the problem of adjustment is provided by complete isolation and withdrawal to the point where motility virtually ceases, characteristic of catatonia. Unusual positions may be maintained for hours, giving rise to the term "flexibilitas cerea" or "waxy flexibility", whereby the limbs
maintain any position in which they are placed. Although inactivity is characteristic of catatonia, there are occasional outbursts of violence, indicating no gross physiological disintegration of the motor system. It has been suggested that the catatonic is deeply engrossed in the solution and rationalization of his problems and abnormal thoughts.

4) Hebephrenia--This subgroup is often considered a catch-all term for behavior clearly schizophrenic, yet incongruous with the symptomatologies of the other categories. The main characteristics of hebephrenia are silliness, inappropriate emotional response, bizarre ideas, and the indiscriminant use of word--salads or neologisms, seemingly disconnected words or phrases by the patient containing no intelligible meaning. In hebephrenia, as may generally be stated for schizophrenia, the most marked symptom involves the secondary consideration given to adjusting to reality and the severe disruption of the social role (9,41).

Developmentally, the schizophrenic psychosis may often be traced to discouragement of childhood social experiences. Social adjustment beyond the parental relationship seems to constitute a crucial step in personality development. If the social interest has initially painful effects, one mechanism by which these effects may be removed is to suppress the interest. Reinforcement of this suppression by an overprotective family environment tends to diminish social contact beyond the home and with passing time, especially the onset of puberty and the social demands required during adolescence, the forces tending
toward maladjustment become painfully apparent. Fantasy experiences uncorrected by social reaction may compensate partially for lack of sociability. Increased isolation occurs and self-esteem is gradually lost. We tend to judge ourselves by the reaction of others to our social pretensions. If social contact is diminished, no baseline is established for such a judgment and misinterpretation of the motives and reactions of others results. The potential schizophrenic then reacts in the various ways developed in the schizophrenic subgroups, i.e. with withdrawal, indifference, denial, or panic (41).

Complementary to the developmental theory presented here, is the learning theory approach suggested by Widnick. This theory employs the fact that schizophrenics presumably have an abnormally high drive state. This condition results in more rapid conditioning to simple tasks than a comparable normal group. According to the Hullian theory of drives, schizophrenics should also generalize to a new set of stimuli more easily than normals. Consequently, the schizophrenic is initially a highly anxious person whose drive state is increased by a precipitating stress. Generalization of the anxiety response to a new set of stimuli takes place and there is a large increase in the number of remote and clang associations. Chronicity, representing a low drive state (although this fact is questionable indeed) develops from a lower anxiety level, presumably the result of reaction formation of remote associations during generalization. Chronicity also produces bizarre (but anxiety-reducing) behavior (102).
Thought processes in schizophrenics are extremely inadequate in dealing with social communication. The bizarre statements and neologisms of the hebephrenic, for instance, emphasize the patient's isolation and the indifference which he maintains. Delusions provide convenient defenses against inner feelings repugnant to the patient, constituting a distinct misinterpretation of experience, particularly in the context of social contact. Communication with schizophrenics is difficult to establish since they are usually unwilling to enter into the listener's perspective and because the desire to interact socially has been strongly suppressed. Consequently the therapeutic relationship, so crucial to dealing with neurotic behavior, is essentially inadequate in treating the schizophrenic.

Kallman suggests that a genogenetic basis for schizophrenia is indicated, since the disorder occurs simultaneously more often in monozygotic twins, with presumably the same gene make-up, than with dizygotic twins, siblings, parents, and least in the general population (range 86% concordance in identical twins to less than 1% in the general population). Although other workers have failed to present such striking correlation, the general tendency to increasing concordance with increasingly similar gene make-up has been established (20). This data has been partially explained by some psychologists. First, identical twins are a special case in which the environment is often adjusted so as to be similar for each twin. Thus, an unusually concordant environment should lead to an usually high rate of concordance in schizophrenia. It should
be noted, however, that Kallman has produced two cases in which the environments of monozygotic twins were different. Nevertheless, schizophrenia was concordant in both cases. Assuming for a moment that there is a genogenetic factor involved, Sheldon's somatotypes may provide an explanation for the correlation. Temperament and physique are presumably inherited, rather than acquired, characteristics. Sheldon found a moderately high correlation between schizophrenia and ectomorphy which, it will be recalled, was associated with such traits as sensitivity, awkwardness in social situations, introspection, and nervousness. Therefore, the genetic factor might be explained by the inherited tendencies of temperament and physique, rather than a strictly modified or aberrant gene composition (20,41).

In summary, schizophrenia is considered to be the result of early isolation from the learning experiences of social adjustment caused by painful rejection in childhood social situations. Typical schizophrenic withdrawal and indifference, manifested in a variety of ways, is the compensating mechanism for this isolation. Complementing the environmental theory is the application of learning theory to schizophrenia. Sheldon's correlation of ectomorphy, anxiety, and schizophrenia would indicate that schizophrenics are highly anxious persons, reacting more rapidly to conditioning and generalizing to a greater extent than normals. Schizophrenia, then, is conditioned to a single anxiety response (the precipitating stress), the response is generalized, and anxiety levels are lowered. It should, in any case, be fairly obvious that Freud's observation
that anxiety and defense are at the core of emotional maladjustment has been proven with some degree of conclusiveness.
Chapter Three

PSYCHOTHERAPY IN NEUROSIS AND PSYCHOSIS

The nature of neurosis and schizophrenia from a psychogenic viewpoint has been briefly considered. From the previous chapter it can be ascertained that anxiety and defense are at the core of maladjustment, some technique must be devised whereby inappropriate defense mechanisms against anxiety feelings must be relaxed. The processes of free association, transference, and abreaction were mentioned as such techniques. The methods involved in treating both neurotic and psychotic patients will now be considered.

The task of psychotherapy is an awesome one. In a relatively short period of time the counselor is expected to reverse or alleviate a learning process of long-standing, whose elements may still be present in the patient's daily environment. The forces on the counselor's side, however, are powerful, for never has the patient been in the unique position of verbalizing his guilt, problems, and anxieties to such an interested listener. More than this, the listener is an expert, trained to aid the patient in alleviating his disturbances, and it is with the idea of securing assistance that the patient has come to the counselor (41).

As indicated in the previous chapter, the main device by which the counselor may secure an improvement in the patient is by a corrective emotional experience, an emotional reliving of the initially suppressed anxiety, manifested later in an inappropriate manner. This is, of course, abreaction. The two primary constituents of abreaction are a reappraisal of
these anxieties and a relaxation of the defenses against these anxieties (13). The following methods have been found useful in this regard.

Non-directive psychology is the shortest therapeutic method developed and herein lies its primary advantage. The non-directive method relies, to a large extent, upon the patient's willingness to communicate his feelings to the counselor in an active manner. The therapist, on the other hand, remains in the background and refrains from introducing any form of interpretation during treatment, although the roots of the patient's difficulty may be apparent from the initial meetings. The client is instructed to take the lead in introducing topics for discussion, while the therapist maintains a passive, permissive role in the discourse. The primary function of the therapist is to draw out and clarify the emotional content of the patient's discussion. Thus, the patient might communicate unwittingly an emotion-laden thought. The therapist must recognize the emotional potential of the thought and restate it in such a way that the patient, too, will realize its significance. The patient, of course, is initially impressed with the fact that he must take the lead in the conversation, i.e. he must structure the therapeutic situation. The counselor is involved with the recognition, acceptance, and clarification of feelings. In general, negative feelings are the first to be expressed by the patient and may continue throughout several of the initial sessions. Eventually, however, positive feelings, hinted at first, will become evident and, after prodding by the therapist, become reinforced.
Finally, insight is achieved and the patient initiates positive impulses of which he was previously incapable. Breaking the therapeutic situation may present difficulty, but the patient is gradually encouraged to leave it with the assurance that he may return if he so desires. The main difficulty in the non-directive method seems to be the limitation that in such an abbreviated length of therapy the neurotic nucleus may be so repressed and hidden beneath protective defenses that it is not touched at all. Rather, secondary symptoms may be alleviated, while the primary disturbance remains fully active.

A second limitation, of course, is the fact that the therapist plays such a passive role in comparison to other forms of treatment that interpretation of symptoms is displaced from a primary to a secondary position when, in fact, it could be of great value. Standard psychoanalysis, while more lengthy, takes these matters into consideration, deals with them, and is consequently more effective (41).

Although every analyst develops his own techniques and often adapts his method to the individual patient, certain consistencies appear in every psychoanalytic method to justify the use of the term "standard psychoanalysis". The first basic process involved is the technique of free association. Theoretically, this technique is validated by the fact that, since the patient is aware of the irrational manifestations of his anxiety and is primarily concerned with their removal, then any thought expressed during the therapeutic session will be involved, either directly or indirectly, with the neurotic nucleus (13). By employing free association the
analyst is able to lower the massive defenses of the seriously neurotic patient and to ascertain the nature of the basic conflict by interpretation of the various symbols created by the patient. Initial resistance is usually to be expected. Once the patient feels secure in the therapeutic situation, however, his anxiety will be lessened and at this point the analyst may interject interpretations whenever they are deemed helpful. In this, of course, the psychoanalyst is in sharp contrast to the non-directive counselor. The psychoanalyst freely offers interpretations to the patient, particularly in regard to thoughts which are apparently being withheld. By this process, then, the patient may view his defenses rationally and put himself to the task of freely communicating.

Resistance and repression are the forces which the analyst must recognize in the patient. The patient must, in turn, be made to realize that the fear, for which his defenses have been erected, are not as great as he supposes. In the security of the existing relationship the patient is strengthened and with encouragement his defense mechanisms are relaxed (13).

Once this relaxation occurs the patient's emotional reactions come to bear on the analyst in the process of transference. In standard psychoanalysis transference neurosis is considered to be essential in that it indicates that the forces of the neurotic nucleus have been directly aroused. Transference is an outgrowth following naturally from defense relaxation and not a suggestion of the analyst. The patient deals inappropriately with the therapeutic relationship in an emotional sense and it is the realization of this inappropriate behavior, coupled with the violent emotional reaction,
which brings the end of therapy into view (41).

During the course of treatment dreams are often mentioned to the analyst. As pointed out previously, dreams provide a means by which defense mechanisms become lowered and anxieties may be portrayed symbolically. Therefore, dreams may facilitate analysis by indicating to the examiner the content of thoughts which are being withheld and even the distinct nature of the neurotic conflict (13, 41).

The third method of therapy is an abbreviated form of standard psychoanalysis in which the examiner manipulates the therapeutic situation to accommodate the individual patient. Many psychoanalysts consider the violent emotional reactions of many patients during transference and abreaction unnecessary, if not harmful, except as directly related to the central core of the neurosis. This fact is particularly true of patients having a low emotional threshold. Therefore, the analyst may vary his attitude and the sense of his interpretations to the patient, thus regulating the intensity of the patient's emotional responses. Often outside activity is encouraged and a functional attitude on the part of the analyst is displayed, thus allowing the patient to test the efficacy of his new perspective. Any method tending to shorten the lengthy process of psychoanalysis may be classified under the heading of the principle of flexibility (41).

Summarizing the main points concerned with the treatment of neurotics, an initial therapeutic relationship is established in which the patient is placed in the unique position of being examined by an expert, trained to restore health.
A permissive atmosphere is dominant in which the mental health of the patient is considered primary as evidenced by the interest and encouragement of the analyst. The expression of feelings is encouraged by the process of free association and resistance and repression indicated. The emotional content of thoughts is reinforced by the patient's recognition of his defenses and the interpretations of the analyst. Transference occurs after defenses are sufficiently relaxed and the core of the neurosis aroused. Finally, new behavior is demonstrated in the final stages of the therapeutic sessions.

If the treatment of neurosis seems complex, then the psychological treatment of schizophrenia appears to approach the impossible. The therapeutic relationship is crucial to successful treatment and is a communicative understanding between patient and examiner. It will be recalled from the previous chapter that one of the marked behavioral abnormalities consistently found in schizophrenia is the apparent suppression of the desire to communicate and interact socially. Therefore, the necessary communicative channels are essentially non-existent between examiner and patient, defeating the aims of the therapeutic relationship. Indeed, the schizophrenic in rejecting the existence of external reality, rejects the examiner as well. The main problem, then, is to encourage activities whereby the patient will be given the opportunity to re-establish social interaction. With these goals in mind occupational therapy, the attitude of the ward personnel, educational therapy, in short, the constituents of the "therapeutic community", all attempt to bring about a new rapport
between the schizophrenic and reality. Once such a goal is attained the possibilities of psychoanalytic treatment can be considered. The principle of flexibility takes on added importance when dealing with the schizophrenic. Although a patient may take the first cautious steps toward social contact, this desire can be promptly suppressed by the constant reminder of still-present emotional difficulties. The goals of psychotherapy, then, take on a new character in that adequate adjustment to reality becomes more important initially than the corrective emotional experience. It is interesting to note that schizophrenics, so sensitive to the reactions of others, are capable of extremes of love and hate toward the analyst once the therapeutic relationship is established (41).

Within recent years several chemical and mechanical agents have been introduced in order to facilitate psychotherapy. Insulin shock and electroconvulsive therapy have produced marked periods of lucidity during which concomitant psychotherapy may achieve its necessary goals. These methods, however, have been largely replaced by the tranquilizing drugs, reserpine (Serpasil) and chlorpromazine (Thorazine) to mention two, which will now be considered.
Chapter Four

DRUG THERAPY--CLASSIFICATION, ACTION, AND EFFECT

Since the days of Sakel and other research workers in the field of mental illness, various forms of physical therapy, e.g. E.C.T., hydrotherapy, and insulin shock, have been utilized with varying degrees of success. Initially, as, for example, with the use of insulin, greatly encouraging results have been obtained and the spark of hope among those workers clinging wishfully to the hope for an absolute cure for schizophrenia has been aroused (33). However, in every case further research has lowered the values of early results markedly, usually to the point where the use of the treatment is greatly limited clinically. Early in the 1950's, Dr. Nathan Kline reported a new drug derived from the roots of the plant Rauwolfia serpentina which brought about favorable behavioral changes in schizophrenia. This drug he named reserpine, the first of the ataractic drugs (10).

Early research indicated that the use of reserpine (trade name, Serpasil) did indeed produce a calming effect on mental patients, allowing psychotherapy to gain a foothold with previously inaccessible patients. Some workers, however, began praising reserpine rather prematurely as an absolute cure for schizophrenia (42). Shortly after the introduction of reserpine, chlorpromazine (Thorazine) was synthesized and is now in widespread use. This compound possesses many of the tranquilizing qualities of reserpine, while eliminating the undesirable side-effects observed in reserpine administration (10).

Thus began the era of the tranquilizers. Since 1950
several new drugs have appeared, each claiming a specific quality to deal with the myriad behavioral manifestations of schizophrenia. Notice that the use of these drugs as a form of therapy was derived from empirical, rather than deductive, evidence, as was the case with previous therapies. In general, research since the inception of the "tranquilizer era" has indicated that these drugs are indeed helpful in facilitating remission in schizophrenia, though not in the order of the original claims. The value of the use of reserpine, even as a therapeutic adjunct, has been seriously questioned by some workers. It will be expedient to classify the tranquilizing drugs by structural formula and valuable to discuss their psychological and physiological effects. In dealing with the effectiveness of these drugs, however, one fact should be kept in mind. Several workers have noted a distinct bias produced by a physical difference existing between the active drug given to an experimental group and either an inactive or active placebo given to controls. In patients placebos have often produced a greater beneficial effect than the drugs themselves (25,52).

The phenothiazines, of which chlorpromazine is the outstanding representative, are employed more frequently in clinical practice than any of the other drugs and have demonstrated the most general therapeutic effect (42). The basic structural formula and a few common representatives are illustrated below.

![Phenothiazine nucleus](image)

Figure 1  The Phenothiazines (6)

```
a. Phenothiazine  
b. Chlorpromazine  
c.(Hemlaril) Thiordazine  
d.(Compazine) Prochloropenazine  
e.(Stelazine) Triluropenazine  
f.(trilafon) Perphenazine
```
In general, the pharmacological action of the phenothiazines is involved with adrenergic blocking in the autonomic nervous system. The drugs exhibit atropine-like and antihistaminic properties, also acting as anti-emetics. Sedation, hypnosis, and often anaesthesia are usually present. Conditioned reflexes are blocked (8). Interestingly, the phenothiazines potentiate the action of analgesics, anaesthetics, and certain other drugs, and are psychologically antagonistic, in part, to the effects of LSD-25 (34). Good prognosis in treatment with chlorpromazine may be correlated with raised cupric ion concentration in the plasma (51).

Psychologically, overt psychosis and drive levels are decreased, while introversion and suggestibility are increased (119). The basic processes, psychological and/or physiological, are still at work and merely the secondary or accessory symptoms of Bleuler modified or removed (8,9).

Thus, it may be assumed that the phenothiazines, as well as the other tranquilizers, do not inhibit fundamental processes in schizophrenia, but rather make the patient more amenable to psychotherapeutic means of treatment. At least the drugs are distinctly helpful in facilitating more humane treatment of the mentally ill.

The second group of drugs, the Rauwolfia alkaloids, are related chemically by the presence of the yohimbine nucleus. Three representatives are listed below. These drugs have all been isolated in the pure state.
Reserpine (Serpasil)
(methyl reserpate; 3,4,5 trimethoxy benzolic acidester)

Deserpidine (Harmony)
(ll-demethoxy reserpine)

Also note: Reserpamine (Moderil)-3,4,5 trimethoxy cinnamic acidester

Figure 2 The Rauwolfia Alkaloids (9)

Pharmacologically the Rauwolfia drugs demonstrate a general suppression of the sympathetic nervous system, presumably by inhibiting the sympathetic nervous centers located in the hypothalamus. Sedation, though not anaesthesia, is produced by these drugs and conditioned reflexes are blocked (9).

These drugs liberate serotonin from the intestines, blood platelets, and brain as measured by an increase in its breakdown product, 5-hydroxyindole-acetic acid, in the urine (10).

This series of drugs produces essentially similar psychological effects as those of the phenothiazines. However, side effects such as marked depression and increased physiological difficulties, not apparent with the phenothiazines, are often demonstrated in the use of reserpine. The time of maximum therapeutic action is usually spread over a period of three to four weeks (9,10).

The third drug group of importance is the diphenylmethane group. These drugs, of which Frenquel is the outstanding representative, have been utilized in neurotic, as well as psychotic, states in varying degrees of success. The structural formula
of Frenquel is given below.

![Frenquel molecule]

**Figure 3**  
Azacyclonol (Frenquel) (3)

Pharmacologically, the diphenylmethanes are anti-hista-
minic and exert an atropine-like action. They antagonize
some of the effects of serotonin and in large doses may pro-
duce convulsions. The sedative and hypnotic actions, common
to the previous classes of drugs, are not apparent in the
diphenylmethanes. Also, the group may facilitate, rather
than inhibit, conditioning. The psychological effects remain
unknown (6). Frenquel, however, effectively blocks the LSD
psychosis (61).

The fourth class of drugs used in treating psychotic
states is the substituted propanediols which, as can be seen
from the structural formulae below are, basically modified
glycols.

![Propanediol molecules]

**Figure 4**  
The substituted Propanediols (3)

This class of drugs does not effect the function of the
autonomic nervous system, as was evidenced in the previous
groups discussed. Rather, muscle spasms are relieved by a decrease in the conductivity along interneuronal pathways and convulsive thresholds to electric and chemical stimulation are raised. Larger doses produce a reversible paralysis of the voluntary muscles without affecting the circulation or respiration. These drugs have no effect upon conditioned reflexes.

Since these drugs raise the "frustration threshold" the performance of behavioral tasks under stress situations is permitted. In usual doses the propanediols do not effect tasks requiring judgment or skill. Thus, the application of these drugs to the psychotic state is obvious (6).

The final class of drugs in general use is the substituted amides, which include several sedatives and hypnotics. The common structure and several representatives are indicated below.

![Chemical structures](image)

| General structure | Pentobarbital (Nembutal) | Glutethimide (Doriden) | Oxanamide (Quiaactin) |

Figure 5   The Substituted Amides (6)

In large doses these drugs produce anesthesia and in normal doses induce sleep. In doses large enough to abolish consciousness, paralysis of the skeletal muscles results. The substituted amides act as anti-convulsants by increasing the threshold of stimulation required for neuronal activation (6). These drugs decrease adrenalin levels in plasma (119).

Psychologically, extroversion may be increased, especially
in hyperexcited neurotic patients. Performance on a variety of motor tasks is markedly inhibited (8).

There are four regions of the brain of particular importance in determining the psychophysiological action of the tranquilizing drugs. Although other effects may be present and of considerable importance, these regions, which are to be discussed, are of known function and the effects of the drugs can be determined.

The cortex is the seat of thought and judgment. The pharmacological effects can be grossly measured by observation of electrical brain-wave recordings. Of the five classes of drugs mentioned the substituted amides have the most pronounced effect on the cortical region, decreasing the frequency of brain waves and increasing the amplitude of the waves. This effect resembles that noticed in natural sleep and explains in part the impairment on psychological tests noticed when subjects are under the influence of these drugs (8).

The hypothalamus is the regulating gland for autonomic functions. Again, electrical recordings are utilized to indicate the effects of various drugs. Two methods have been devised to measure responses from the hypothalamic area. Robert Heath et al, studying wave patterns from the septal region of the brain in animals and humans, implanted chronic electrodes in the brain of his subjects, employing a stereotaxic device to insure accurate placement. Heath was able then to record the brain waves of schizophrenic patients, both treated and untreated, and the brain waves of monkeys injected with various hallucinogenic drugs. The obvious difficulty with such a method is that immutable brain lesions
are created. The alternative method to measure drug effects involves the determination of the amount by which the drug in question lowers the threshold of convulsions induced by electroshock seizures and chemical convulsants. Both methods indicate that the phenothiazines, the Rauwolfia alkaloids, and the diphenylmethanes are stimulants to the hypothalamic centers (8,15).

The limbic system, involving the rhinencephalon or visceral brain, is thought to be of importance in emotional processes (15). The effects of the drugs are measured by analyzing the spontaneous potential or observing the occurrence and duration of after-discharge produced by electrical stimulation of this area. The phenothiazines and Rauwolfia alkaloids produce seizure discharges in this area. These discharges do not readily spread to other areas. The propanediols and substituted amides abolish or shorten after-discharges produced by electrical stimulation.

Finally, the reticular formation, consisting of the brain stem and midbrain area, controls wakefulness and sleep. The substituted amides and all hypnotics suppress cortical arousal by stimulation and depress the reticular formation. The propanediols do not block the reticular formation. The other drugs slightly depress this area.

The method of action which these drugs exert may be generally hypothesized to occur in the following manner. Psychotic patients show a lowered responsiveness to stimulation and drugs, presumably due to the low reactivity of autonomic centers in the hypothalamus. The phenothiazines and the Rauwolffia alkaloids stimulate the hypothalamic area and thus
should be of value in reducing the psychotic state. A stimulating effect on the limbic system should abolish emotional flatness and the seeming indifference generally encountered in schizophrenia (8).

Mention should be made in this section of the stimulating drugs which have recently come into clinical use. These drugs can not be usefully classified by the use of structural criterion. However, in general they fall into distinct biochemical categories.

The most common stimulants used and the most familiar to the general public are the analeptic drugs, of which Benzedrine and Dexedrine are the most prominent representatives.

\[
\begin{align*}
\text{CH}_2\text{C}_9\text{H} & \text{C}_9\text{H}_3 \\
\text{NH}_2
\end{align*}
\]

\(d,l\text{-}2\text{-}\text{amino}-1\text{-}\text{phenylpropone; Dexedrine, }d\text{-isomer}

Figure 6  Benzedrine (d,l amphetamine) (8)

These drugs antagonize the action of central nervous system depressants and produce hyperexcitability. Consequently their use in psychotic states is limited to those patients suffering from a markedly lowered activity of the central nervous system. In depressive neurotics and depressive maladjustment these drugs are of particular importance. In large doses euphoria and confusion are produced.

The second group of stimulants is the inhibitors of monoaminoxidase (MAO inhibitors) usually containing the general structure: \(R--\text{NH}--\text{NH}--R'\). Iproniazide, shown below, was the first of these drugs to be considered therapeutically effective. Some hypothetical evidence has been advanced for the use of
MAO inhibitors in that adrenalin and serotonin have been linked with the schizophrenic process. These drugs alter the metabolism of both these substances, the levels of adrenalin in the body being markedly changed (8,82). The significance of this observation will be discussed in the chapter dealing with biochemical theories of schizophrenia.

Figure 7 Iproniazid (Marsilid) (8)
Chapter Five

STATISTICS IN EXPERIMENTAL RESEARCH

The use of statistics in experimental research is finding wide application in the examination of physiological data. Indeed, in the studies involving schizophrenia and the physiological abnormalities presumed to exist in this condition, the primary means of differentiating normal and experimental groups is by the use of statistical techniques. In some studies unwarranted use of statistics has led to the publication of, at best, misleading data. Therefore, some basic statistical concepts will be presented in anticipation of the later studies which will be reviewed.

Initially a distinction should be made between the two types of statistics in use—the parametric and non-parametric types. Parametric statistics refer to a statistical model which specifies certain conditions about the parameters of the population from which a sample is drawn. A non-parametric test specifies no conditions about the population, but assumes that the observations are independent and that the variable under study has underlying continuity. The latter is potentially very useful in the behavioral sciences since its assumptions are weaker than those of parametric statistics. In the latter it is often difficult to ascertain the nature of the underlying distribution of events.

Frequently an average or typical score is of great use in comparing the results of various tests. The measures of central tendency are the mode, the mean, and the median. The mode is defined as the most frequent score in a group of scores,
the mean is the arithmetic average of these scores, and the
median is that point found half way in the number of cases
composing a frequency distribution. The variability of points
surrounding the median is measured by the interquartile range,
the two points in a distribution of cases defining 50% of the
values surrounding the median. The standard deviation measures
the variability of points around the mean in a normal distribution
and is defined as the root-mean-square deviation from the mean.

In the natural sciences measurement is for the most part
objective, that is having reference to an external standard
which exists apart from the control of the measurer. Often
in psychological research, however, the observer selects an
appropriate standard by which to measure the quantity in ques-
tion which is usually an arbitrary selection. Such a method is
called scaling and for each type of scale only certain arith-
metic operations are permitted. The nominal scale merely
assigns a letter or a number to the qualities being measured
to indicate that a difference exists between them. Since
there is no indication of the degree of difference which exists
between the quantities, the only appropriate measure of cen-
tral tendency is the mode.

A more powerful means of measurement is the ordinal scale,
which indicates the fact that a "greater than" or "less than"
relationship exists between the quantities measured. Thus
the ordinal scale may employ both the mode and the median as
measures of central tendency.

The third, interval, scale places the quantities on a
continuum on which the distance between any two points is
known. Not only is the "greater than" or "less than" relationship indicated, but also the degree to which the quantities differ. Since real numbers are utilized on the interval scale, the mean and the standard deviation may be utilized. Standard I.Q tests are examples of the employment of the interval scale.

Finally, the ratio scale has numbers which have an inherent arithmetic relationship to each other. Unlike the interval scale, there is a true zero point and a known ratio exists between any two scale values. Thus, any arithmetic process may be used when dealing with this scale.

In a frequency distribution in which the only influential factor is chance, the number of times in which one of two events will occur can be specified by the binomial expression \( (p+q)^n \), where \( p \) is the proportion of times that the event in question occurs, \( q \) is \( 1-p \), and \( n \) is the number of trials which are made. The binomial expression can be approximated by the normal curve, whose equation is known, and it is this normal curve which finds widespread application in psychological research. Thus, in a set of data, influenced only by chance, the probability that a certain event will occur can be compared to the hypothetical distribution of outcomes expected.

In a specified experimental design there are always two or more groups observed. One of these, in the simplest case, is the experimental group which is tested under certain conditions for the effect of the variable in which the experimenter is interested. The second group, or control, is observed under comparable conditions, but is not subjected to the influence
of the variable in question. If only chance factors influence the experimental group, and between the two groups a difference occurs, then assuming that there is adequate control of the independent variables, this difference may be attributed to the influence of the dependent variable. The principle underlying this experimental design is formulated as the null hypothesis, defined thusly: In two experimental groups subjected to similar conditions in which only chance factors are operating, the expectation is that the probability of a specified event occurring in one group, if taken to an infinite number of trials, is equal to the probability of the same event occurring in the second group. If a difference of some specified magnitude does occur, then the null hypothesis is rejected and the alternate, or affirmative hypothesis, that factors other than those of chance are exerting an influence, is accepted, assuming, again, that the independent variables have been adequately controlled. A statistically significant difference is an arbitrary probability which specifies the number of times that the experimenter is willing to be wrong in accepting or rejecting the null hypothesis. Two types or errors can be made. Either the null hypothesis is rejected when it should be accepted (type I) or it is accepted when it should, in fact, be rejected (type II). Generally a probability or significance level of $p<0.05$ is selected above which the null hypothesis is accepted. Mention should be made here of the region of rejection, which is that part of the normal curve whose data are so extreme that, if the null hypothesis is rejected, the probability is very small that a type I error has been made.
When choosing a statistical test the following criteria must be considered:

1. The level of measurement applicable to the experiment.
2. The power of the test to be used.
3. The applicability of the test to the experimental design.
4. The power-efficiency of the test, i.e. the increase in power necessary to make test A as powerful as test B, assuming B to be the more powerful. The power of test A may, for example, be increased by increasing the population size. A non-parametric test, then, can be made as powerful as a parametric test by this means.* Both tests assume that the scores have been independently drawn from the sample (35).

In summarizing what has been said concerning essential design features and the choice of a statistical model, several factors must be present. Randomization of the sample is necessary to insure the independence of scores drawn from the sample. Replication and the use of adequate controls are crucial to reject the null hypothesis with the certainty expected by the power of the test. The assumptions of the statistical test

*Note: Frequently the non-parametric test is compared with the most powerful parametric test, the F test. The assumptions underlying this test are as follows:
1. Observations must be independent.
2. Observations must be drawn from a normally distributed population.
3. The population must have the same variance.
4. Measurement must be on at least an interval scale.
5. Effects must be additive. (35)
must be fulfilled if the results are to be meaningful. Bias
must be eliminated, again to insure that scores are independently
drawn. Finally, the level of measurement and the error which
can be allowed must be either stated or implied in the exper-
imental design.

Certain features, though not essential to the design, can
considerably increase the efficiency of the experiment. Var-
ious designs, such as the Latin-square design which segregates
unwanted variation from experimental error, considering each
variable to be constant over a specified range of conditions,
or the "randomized blocks" design in which all interactions
are considered to be zero, increase efficiency by minimizing
the number of subjects necessary for the experiment and con-
serving more data than other less-efficient designs, which
measure the effect of several variables over the range of each
condition. The two former tests are only applicable, how-
ever, when the assumptions specified are met. Other techniques,
such as covariance analysis, may be employed to correct for
known, but uncontrolled sources of error. The experimenter
may even manipulate certain sources of error so as to reduce
experimental error in the final analysis. It should be empha-
sized again that these design features are not essential to
the make-up of the design itself and, indeed, are unwarranted
if the assumptions underlying each are not fulfilled (25).
Chapter Six

THE PSYCHOTOMIMETICS AND MODEL PSYCHOSES

The use of artificial mechanisms to escape the overpowering burdens of life dates back to the very beginnings of man's recorded history. Alcohol, hashish, opium, and others, have played an important part in the cultures of every nation. Only the means of escape differs, the causes remain the same and are firmly rooted in man's nature. Above all, there is the desire to transcend reality. The historical background of these drugs will be examined for a moment. Included will be the observations of several non-scientific observers who have attempted to relate the curious phenomena which they experienced after taking these drugs.

The use of an intoxicating agent in the rituals of certain European and Asian tribes, notably the Koryakian and the Yukaghira, located near the Tilgilak and Koryakian borders on the Russian Pacific coast, was first reported by the Swedish theologian and scientist, Samuel Oudemann, in 1784. His work was based upon the writings of Georg Wilhelm Steller, a German scientist who, with the Dane, Vitus Bering, explored the area around the Kamchatka peninsula and reported the use of mushrooms, dried and eaten by the inhabitants of this area, consuming at the same time large amounts of cold water. Within half an hour the intoxicant exerted its effect, characterized by spasmodic convulsions, euphoria, and fantastic illusions. Oudemann identified the mushrooms as Amanita muscaria. In his writings Steller gives the following account:
The ones who, on account of poverty, can not buy the mushroom get hold of the urine of the intoxicated and drink it. By this, they get the same fury and the urine has the same effect down to the fourth or fifth man. . . if one kills such a reindeer (who has eaten the mushroom) and eats the meat at once, one will get the same kind of fury as if one had been eating the mushroom itself.

(32)

The literature regarding the mushroom cult of the Koryakian tribes has been summarized by the studies of Waldemar Joeschelson in his investigations of the Russian Pacific area in 1900-1901. One of his observations has the Koryaks wearing broad-brimmed hats in imitations of the poisonous mushrooms to which they believed themselves changed. Similar experiences have been reported among the migrant Norwegian tribes known as Berserks during the period 870-1050 A.D. It is thought that the folklore and religious significance of the use of Amanita muscaria in these two instances is the same (32).

Thousands of miles away, in the primitive mountain areas of Mexico, the rites of mushroom intoxication are today related to the sacraments of Christianity. The tribes inhabiting this tremendous, but relatively inaccessible area of Mexico, call the mushroom "teonanacatl"—God's flesh—although there are actually six different species, all members of the family Psilocybe. The primary active component is thought to be the recently-synthesized hallucinogen psilocybin. R. Gordon Wasson, in his extensive investigations in this area, reports his rather vivid hallucinogenic experience following the ingestion of the crude mushroom buttons.

. . . The visions came whether our eyes
were open or closed. They emerged from the center of the field of vision, at the pace that our will chose. They were in vivid colors, always harmonious. They began with art motifs, angular such as might have decorated carpets or textiles or wallpaper of the drawing board of an architect. Then they evolved into palaces all laid over with semi-precious stones. Then I saw a mythological beast drawing a regal chariot. Later it was as though the walls of our house had dissolved, and my spirit has flown forth, and I was suspended in mid-air viewing the landscape of mountains with camel caravans advancing slowly across the alopess, the mountains rising tier above tier to the very heavens.

Later in this account Wasson describes the feeling brought about by the mushrooms.

...the effect of the mushrooms is to bring about a fission of the spirit... a kind of schizophrenia, with the rational side continuing to reason and to observe the sensations that the other side is enjoying.

(118)

In the native religious groups of our own Southwest appears the widespread use of the cactus plant termed peyote by the Indian tribes and scientifically named Amhalonium Lewinii (Lopophora Williamsii). The Spanish conquistadors described this cactus and the rites connected with it when they first invaded the Aztec nations. The use of peyote later spread to the Plains Indians of the Southwest and is still used in the communion rites of the Native American religious groups.(10)

The active component of peyote is the alkaloid mescaline. Aldous Huxley describes his experience under the influence of this drug in a very intense manner.

Half an hour after swallowing the drug
I became aware of a slow dance of golden lights. A little later there were sumptuous red surfaces swelling and expanding from bright nodes of energy that vibrated with a continuously changing, patterned life. At another time the closing of my eyes revealed a complex of gray structures within which pale, bluish spheres kept emerging into intense solidity and, having emerged, would slide noiselessly upwards out of sight.

(18, p.16)

Not all of Huxley's perceptual changes were as obvious as these, however. Here he describes changes of a more subtle nature.

The books glowed...with brighter colors, a profounder significance. Red books like rubies; emerald books; books bound with white jade; books of agate; of aquamarine; of yellow tapaz; lapis lazuli books whose color was so intense, so intrinsically meaningful that they seemed on the point of leaving the shelves to thrust themselves more insistently on my attention.

(18, p.19).

In general, then, temporal and spatial relationships existed for Huxley during the mescal experience. They were rendered meaningless, however, by other considerations. Withdrawal was evidenced during the experience and, from the quotations cited, it can be seen that there is an exceptional interest in color and inanimate objects. Huxley claimed that he suffered an intellectual impairment, but was aware of a dual nature in himself, one the objective, rational mind, the other the subjective, sensual body existing as completely separate entities (18).

The eating of mushrooms similar to those described was investigated by Bunadino de Sahagún, who worked among the Mexican Indians from 1529-1590. De Sahagún claimed that these mushrooms caused inebriation, hallucinations, and excited
lust (32). His descriptions conflict somewhat with those of Wasson and Huxley who claimed that they were intellectually sound and that the visions which they had were purely aesthetic (18,118).

One of the outstanding mycophilic literary pieces is found in Carroll's *Alice in Wonderland*. Having complained to a hookah-smoking caterpillar that she is discontented with her size, Alice is advised that the eating of a proximate mushroom will make her taller or shorter according to which side of the mushroom she eats. Nibbling one side she shrinks to minute size; eating from the other she is immediately mountainous, her neck ascending skyward leaving the remainder of her body far below. These fantastic changes in body image are not unknown to mushroom-users(32).

It has been noticed by several authors that the psychotomimetic drugs induce a state of split personality, a separation of the rational and sensual entities in personality, and thus, owing to a literal, but inappropriate use of Bleuler's word, schizophrenia, a true state of mental illness. It would seem, however, that these drugs might have some use in the study of mental illness because of the unusual behavioral manifestations which they produce. Critics of the use of "model psychosis" have repeatedly pointed out that schizophrenia is not a definite split in the mind, but, instead, a fragmentation of the personality. Bleuler himself characterized schizophrenia as a compartmentalization of personality traits and a dissociation of associative pathways exemplified in the characteristic ambivalence of schizophrenic patients (9). Nevertheless, the psychedelics [mind-manifesting], to use
Hoffer's recently-coined word, are being used more and more to gain an intimate understanding of schizophrenia on both the physiological and psychological levels. In order to validate the experimental usage of these drugs the objections raised against the model must be answered. These objections fall mainly into two categories, first that the psychedelics resemble the toxic psychosis more than the functional psychosis, and two, that visual hallucinations, rarely apparent in schizophrenia, predominate in drug-induced psychosis and auditory hallucinations, often found in schizophrenia, are usually absent in the action of psychedelics.

The first objection states, in substance that the differences between experimental psychosis and schizophrenia are more important than the similarities. The question is implied in this statement, what are the differences between the two states? One difference, of course, is the fact that experimental psychoses are caused by a known chemical factor, whereas schizophrenia is "functional" in character. The physical cause for schizophrenia, however, is unknown, rather than non-existent, and the classification itself is dependent upon the diagnostic techniques of the qualified observer.

The sequel to this contention would be that the psychedelics do not reproduce faithfully the behavioral manifestations of schizophrenia and on this basis their experimental value is questionable. It is not claimed, however, that any one of the drugs employed experimentally is the cause of schizophrenia, but, rather, that each reproduces a certain aspect of the schizophrenic syndrome. All of the psychedelic drugs, mescaline, amphetamine, psilocybin, LSD-25, to mention only a few, exhibit
differnet behavioral characteristics among themselves and have potencies of varying strength. It is to be expected, therefore, that if there is a toxic factor in schizophrenia, then it, too, will exhibit its own peculiar characteristics, similar, but not equivalent to those of the psychedelics. It should be mentioned, in this connection, that some subjects undergoing amphetamine psychosis are clinically indistinguishable from schizophrenics when diagnosed by "blind" psychiatrists. The diagnostic tools of psychology, unreliable as they sometimes may be, often indicate schizophrenic reaction or a schizo-affective trend in normal subjects under experimental psychosis (16). Therefore, diagnostically speaking, the experimental and actual states may be confused. Further, in dealing with experimental psychoses, it must be remembered that most normal subjects could not be expected to develop a true schizophrenic reaction, complete with confusion and fragmentation of personality. The situation between the two states differs markedly since the experimental subject can rationalize his feelings of unreality by attributing them to the drug which he has ingested. In contrast, the true schizophrenic has no such frame of reference with which to defend against the odd sensations that permeate his mind and body, and consequently the two states should differ to some extent for this reason.

Most of the psychedelic drugs induce a state of autonomic stimulation similar to that observed in the toxic psychosis. Further, all of the psychedelic drugs are extracted from plants or synthetically produced products, rather than of
animal origin. However, as indicated above, the behavioral symptoms produced are remarkably similar to schizophrenia in some cases and are distinct from the behavioral states in toxic psychosis. The psychological and physiological similarities between schizophrenia and the schizophrenic model will be enumerated later in this chapter. It should be noted that Hoffer and Osmond found adrenochrome, an adrenalin breakdown product, schizogenic, i.e. lacking the autonomic stimulating properties of the psychedelics while producing the behavioral characteristic of the syndrome (64). More recently Heath and his coworkers have reported schizogenic properties resulting from the injection of a certain protein which has been isolated from the plasma fraction of schizophrenic patients (77).

The second objection to the use of psychedelics in research seems to be more of a case of misinterpretation than of actual fact. Though many of the initiates into the use of the drugs report true visual hallucinations, the visual component of the experiences seem to become less intense, and in some cases completely absent, upon repeated use (45). Wasson, in his report, emphasized the visual experiences which he undergoes (118). Huxley, however, taking mescaline for the first time, does not report true hallucinations, but emphasized the visual distortion which takes place (16). Humphrey Osmond, who received adrenochrome by subcutaneous injection for the first time, reports marked perceptual changes, particularly in inanimate objects. Notably absent were true hallucinations (84). Other subjects studied in the investigations
of Hoffer, Osmond, et al, have exhibited autism, intensification of color stimuli, and a marked distortion of body image. Few, however, have reported true hallucinations as such (16).

Euler, in his book, notes that auditory hallucinations are predominant in the schizophrenic psychosis, whereas other hallucinations, visual, tactile, olfactory, or gustatory, are rarely present. He does not distinguish between perceptual changes and visual hallucinations, however (9). Many remitted schizophrenics have reported in their autobiographies that visual distortion was indeed present, disturbingly so. Many patients, unable to express these perceptual anomalies, may revert to standard clichés regarding "feelings of unreality". Visual hallucinations are often present in the acute stages of schizophrenia (16).

In regard to the presence of auditory hallucinations, one point needs qualification. It would not be difficult for an observer to misinterpret a patient's claims of "voices" as existing completely apart from auditory stimulation. Undoubtedly some, if not many patients, merely personify actual sounds and distort them into "voices" by subjective association. Auditory hallucinations, then, may, in some cases be no more than auditory distortion. On the other hand, auditory hallucinations have been reported in the administration of taraxin (77).

In presenting the material dealing with the psychedelic drugs, it would be convenient if some common technique could be utilized to form a skeletal structure within whose bounds
the drugs could be more readily understood. This method was attempted in the consideration of the tranquilizing drugs by dividing these drugs into compounds of similar structure.

A secondary system was developed in regard to the stimulants in which a physiological, rather than a chemical criterion was judged to be more inclusive. Likewise in the psychedelic drugs a common bond runs, as expected, throughout the group. Structurally, all of the drugs contain the indole nucleus or groups that may be transformed to this nucleus in vivo. This is not to say, however, that all indole compounds are hallucinogenic. This criterion, then, crudely separates the psychedelic drugs from other types of active compounds. A second criterion offers a profitable means of classifying the psychedelics, namely by a study of biochemical activity. This concept, developed extensively by Hoffer and Osmond, considers the action of drugs related by the following diagram:

1) acetylcholine → esterase

2) epinephrine → dihydroxy-N-methylindole

\[ \text{adrenochrome} \quad \text{trihydroxy-n-methlyindole} \]

Figure 1  Relationship of the Psychedelic Drugs (16, p.199)

The rationale behind this diagram is explained by a quotation from these workers.

...all substances which increase the concentration of acetylcholine, epinephrine, adrenochrome and adrenolysis or combinations of these in the brain are psychotomimetic.

(16, p.200)
The drugs will be considered, then, under the following headings: 1) psychedelics structurally similar to epinephrine, 2) psychedelics interfering with acetylcholine function, and 3) psychedelics structurally similar to adrenochrome.

1) Mescaline

Historically the use of mescaline, the most active of eleven alkaloids found in the cactus plant Anhalonium Lewini, dates back for centuries in the religious rituals of several Indian tribes in Southwestern United States and Mexico. Mescaline is a non-addicting drug and, in a sense, non-intoxicating. Structurally it resembles epinephrine closely as seen by the structural formulae below:

\[
\begin{align*}
&\text{mescaline} \\
&\text{epinephrine}
\end{align*}
\]

Figure 2 Comparison of Mescaline and Epinephrine.

Mescaline was identified as the active component of peyote as early as 1890, and was studied with great intensity by the pharmacologist Ludwig Lewin in the early 1900's. Havelock Ellis has reported mescaline's effects as early as 1898 (10). Mescaline is easily synthesized in the laboratory, employing 3,4,5 trimethoxybenzaldehyde as a starting material.

Mescaline is far less potent physiologically and psychologically than LSD-25, the effective dosage level in humans ranging from 300-500mg, and compared with 100-200μg. in LSD-25. This dosage level is for oral administration, however, and it
is significant to note that mescaline injected into the brain ventricles of cats is more potent than any other hallucinogen in producing behavioral disturbances (16). The action of mescaline, however, is still inconclusive. Narrazzi, in comparing the electroencephalographic effects of LSD, serotonin, adrenalin, and mescaline found that all inhibited the post-synaptic component of the transcallosal response, with LSD and serotonin being the most powerful inhibitors (100). Interestingly, the mescaline experience can be altered by the injection of large quantities of succinic ester. Presumably, this is due to the fact that the oxidation of succinate in brain tissue is unaffected by mescaline, unlike the oxidation of glucose, lactate, pyruvate, and glutamate. This fact suggests that part of the mescaline experience may be attributed to the inhibition of oxidative processes in the brain tissue. There is no effect on the oxidative phosphorylation of rat mitochondria and no evidence to suggest that mescaline is degraded into hallucinogenic breakdown products. One suggestion indicates that since there is no specific amine oxidase for mescaline in the body, it circulates for a long time and can be incorporated into the body proteins, exerting its effect in this manner (16). Another suggestion claims that mescaline competes with adrenalin for receptors. In this connection, Fischer has employed several adrenergic blocking agents, among them mescaline, and measured the comparative affinity which each exhibits for wool "model" receptors. He found a positive correlation between affinity for wool and toxicity. The suggestion was made that non-hallucinogens which demonstrate a
high affinity for wool should modify the psychotic experience by competitive inhibition of the active hallucinogen (65).

In conclusion, then, two mechanisms are suggested by which mescaline exerts its effect, although these mechanisms have not yet been conclusively proven. Some evidence has accumulated indicating that mescaline interferes with cerebral oxidative processes. Also, mescaline may increase the level of epinephrine in the body, by competing with this substance for receptors.

Amphetamine and its related compounds

Amphetamine has already been mentioned in connection with drug therapy, as one of the stimulating drugs. In ordinary quantities it produces anxiety, tremors, insomnia, and mental alertness. In somewhat larger doses, however, a state closely resembling the schizophrenic psychosis is produced. Indeed, the fact has been mentioned that often the two conditions are clinically indistinguishable.

Physiologically, amphetamine acts mainly on the central nervous system, rather than the peripheral nervous system (3). Amphetamine is very similar structurally to the adrenergic compounds and may, like adrenalin be considered a derivative of phenylethylamine. This is suggestive and its significance will be considered later. It will suffice to say that many drugs similar to adrenalin are anxiety-producing and may act as receptor competitors with adrenalin to increase adrenalin levels.

Others

Peyote, in addition to the presence of mescaline, contains
several other psychédélic substances, including anhaloxidine, bulbocapnine, and, in general, a group known as the tetra-
hydroisoquinolines. These substances are predominantly central excitan
tes, pellotine, for example, producing convulsions in
dogs and cats. Bulbocapnine, on the other hand, has been
reported to induce catalepsy in humans after intravenous in-
jection of 150-200mg. The experience is characterized by
muteness and hostility. It has, once again, been suggested
that may effect epinephrine by competitive inhibition. There
is little doubt that all of these alkaloids supplement or modify
the experience under peyote.\(^{(9)}\)

2) The psychédélicos interfering with the function of acetyl-
choline may act in one of two ways as indicated by figure one.
The drug may affect the function of cholinesterase or it may
antagonize the action of acetylcholine itself by competing
with it for receptors. Three types of esterase inhibitors
are known, the eserine alkaloids, the fluorophosphates, and
the ergot alkaloids. Because eserine has such a strong effect
on muscles in humans, only small amounts may be utilized, far
below the level necessary to produce psychological changes.

Diisopropylfluoride, used at one time in the treatment
of myasthenia gravis, produces nightmares, mental confusion,
and true hallucinations. Its use has subsequently been dis-
continued for this reason. Occasional psychotic episodes
have been reported when prostigmine, a derivative of eserine,
was used in the treatment of myasthenia gravis. Other cases
of insecticide poisonings implicating the fluorophosphates
have produced psychotic episodes (16).

LSD-25 was first isolated in 1943 from ergot fungus by the Swiss chemist Hofman working at the Sandoz Chemical Company in Basel. Unaware of the psychotomimetic properties of LSD, this scientist, having apparently absorbed some of the chemical through his skin, suddenly became aware of acute perceptual changes taking place. It was later discovered that doses as small as 20 mg. were sufficient to produce hallucinations in susceptible persons (10). LSD, then, has become one of the most widely used of the hallucinogenic drugs, and its action, though still unclear, has been studied extensively. Some attempt has been made to use LSD in therapy on the theory that the more prominent psychotic symptoms would be more clearly recognizable. These attempts have met with minimal success, however. It is interesting to note that schizophrenic subjects seem to require a greater amount of LSD to produce psychological manifestations, i.e. there seems to be a tolerance for LSD in schizophrenics (16).

Psychologically, LSD produces a variety of effects lasting approximately eight hours. The visual component of the LSD experience seems to be the most prominent feature of the "model psychosis", although there is some indication that the intensity of the visual changes is lessened after repeated administration (45). Salvatore has described the onset of psychological effects chronologically, using a dosage level of 12 \( \mu g \) /kg. In the first hour the normal processes of anxiety and apprehension are present, with the somatic symptoms gradually intensifying and reaching a peak during the second hour.
In the third hour perceptual distortion accompanies the somatic effects and feelings of unreality reach a peak, continuing strongly into the fourth hour. During these periods there is a distinct feeling described by Salvador as "awayness", the creation of a barrier between the individual and the external world. During the fourth hour thought confusion is apparent which is interpreted as a realization that intrapsychic mastery of the symptoms has failed. In the fifth hour there is a period of pseudo-integration, called the "trough", during which the symptom groups decline markedly, only to reappear a short time later, though gradually decreasing in intensity after the sixth hour of experience (114).

Hoffer and Osmond divide the action of psychotomimetics into two general categories, direct and indirect. The action of a given drug may, of course, overlap and, indeed, the effect produced is usually the result of a variety of specific actions. A direct action occurs when the drug itself acts to produce a physiological or biochemical change, such as synaptic inhibition or interference with glucose metabolism. An indirect action results from the increase or decrease of a naturally-occurring substance such as acetylcholine, which causes an abnormal set of reactions. The activity of LSD may be conveniently studied in this manner (16).

Direct action
LSD seems to have several abnormal electrical properties. Rubin, in reviewing the physiological properties of LSD, notes that LSD causes a change in alpha-rhythm responsiveness (112). Interestingly, Blum has noted a similar lowering of alpha-rhythm
responsiveness to photic stimuli in schizophrenics (54). Several workers have also cited the fact that LSD is a central synaptic inhibitor, evidenced in the brains of cats. This inhibition is primarily located in the transcallosal tract, the suprasylvian striate, and the lateral geniculate synaptic regions (1, 100). It should be noted, however, that large doses of LSD are necessary to produce this effect (16). Marrazzi has tested several substances, among them LSD, mescaline, serotonin, and adrenaline employed as a base, and has found that each is a cerebral synaptic inhibitor with serotonin the most powerful. He has suggested that there is a correlation between synaptic inhibition and psychological potency (100). The evidence for this has been disputed, however, particularly since serotonin exhibits no hallucinogenic properties of its own (16, 88). LSD, however, is a mild inhibitor and it seems plausible that a part of its effect may be exerted through this mechanism.

The effect which LSD exerts upon glucose metabolism has been the subject of considerable research. Rubin, in his review, states that intermediary carbohydrate metabolism is disrupted as indicated by an increase in hexosemonophosphate (HMP) and a concomitant increase in glycogen metabolism. He goes on to say that a block probably occurs in HMP breakdown (117).

The relationship of LSD to liver function is clouded. It is known that LSD does enter the liver in large quantities and presumably is metabolized there as indicated by the activity of C\textsuperscript{14}--labelled LSD (16). There is little evidence for a
gross disturbance of carbohydrate metabolism, however, and Kety's criticism in regard to schizophrenia would seem to apply here, also, namely that the metabolism of glucose is too general a mechanism to account for the selective events taking place in the LSD psychosis (21). It should be noted, too, that LSD, unlike schizophrenia, is an autonomic stimulator and thus its applicability to the demonstration of a physiological factor in schizophrenia is questionable (1,77).

LDS is a powerful antagonist of serotonin in many biological systems (1,16,36,112). Because of these findings some authors have attempted to extrapolate the evidence so as to assert that the action of LSD is due to serotonin inhibition in the brain. The function of serotonin in the brain is still unclear. The evidence for the serotonin theory of schizophrenia and the criticisms to which it has been subjected is reviewed in the chapter dealing with the biochemical theories.

Indirect action

LSD is a strong antagonist to acetylcholine esterase thus increasing the level of acetylcholine in the body. As noted before, raised amounts of acetylcholine may be sufficient to cause psychotic-like states and LSD may exert a portion of its effect through this mechanism. However, brom-LSD is also an inhibitor of esterase activity, but is not a hallucinogenic compound (16).

Most reviewers have concluded that the primary effects of LSD are exerted somewhere in the pituitary-adrenal axis (111,112). LSD has no effect upon the symmetry of spider webs, however, the threads are invariably thinner, indicating adrenal
exhaustion (16). Rubin cites evidence indicating that LSD leaves the adrenals somewhat unresponsive to stimulation by corticotropin (112). Liddell and Weil-Malherbe have presented evidence indicating that adrenalin plasma levels show an initial rise after the intravenous injection of LSD, then drop below the initial level, and finally show a secondary rise to the baseline or slightly above. These authors found a correlation between adrenalin levels and psychological effects (96).

This work has been confirmed by the studies upon mescaline and LSD by Sakamoto (113). Melander and Martens have found that psychological changes produced in cats by adrenolutin, an adrenalin breakdown product (103). Gradually increasing the dosage level of LSD from small, non-hallucinogenic quantities to larger doses produces a tolerance to LSD. Also, compounds structurally similar to LSD, notably methedrine (MLD-41), but of less potency, likewise produce tolerance to LSD psychosis (45). This effect may be due to adrenal exhaustion and, thus, lack of substrate to be metabolized into psychotomimetic derivatives, if this is the action of LSD (16). The evidence now available at least indicates an abnormality existing in the pituitary-adrenal axis.

Acetylcholine antagonists

These drugs work by blocking acetylcholine-sensitive receptors which effect either the operation of sympathetic synapses or the activation of smooth muscle and secreting glands. These drugs are mainly atropine-like.

Atropine itself has found great use in eye surgery and is better known, perhaps, as belladonna. It is a white,
crystalline alkaloid extracted from the plant Atropa bella-donna. This alkaloid causes paralysis of all responses to parasympathetic stimulation at and above threshold doses. Atropine psychosis has been observed during its use in eye surgery where the drug is utilized in the post-surgical treatment of retinal detachment. In large doses the toxic confusional state is clearly distinguishable from schizophrenia, but in smaller doses the changes are more subtle and the differentiation considerably reduced. There is little doubt that the action of atropine is due mainly to its effect upon acetylcholine levels caused by blocking the nicotinic receptors of this hormone. The psychological effects may be due both to the increase in acetylcholine level and the levels of the sympathomimetic amines (16).

The piperidyl benzilates are chemically related to atropine and, when administered to humans, exhibit atropine-like changes, notably dry mouth, tachycardia, and blurred vision. Abood, who first reported the psychological and physiological effects of these drugs, claims that both visual and auditory hallucinations were present, as well as marked thought disorder. The standard dose is between 10-15mg. orally. The main effect of these drugs seems to be linked to the suppression of parasympathetic responsiveness.(1)

3) Indole psychedelics resembling adrenochrome

The effects of the most prominent member of this series of compounds, LSD, have already been reviewed. Mescaline, though not an indole, may become one by a fusion of the side
chain to the ring. Whether this occurs in vivo or not is still conjecture. There are several plant alkaloids which possess both the indole structure and psychotomimetic properties. Two will be represented here.

Psilocybin is the most active component of the alkaloids isolated from the mushrooms investigated by Wasson and Heim and purified in crystalline form by Hofman. The physiological properties are quite similar to LSD, raising the blood pressure, increasing the rate of heart beat, causing pupillary dilatation and occasionally nausea, dizziness, and sweating. Psychologically, psilocybin induces feelings of "strangeness", anxiety, thought disorder, altered sensory perception, and produces elementary and true visual hallucinations, as well as a marked alteration in body image. Isbell has determined that psilocybin is about one hundred times less potent than LSD. For this reason its application in preference to LSD seems limited. However, because the psilocybin experience is considerably shorter than that of LSD it may have some application in experimental work. Presumably LSD and psilocybin mediate their effect in the same manner physiologically (16, 87).

Harmine is the active component isolated from the seeds of the ancient Mexican plant deity Rivea corymbosa. The drug itself was named ololiuqui by the Mexican Indians and, as in the case of peyote, played an important part in religious ceremonies. Harmine possesses the basic structure of the indoles and may be considered the structural precursor of the indole hallucinogens. Its effects resemble closely those of
mescaline with the dosage levels being approximately the same. The visual component of the oloiuqui experience predominates and the experience is usually accompanied with nausea and sweating (10).
Chapter Seven

BIOCHEMICAL AND PHYSIOLOGICAL ABNORMALITIES IN SCHIZOPHRENIA

As mentioned in the introduction, the search for a chemical or physiological cause for schizophrenia has been a long and, to a large extent, fruitless one. The idea that a biochemical abnormality could be the cause of schizophrenia has received indirect confirmation in the fact that vitamin deficiency, particularly a deficiency of thiamine or niacin, is known to cause mental aberrations. Even more directly, such mental diseases as phenylketonuria and methemoglobinemia are known to be caused by innate metabolic disorders, thus giving credence to the possibility of a similar dysfunction existing in the "functional" disorders.

Until very recently there was no method which could properly be termed therapeutic in this field, despite the appearance of several physiological treatments which claimed therapeutic value, but which, in fact, provided only passing relief and often no relief at all. Electric shock, insulin shock, and hydrotherapy may be numbered among the latter. In many desperate cases prefrontal or transorbital lobotomy was employed to calm the more active patients. The surgeons performing this operation rationalized the permanent brain damage which resulted by underlining the patient's pathetic condition and emphasizing the fact that hope for these patients was virtually non-existent. This operation, performed by inserting a measured scalp through the orbit of the eye or through holes drilled in the skull, slices the associative neurons of the frontal lobes. It does not remove any of the symptoms of
schizophrenia, but instead, relieves the patient's concern about them (10). Today, however, the operation is outlawed in most states and its use has dropped virtually to zero.

Psychotherapy has, in large measure, replaced physiological treatments and has grown within the framework of a disease of unknown origin, isolated from a large part of the medical field. Although psychotherapy has produced results favorably effecting the expected remission rate of schizophrenia, its limits are readily seen in the fact that it does not "cure" a patient in the same sense that a person with measles is cured, but, rather, it helps the patient make a new adjustment to his difficulties by placing him in a relearning situation where social situations can be developed and, indeed, are specifically encouraged (102).

With the advent of drug therapy, psychotherapy made a large jump ahead and is now able to reach the inaccessible patient on a new level of communication. However, despite the fact that some hospitals claim a remission rate of 75% or better, this says nothing of the relapses which may occur in 40-50% of the remitted patients. More important, the primary symptoms are still present beneath the adjusted exterior, indicating that despite all efforts the fundamental process has not been altered to a great degree. Consequently research workers continue to hunt for that slight physiological difference which should be present in the schizophrenic, but which has proved so frustratingly elusive. The following account is a review of many studies which suggest that such a defect does exist. Although isolated bits of evidence will be presented here,
it should be kept in mind that if any primary process is defective in schizophrenia, its effects will be manifested throughout the body chemistry of the subject. As in the study of personality in which no single factor may be isolated from the whole and called most important, so in the study of the body chemistry, all factors must be considered as part of a unified scheme comprising the total individual.

Mention should be made at the first of the difficulties confronting the biochemist when dealing with the "functional" disorders. There is some evidence that argues for the fact that schizophrenia itself is merely a catch-all term covering a variety of etiologically dissimilar disease syndromes. Often difficulty is encountered in obtaining clearly defined cases of schizophrenia, not to mention the rather arbitrary subgroups. Samples drawn from a hospital population are invariably heterogeneous with respect to age, onset, disease subgroup, and chronicity, each having its own independent effect on data. Long periods of hospitalization produce special difficulties, particularly in those hospitals where the hygienic standard is low. Differences in body chemistry may result from the residual effects of previous treatments, This factor is of particular importance after a patient has undergone drug therapy which may hopelessly confuse biochemical data. One group which supposedly had found a difference in the aromatic excretion pattern of schizophrenics later discovered that the results were directly attributable to coffee intake in the patients. Often secondary effects resulting from acute stress are confused with primary disturbances.
Finally, and most important, the factor of subjective bias is ever-present, even in the so-called "blind" studies. It is of particular importance in psychiatric research to minimize the chance for subjective bias, for animal studies, which are relatively easy to control, have little application in schizophrenic research. In order to study psychosis to any extent human beings must be employed in the study; hence, the importance of the "model" psychosis. However, if these difficulties are kept in mind, the sources of error can be greatly minimized, if not eliminated, and the results of data interpreted accordingly. The examples of Kety at the National Institute of Mental Health and Gottlieb at the Lafayette Clinic are outstanding for the control methods which were used (21).

A great deal of study has been done on carbohydrate metabolism in schizophrenia. The initial impetus for these studies came from the observation that schizophrenics seem to exhibit a large tolerance to insulin (1). Sakel, convinced that this fact might provide a means of therapy, used insulin coma to produce a situation in which reintegration could occur. Although remission rates four times greater than normal expectancy have been claimed, other evidence indicates that these figures are mistakenly high (99). Also, there is the inherent danger that death will result from coma (occurring in approximately 0.33% of cases treated) (3), and the disturbing fact that each time the oxygen consumption of the brain is lowered by decreased glucose levels, several brain cells are permanently destroyed. Nevertheless, the occurrence of a hyperglycemic factor in schizophrenia is a
rather consistent finding, and any biochemical theory would have to consider this point.

In addition to abnormal insulin tolerance, several workers have reported an abnormal tolerance curve to glucose and fructose, although the data exhibits wide variability (30,99). Kety, in a carefully controlled study at the National Institute of Mental Health has determined that cerebral glucose consumption, as measured by oxygen utilization, is completely normal. In this study, however, the author does not exclude the possibility of local energy changes and, further, presents some evidence to indicate that glucose may be replaced by another substrate in the schizophrenic brain (88). No confirmation has been forthcoming for this observation.

Several studies have been made upon carbohydrate metabolism of schizophrenics under stress conditions, produced either by injection of insulin or epinephrine. In the latter case, McDonald has found a marked increase in peripheral glucose utilization using surprisingly small amounts of epinephrine (.000024mg/kg/min), indicating a heightened sensitivity to epinephrine in vivo. This same worker found normal responses to both insulin and glucagon in the peripheral system (98).

A series of interesting papers have been published by Jacques Gottlieb and his coworkers concerning an extensive examination of schizophrenics and non-schizophrenics with reference to carbohydrate metabolism under basal and stress conditions and energy transfer systems (7,25,68,71). These studies are notable, not only for the valuable results which have been obtained, but for the meticulous use of controls, so
necessary to validate physiological data.

The first clue to the direction which these studies would take was provided by the observation that ATP formation in chronic schizophrenics decreased markedly under insulin stress conditions in comparison to all other groups tested. From this data it was suggested that schizophrenics may suffer a disturbance in erythrocytic energy formation, particularly under stress conditions which required the rapid mobilization of energy.

\[ \text{I. Glycolysis} \]

\[ \text{II. } 2\text{ADP} \rightarrow \text{ATP} + \text{AMP} \]

**Figure 1** Diagram of ATP Turnover (72)

In figure one, normally both mechanisms I and II are utilized in the body. Under stress conditions, however, mechanism I is preferentially utilized by normals, whereas mechanism II is primarily utilized by chronic schizophrenics. Since the former mechanism is thirty times more efficient than the latter, the schizophrenic group would seem to be making an inadequate response to the artificially-induced stress. This criterion did not differentiate all schizophrenic groups from non-schizophrenics at a statistically significant level. Taking the specific activity (defined as radioactive counts/minute/milligram, indicating the rate of incorporation of the radioactive radical $P^{32}O_4^-$). This is, therefore, an index
of the rates of formation and destruction of the particular compounds observed) of fructose 1,6 diphosphate as a criterion, these workers could significantly differentiate all schizophrenic groups from all non-schizophrenics and, thus, suggested that this difference was more central to the pathophysiological defect (72).

In a recent paper concerning lactate: Pyruvate ratios in schizophrenics as an index of anaerobic respiration, Frohman et al were able to differentiate patients from controls at their own clinic under blind conditions and did the same at the clinic of the National Institute of Mental Health (p < .02). From this study these workers implicated a disturbance in a hydrogen transfer system, possibly in the reduction of DPN to DPNH₂ in the Embden-Meyerhoff scheme(67). Further studies into the energy transfer systems of schizophrenics are being carried out.

Other workers, studying energy transfer systems under basal conditions, have reported low values of glutathione in schizophrenics, although the data in question showed wide variation (47,101). Boszormenyi-Nagy and Gerty have reported low phosphate levels in schizophrenic erythrocytes, but this data, too, was variable and uncorrelated with any specific diagnostic category (56). In all it would seem that a good deal of evidence has accumulated indicating a difference in the carbohydrate metabolism of schizophrenics. This may be the result of another process more directly linked with the behavioral manifestations of schizophrenia, rather than the primary cause. Carbohydrate metabolism itself is too general
a mechanism to account for the rather selective features of schizophrenia (21).

A number of workers have implicated the pituitary-adrenocortical axis as a factor in mental illness. The primary motivation for this is based upon the observation that the psychedelic drugs often induce an abnormal response to adrenalin. Further evidence for this involvement of the adrenocorticals is that cortisone and ACTH can bring about euphoria and anxiety states, as well as excitatory behavior (1). Several indices, including eosinophilic levels, uric acid levels, and potassium ion and 17-ketosteroid excretion, have been used to indicate adrenocortical activity. A better index needs to be found, however, since the latter are but gross measures of the function of the adrenal cortex (1). In the studies that have been done, nonetheless, it seems that the response of the adrenal cortex to stress is rather low, particularly as measured by the excretion of 17-ketosteroids whose values for schizophrenics generally fall in the low to low-normal range of the normal curve with some variation. Some attempts have been made to correlate psychological state and 17-ketosteroid level with minimal success. A good prognosis in insulin therapy may be indicated by diminishing fluctuation of ketosteroid excretion and a range within normal limits if the original levels were high or low. Altschule has suggested that the improvement observed in insulin therapy may be due to adrenal exhaustion (34).

Hoagland, Rinkel, and Hyde have studied adrenocortical function in schizophrenia by measuring phosphate excretion patterns. These workers found that phosphate excretion in
schizophrenia was approximately 48-61% that of normal subjects. However, when corticotropin or adrenocorticoid extract was injected into the patient group an LSD-like response occurred in which phosphate excretion rose markedly above the normal levels. These workers then suggested that the evidence seemed to parallel the scheme of Hoffer, Osmond, and Smythies that an adrenalin derivative may cause the schizophrenic state, mediating its effect via an exchange of phosphate bond energy (79, 84).

In reviewing this evidence it would seem that schizophrenics exhibit characteristically wide variation in adrenocortical function, although a large part of the results fall into the normal range of values. The hypothalamus, regulatory center for the autonomic functions, the pituitary gland, ACTH function, and adrenocortical secretion are all interrelated and within this endocrine complex a primary dysfunction may occur in schizophrenia. An adequate biochemical theory would have to consider this evidence.

A short time ago a great deal of interest was generated in the study of amine metabolism and in the function of amino acids in schizophrenia. Chromatographic studies of the urine, which must still be considered a gross, rather than a specific measure of urinary wastes, seemed to indicate a difference in the occurrence of metabolic amine wastes in schizophrenia, possibly in the glutamine-glutamic acid relationship (21, 30). Further evidence supporting amine metabolic dysfunction comes from the investigations of Gjessings into periodic catatonia, in which a correlation was established between nitrogen retention and fluctuation in mental state (29). Another fact
worthy of consideration in this evidence is the structural relationship between the amines and the hallucinogenic drugs, many of which are indolic compounds as previously indicated. Mental aberrations have been reported in metabolic disorders involving phenylalanine and tyrosine (110). The amines, however, perform an uncertain function in the central nervous system, although they are extremely localized and found in the brain, albeit in low concentration (1).

Various researchers have reported low creatinine, high amino acid, and high "toxic" amine levels, although much of this work has been disputed (99). In a recent study Nakao and Ball have reported the isolation of a skatole derivative from schizophrenic urine, probably 6-sulfatoxy skatole and suggest that this compound may be the breakdown product of a naturally occurring indole in schizophrenia (105). In a preliminary report de Almeida Relvas, studying acute psychotics and schizophrenics, found a significant difference between experimental and control groups in every amino acid studied. This work awaits confirmation (58). Studies involving chromatographic or electrophoretic studies of schizophrenic urine present a number of peculiar difficulties. The dietary factors involved are of crucial significance and often are difficult to evaluate. Further, many substances still remain to be identified in the urine. One worker has compared the search for an aberrant metabolite in schizophrenic urine, not to a needle in a haystack, but to a needle among hundreds of similar needles (21). Finally, many metabolites in the urine are unstable and may either react with other substances or polymerize, again confounding the data in urine analysis (1).
Thus, while the results of various studies have interesting implications, much of the work is contradictory and, until more refined techniques become available, must be considered questionable.

A special case of amine metabolism which has been studied extensively is the involvement of the catechol amines, particularly epinephrine, in several states of mental anxiety, including schizophrenia. Epinephrine itself has long been recognized as a substance remarkably toxic in the body above threshold amounts and usually associated with stress conditions (81,104). Chlorpromazine, the remarkable tranquilizer, is reported to lower plasma adrenalin levels (119). The mental effects of LSD are usually preceded by abnormal adrenergic responses, indicating this drug's property of autonomic stimulation. Again, adrenalin is present in the brain itself, particularly concentrated in the hypothalamic area (16). One worker has correlated mental state under LSD intoxication and phasic increase and decrease in plasma adrenalin levels (96,113). In hypoglycemia free adrenalin is lowered in the plasma fraction, presumably a result of its more rapid oxidation under insulin stress. Rising adrenalin levels are correlated with rearrousal (70). Some workers have reported increased catechol amines in schizophrenic groups (16,117). Adrenalin oxidation itself has been reported to be significantly faster in schizophrenia than in normals, although this fact has been questioned because of inadequately controlled ascorbic acid levels in the diet of the experimental groups (21,95). The importance of adrenalin metabolites in schizophrenia may be of primary
significance. This possibility will be reviewed in the following chapter.

A second special case involving disturbed amine metabolism centers around the facts that schizophrenics often demonstrate a remarkable tolerance to the toxic effects of histamine and that there seems to be a negative correlation between allergies and schizophrenia (16). Kobayashi and Freeman, in studying histamine metabolism in schizophrenia, found that histamine is detoxified by two main pathways, one by direct oxidation and the other by methylation of the ring nitrogen. These workers suggested that the remarkable tolerance which schizophrenics demonstrate for histamine is accounted for either by the impairment of another substance at histamine receptors or by the presence of a highly active histamine catabolizing system (90). The fact that removal of the adrenal cortex results in a markedly increased sensitivity to histamine (X30) would seem to indicate this gland's involvement in histamine detoxification and underlines, perhaps, its involvement in schizophrenia (2).

Some work has been done in the study of the basal metabolism of schizophrenics. As in the case of many other studies, the schizophrenic group has shown extreme ranges in thyroid malfunction, although more than half the values fell into the normal range of values. Using tracer methods with I\textsuperscript{131} in catatonic with decreased basal metabolism rates, the iodine take up was found to be essentially normal, indicating that thyroxin itself was being used up. This fact was attributed to an abnormal sensitivity of peripheral tissue for thyroid
hormone (34).

A number of miscellaneous studies have been done which are difficult to classify under a specific heading, but which must nonetheless be explained in a biochemical theory of schizophrenia. Riegelhaupt, using the glyoxylic acid test to measure urinary indole compounds and tryptophan metabolites, found that the test was positive for 80% of the schizophrenics tested and positive in only 20% of the controls. Peracetic acid, which oxidized the side chain of indole compounds, inhibited the test (109).

Fischer claims to have found a toxic factor in the urine of schizophrenics on the basis of his observations using Xenopus levis (66). This evidence was partially disputed by the same laboratory which published the results. Abramson reports that schizophrenic urine has no effect upon the behavior of Siamese fighting fish, who are remarkably sensitive to certain hallucinogens (21). Guppy behavior, which is similarly altered by some hallucinogens, is affected (16).

The condition of peripheral anoxia known as cyanosis is often presented in schizophrenia and is seemingly unrelated to physical activity. An attempt has been made to correlate this observation with disturbed peripheral glucose metabolism by measuring the oxygen content of blood drawn from the nail bed (30, 98).

One study has been done on the local activity of carbonic anhydrase in various cortical regions of the brain. Normally the activity of carbonic anhydrase is highest in the occipital region of the cortex and lowest in the temporal region. In
schizophrenia, however, local differences are obscured and the normal topographical pattern obliterated (39). This work awaits confirmation and its significance is still obscure, although it may provide partial explanation for the associative difficulties which are quite apparent in schizophrenia.

A few electroencephalographic studies have been made upon the schizophrenic brain. Blum found a correlation of .55 between an experimental group consisting of schizophrenic and brain-damaged subjects and a lowering of alpha-rhythm responsiveness to photic stimuli. Although there was a significant difference between patients and controls, this study could not differentiate between schizophrenics and brain-damaged patients (54).

Heath, using implanted electrodes from a stereotaxic device, has taken recordings of various regions of the brain. A large spike and a slow wave was observed in certain regions, notably the septal and hippocampal areas and sometimes the amygdaloidal area. These abnormalities were not observed in remitted patients, but were similar to the effects observed in experimental psychosis (15,74).

Finally, Frohman, in summarizing the work of the group at the Lafayette Clinic, has postulated that there must be a plasma factor present in schizophrenia, either as an abnormal substance or an excess of a naturally-occurring substance, to account for the disturbances which this group has studied in control of carbohydrate metabolism and energy transfer (68).

The most consistent finding that can be extracted from the biochemical and physiological studies is the fact that
schizophrenics usually demonstrate wide variation from the normal in virtually all criteria taken, although most findings fall within essentially normal limits. The difficulties inherent in human studies have been indicated and partially account for this variation. However, so much evidence has been amassed, albeit in a rather disconnected way, to indicate the probability of a chemical abnormality, that the door seems open to a biochemical theory of schizophrenia. The potential value of the theories which have thus far been presented will now be enumerated.
Chapter Eight

BIOCHEMICAL THEORIES OF SCHIZOPHRENIA

The two factors most important in providing a basis for a biochemical theory of schizophrenia have been discussed in the previous two chapters, namely that psychotic-like states can be produced by a chemical means using the psychedelic drugs and that a considerable number of biochemical and physiological abnormalities occur in the schizophrenic. Further, the point that schizophrenia is a "functional" disorder, rather than a physical nature, has been rendered meaningless in the context of this study, since this designation merely indicates that the physical origin of the disease is unknown. The psychological factors involved are real enough and, at present, offer the only reliable criteria for differentiating schizophrenia from other psychotic states. But beneath the psychological level necessarily lie the biochemical processes, just as the mechanisms of genetic transmission lie at a level beneath the biochemical make-up of the individual. Although few research workers deny the fact that an inherited factor is involved with schizophrenia in view of accumulating evidence to the contrary, the extent to which heredity is a causative factor ranges from White's explanation that the inherited traits of physique and temperament are implicated in schizophrenia to Kallman's assertion that genetic aberrations are directly responsible for the disease (20, 41). The work in genetics is still in its youth. Only recently has the basic means of transmission, the proteins DNA and RNA, been elaborated. The mechanisms of genetic transmission still provide
the basis for the work of several research teams in biochemistry. Therefore, although the genetic evidence is valid enough, it offers little hope for a meaningful theory complete with therapeutic implications, in the near future.

The possibility that schizophrenia may be dealt with on the intermediary, biochemical level, however, lies within the realm of the plausible. The following theories have made some attempt to correlate the biochemical data into a useful therapeutic tool.

The serotonin theory was first proposed in 1950 and for a time found many adherents. The evidence has centered around three nodal points, the fact that serotonin occurs naturally in the brain and is structurally related to the hallucinogens, the action of the tranquilizing drugs with respect to serotonin, and the antagonism which serotonin displays to some psychedelics, particularly LSD.

LSD is a powerful antagonist to serotonin in many biological systems. Because of this antagonism some authors have attempted to extrapolate the findings so as to assert that the activity of LSD is due to its inhibition of serotonin in the brain. Several authors have noted that LSD and other psychedelic drugs antagonize the constrictor effect of serotonin on smooth muscles (1,10). Serotonin also potentiates the hypnotic effect of several barbiturates, notably hexobarbitone. LSD antagonized this effect (112). At synapses both LSD and serotonin have inhibitory characteristics. According to Marrazzi's classification, LSD is an inhibitor of medium activity in the same range as gamma amino butyric acid (GABA),
while serotonin is an inhibitor of high activity in the same range as acetylcholine (100). A powerful synaptic inhibitor is probably bound rapidly in the brain and thus would have little or no correlation with psychological manifestations (88).

Brom-LSD (BOL-148) is a non-hallucinogenic derivative of lysergic acid. It, too, is an antagonist of serotonin in vitro, inhibiting barbituate narcosis as LSD does, as well as serotonin's constrictor effect on smooth muscle. It has also been suggested that LSD exerts its effect by suppressing the inhibitory characteristics of the serotonin precursor 5-hydroxytryptophan. Unfortunately BOL-148 also antagonizes this system(16). These facts do not discount the importance of serotonin as a possible factor in the model psychosis. This merely indicates that the facts supporting this hypothesis are questionable.

It will be noted from the structural formula drawn below that serotonin is related to the hallucinogenic drugs, and to epinephrine, norepinephrine, and in general, the catechol amines.

![Figure 1: Serotonin](image)

In fact, injections of the serotonin precursor, 5-hydroxytryptophan reportedly have produced mental aberrations (1). It has also been ascertained that serotonin occurs naturally in the body, being particularly concentrated in the hypothalamic area. Further, reserpine, the amazing tranquilizer,
causes the liberation of serotonin in the brain and may mediate its effect in this manner (10). However, the usefulness of reserpine has now come into serious question. It has been demonstrated rather conclusively that reserpine is not a cure-all or panacea for schizophrenia, but, roughly, speaking, acts like a chemical lobotomy in the sense that the patient no longer worries about his condition and its more morbid manifestations (42).

Isbell has demonstrated that high potency as a psychotomimetic is not correlated with high potency as a serotonin antagonist, but cautiously asserts that the data neither prove nor disprove the "serotonin deficiency" theory (88). Poloni claims to have observed an excess of serotonin in schizophrenic plasma, which he detects by the constrictor action of the blood upon the specially-prepared leech muscle (10). In these observations a case could be drawn for the theory that schizophrenia is caused by an excess, rather than a deficiency of serotonin.

It must be concluded from the available evidence that the serotonin theory must remain purely speculative. The specific effect of serotonin in the brain has yet to be established. The theory suggests few methods by which schizophrenia can be treated. Finally, the biochemical abnormalities observed in schizophrenia are not considered at present in the formation of the serotonin theory. Nevertheless, serotonin is still a possible factor involved in mental health and, for this reason, deserves to be investigated in greater detail.

The second theory that has received a great deal of
attention is the ceruloplasmin-taraxin theory. In 1956 the group working at Tulane University published a paper explaining the observation that schizophrenics oxidized epinephrine more rapidly than normal. Reportedly this was due to the fact that schizophrenics contained raised amounts of a copper-containing protein in the blood, indicated by the observation that oxidation was inhibited by NaCN and facilitated by CuSO4 (95). A short time later Stig Akerfeldt, a European research worker, startled the medical world by announcing a test for schizophrenia. Akerfeldt reported that serum fractions for schizophrenics, manic-depressives, and victims of senile psychosis oxidized N,N’-dimethyl-p-phenylenediamine (DPP) more rapidly than normal serum. The oxidant in question seemed to be ceruloplasmin on the basis of the following evidence:

(1) The oxidant precipitated with (NH₄)₂SO₄ in the same fraction as ceruloplasmin.

(2) Both serum activity and ceruloplasmin were inhibited by NaN₃ in approximately the same percentage (67%), but not by NaF, ammonium oxalate, or cystine.

(3) The oxidizing activity was removed when the serum was dialyzed against a citrate-phosphate buffer at pH=3. The activity was restored after the addition of copper ions, but not ferrous ions. Ceruloplasmin is a copper-containing protein.

(4) Addition of ceruloplasmin to serum indicated that DPP is a substrate for this enzyme. Akerfeldt did indicate in his work, however, that the level of ascorbic acid markedly affected the test, and also noted that several other conditions, especially pregnancy and carcinoma, caused the test to be positive (46).

Abood, working independently on a similar test, reported that he had developed a test which was unaffected by ascorbic acid levels and this became known as the Abood modification.
Because the test was positive for a number of pathological conditions, this worker questioned its diagnostic usefulness (1). Later workers demonstrated that both tests were dependent on lowered ascorbic acid levels and the theory that raised ceruloplasmin levels were a causative factor in schizophrenia temporarily fell into disrepute (21,47,86).

In 1957-1958, however, new interest was aroused when Robert Heath, while working with ceruloplasmin, reported the isolation of a protein, qualitatively different from ceruloplasmin, isolated from schizophrenic serum, but not from normals. This protein, when injected into animals, produced a psychotic-like state and it seemed possible that here at last was an aberrant compound directly correlated with schizophrenia (77). The following paragraphs are devoted to a closer inspection of the work done at Tulane by Heath and his coworkers.

The Tulane group postulates that schizophrenia is a genetically-determined, metabolic disease, resulting from the action of faulty breakdown products in some biochemical system which alter brain physiology (76). They base this postulate on the observations of unusual electrical recordings of the septal, hippocampal, and amygdaloidal regions in schizophrenics and on their findings with respect to taraxemin, the name which they gave to the new protein (15,74). When the evidence for lowered levels of glutathione and increased oxidation of adrenalin in schizophrenics was presented, the Tulane group suggested that perhaps a copper-containing protein, qualitatively different from ceruloplasmin, might account for these differences, if these chemical phenomena were
important to psychotic behavior. Ceruloplasmin extracts, it was noted, occasionally produced mild behavior disturbances in monkeys. During the extraction procedure for ceruloplasmin, when the euglobulins were precipitated by lowering the pH to 6.2, a blue color was present in the precipitate from the schizophrenic serum, but not in that from the serum of normals. The differing substance was extracted from the blue-colored precipitate and the end product of the isolation, taraxein, obtained. When injected into monkeys taraxein produced a marked catatonic-like state and, when electrical recordings were taken, using implanted electrodes, the EEG showed the essential characteristics of recordings from schizophrenics, particularly those recorded in the septal region. In a preliminary study in human volunteers subjects developed the symptoms described for schizophrenia, according to Bleuler's "fundamental" and "accessory" symptoms. The symptoms were schizophrenic, rather than toxic, in nature, and none of the symptoms of autonomic stimulation, characteristic of LSD, were displayed (77).

In a more carefully designed experiment involving fifteen inmates of Louisiana State Prison, screened for previous mental disorders in their families and in themselves, three schizophrenic patients in remission, and two non-psychotic volunteers, one and one half to five milliliters of one of the following substances was administered to each subject: (1) taraxein, (2) a fraction from normal serum processed by the same procedure employed for extracting from schizophrenic serum, (3) ceruloplasmin, (4) normal saline, and (5) sodium
amytal. Significantly, in no instance did a subject react with psychotic symptoms other than with taraxein. On the other hand, all of the volunteers injected with taraxein developed the clinical symptoms of schizophrenia, characterized by blocking, thought deprivation, autism, and depersonalization. It was also concluded that the behavioral changes were a result of taraxein itself and not a result of the process by which taraxein was extracted. Finally, it was ascertained that LSD did not produce taraxein and that Thorazine does not act on the protein (78).

Although initially some workers had difficulty in duplicating Heatn's extraordinary success, Melander and Martens, in 1959, were successful in confirming the psychosis-producing effect of taraxein. They too, demonstrated that the low molecular weight phenothiazines had little effect on the taraxein psychosis and made the interesting observation that taraxein potentiates the activity of adrenolutin in cats and humans (103).

Thus, for the first time there is some indication that schizophrenics do possess a distinctly different substance in the body than normal subjects. It is ironical that the discovery should be made during the investigation of another theory which has since fallen into disrepute. The scientific literature is filled with such occurrences, and a useful theory should not be discredited on the grounds that its discovery was accidental.

The adrenochrome theory, proposed by workers at the University of Saskatchewan, Canada, is perhaps the most ingenious and plausible theory yet proposed to explain the schizophrenic syndrome. Although some of the evidence presented in support
of the theory has been disputed by other laboratories, the work which this group has done stands as a hallmark for scientific investigators, not only for the ingenuity displayed in the theory itself, but also for the courage and tenacity which these workers have maintained in investigating the complexities of mental illness. The development of this theory, should at the very least, provide an invaluable guide for future researchers in the field. For this reason the adrenochrome theory will be given a rather extensive review. The evidence for the theory is still being accumulated, the most recent paper having been published less than a year ago.

Although the importance of the adrenal medulla and the adrenal system in general had been ascertained as early as 1929, it was not until the early 1950's that workers in the field of schizophrenia began to speculate upon its significance with regard to mental illness. John Smythies made the observation that occasionally asthmatics, who used adrenalin for relief, developed feelings of strangeness, particularly after receiving a dose of deteriorating or "pink" adrenalin. Hoffer and Osmond, pondering the significance of this observation, determined that the active component of pink adrenalin was an adrenalin metabolite known as adrenochrome. When the structure of adrenochrome was written out it was discovered that this metabolite was structurally related to every hallucinogen known at that time (64). Written below are the structures of adrenochrome, harmine, and mescaline.
Figure 2  Comparative structures of adrenochrome, harmine, and mescaline.

In a preliminary experiment Humphrey Osmond received 10mg. of adrenochrome and went through a period of marked behavioral alteration which lasted nearly twenty-four hours. This change was characterized by lack of insight, overactivity, and poor judgement. Osmond made the following comments concerning his experience.

After the purple-red liquid was injected into my right forearm I had a good deal of pain. I did not expect that we would get any results from a preliminary trial and so was not, as far as I can judge, in a state of heightened expectancy. The fact that my blood pressure did not rise suggests that I was not unduly tense. After about ten minutes, while I was lying on a couch looking up at the ceiling, I found that it had changed color. It seemed that the lighting had become brighter. I asked Abe and Neil if they had noticed anything, but they had not...I felt that I was at the bottom of the sea, or in an aquarium among a shoal of brilliant anemones in this pool. Abe and Neil kept pestering me to tell them what was happening, which annoyed me. They brought me a Van Gogh self-portrait to look at. I have never seen a picture so plastic and alive. Van Gogh gazed at me from the paper, crop-headed, with hurt, mad eyes and seemed to be three dimensional...We reached Abe's home where I felt cut off from people, but not unhappy...I felt no special interest in our experiment and had no special satisfaction at our success, although I told
myself that it was very important... I slept well. Next morning, although I had only slept a few hours, life seemed good... I was completely aware of the possibilities arising from the experiment... With those whom I felt did not appreciate the importance of the new discovery I could have easily become irritable, but I was able to control myself.

(10, p.185)

The implication of the adrenal system in mental illnesses does not come as a surprise. Cannon postulated the well-known "flight or fight" principle in 1929, in which the emotion of fear and anger were associated with the in vivo levels of adrenalin and nor-adrenalin (11). Further, many of the drug studies indicated adrenal dysfunction, either directly or indirectly, as already reviewed.

Adrenalin breaks down by three main pathways as indicated by figure three. In the first pathway epinephrine is broken down by the action of monoaminoxidase (MAO) to dihydroxymandelic aldehyde, in the deamination of the side chain. The second pathway is a system employing sulfoesterase in which sulfate esters are formed and excreted. The third pathway, postulated by Axelrod in 1957, suggests an O-methylation pathway in which epinephrine is ultimately metabolized to 3-methoxy-4-hydroxymandelic acid. A fourth pathway may exist in vivo which would produce adrenochrome as a metabolite, namely a phenolase system utilizing copper/fion or possibly ferritin as a catalyst. Although such phenolase systems do exist in the body, whether such systems are involved with epinephrine metabolism is still unknown (14,50,81). Kopin, in studying the differential rates of reaction in the alternative metabolic
Figure 3  In vivo synthesis and degradation of epinephrine

(14,50,81)
pathways for epinephrine, was able to account for 95-98% of all epinephrine produced, neglecting a phenolase system (see figure 4) (91). Nevertheless, substances which block amine oxidase activity may produce a psychotic-like state, suggesting that inhibition of alternative pathways will force metabolism to be directed through a phenolase system.

Cocaine blocks both the sulfoesterase and MAO pathways (16). Epinephrine is very toxic and must be destroyed immediately above threshold doses. Since cocaine inhibits two of the known pathways of epinephrine breakdown, another system or systems must be present to metabolize the accumulating substrate. The O-methylation pathway is partially dependent on deamination by an amine oxidase. Since the phenolase mechanisms are present in vivo, perhaps this system provides a means by which epinephrine can be metabolized. The author reviewed no literature regarding the urinary metabolites excreted during cocaine toxicosis.

If adrenochrome is present in vivo the self-perpetuating nature of the disease is evident from figure five. An external stress factor induces the anterior pituitary gland to secrete ACTH. This hormone in turn, stimulates the suprarenals, the medulla secreting epinephrine and the cortex secreting a number of corticoid hormones. The epinephrine in the schizophrenic is broken down to the normal metabolites, and also to an active, "schizomimetic" substance, adrenochrome, which gives rise to the various abnormalities noted in schizophrenia. The psychological changes which take place result in a type of internal stress (also adrenochrome itself may
Figure 4 Summary of epinephrine metabolism in man (91).
cause a stress situation directly) which again induces the secretion of ACTH (36).

Following the initial success of the Saskatchewan workers, other groups, attempting to duplicate the interesting findings, were unable to reproduce the behavioral effects noted by Osmond. Hoagland, Rinkel, Hyde and Solomon, using commercial adrenochrome, reported that adrenochrome was not hallucinogenic as previously indicated, but that the active component of the deteriorating adrenalin received by Osmond was a substance known as adrenoxine (presumably adrenolutin) of which adrenochrome was the direct precursor. These workers stated that adrenalin was metabolized to adrenochrome by the action of tyrosinase then acted upon the intermediate substrate to form adrenoxine (79). The answer to this discrepancy may lie in the observation of Hoffer and Osmond that commercial adrenochrome is actually the stable semicarbozone derivative of adrenochrome (16).

In investigating the properties of adrenolutin, the Saskatchewan group confirmed the fact that this compound did indeed produce behavioral changes similar to those of adrenochrome. Injections of adrenolutin produced a marked lowering of anxiety, a loss of insight, and the recipients displayed bizarre and inappropriate actions, as well as a dulling of the abstract intellectual capacities. Osmond had thought his experience under the influence of adrenochrome quite pleasurable. Adrenolutin, however, acted as a slight depressant (81).

Chemically, adrenolutin is a bright yellow, crystalline
substance, sparingly soluble in organic solvents and in water. On standing adrenolutin reacts to form 5,6; 5',6' tetradihydroxy-N,N'dimethylindigo. The structural formulae of these compounds are written below.

![Chemical structures]

**Figure 6** The reaction of adrenolutin to form 5,6;5',6' tetradihydroxy-N,N' dimethylindigo

Adrenolutin is synthesized by treating aqueous adrenochrome with alkali in the presence of sodium dithionite and then acidifying. The solid substance is recrystallized from a water-dithionite solution. Adrenolutin in vivo increases oxygen uptake and is approximately twice as active as adrenochrome (81). As previously indicated, taraxein potentiates the activity of adrenolutin in cats and humans (103). The urinary "epinephrines" reported by Sulkowitch and Altschule were adrenolutin-like substances (117).

Adrenochrome is very unstable chemically in solution and this may account for the difficulty which has been encountered in isolating adrenochrome from plasma fractions. In crystalline form it has a deep violet color with the melting point at 112°C with decomposition. The data concerning ultraviolet and visible absorption spectra in aqueous solution are as follows: \( \lambda_{\text{max}} = 301,487 \), \( \lambda_{\text{min}} = 262,361 \) The \( R_f \) for
adrenochrome in water on Whatman #1 paper: $R_{fH2O} = 0.8 \pm 0.02$

Adrenochrome rearranges to adrenolutin in the presence of zinc ions. Reducing agents for adrenochrome are ascorbic acid, cysteine and sodium borohydride, and penicillamine. In biological systems adrenochrome is metabolized to two products, one an indole which loses water to form 5,6 dihydroxy-N-methylindole, the other an indole which isomerizes into adrenolutin in the presence of alkali. Adrenochrome is a quinone acting as an oxidative catalyst in biological systems (16).

Hoffer and Osmond have completed several experiments using both adrenochrome and adrenolutin. From their studies it can now be ascertained that both of these studies are indeed psychotomimetics. It can be concluded, also, that the psychological effects of the two drugs are schizophrenic, rather than toxic in nature. In monkeys it appears that adrenochrome produces a catatonic-like state. In humans, however, the effects are somewhat different. About ten minutes after the injection of 3mg. of adrenochrome subtle visual changes take place in which colors and inanimate objects seem to have changed in a qualitative way. Body-distortion is marked, the extremities often appearing grotesquely enlarged. The subject's mood varies among individuals from euphoria to acute depression. Perceptual changes, but usually not hallucinations, occur, in which distances become difficult to judge. There is usually a disorientation with respect to time and space. Finally, as exemplified in Osmond's experience,
Hostility is present along with withdrawal and often delusional reactions. Interestingly LSD potentiates the adrenochrome experience (16).

The adrenochrome EEG in animals seems to be quite similar to that produced by LSD and epinephrine injected directly into the brain ventricles. It is suggested from the EEG evidence that these substances might act directly upon the reticular formation. This suggestion receives some confirmation in the observation that both LSD and adrenochrome produce hypothermia in rats. Since oxygen consumption remains unaffected it is evident that both drugs exert a central effect upon the temperature regulating mechanism of the hypothalamus (16,81).

Schizophrenics have been reported to exhibit a great tolerance to toxic properties of histamine. This fact can be explained in part by the adrenochrome theory, since adrenochrome is a mild antagonist to histamine. Although adrenochrome is only mildly antagonistic to histamine, a constant supply of the metabolite, which presumably exists in vivo, would exert as strong an effect as a more powerful antagonist which is readily metabolized and excreted. Adrenochrome is also an antagonist to thyroxin. This fact explains the observed abnormality of thyroid hormone distribution in the body of schizophrenics (83).

If adrenochrome is present in the bodies of schizophrenics but not in normals, then logically the waste systems of schizophrenics would be expected to contain a higher level of indolic
compounds than that of normals. Sulkowitch and Altschule have found an excess of adrenolutin-like indoles in schizophrenic urine (117). The 6-sulfatoxyskatole derivative found in the chromatographic analysis of schizophrenic urine by Nakao and Ball was presumably a breakdown product of indolic compounds in the body of the subjects tested (105).

Glutathione and ascorbic acid levels in schizophrenia have been reported as being unusually low (47,101). These abnormalities may be explained by the presence of adrenochrome, since this substance is an oxidant of both glutathione and ascorbic acid.

The tendency to hyperglycemia in schizophrenics is one of the most consistent results reported among the physiological data compiled for this disease (1,21,99). It has been noticed, too, that rarely are diabetes mellitus and schizophrenia found in the same person. This anomaly might be explained in this manner. Epinephrine is used up under insulin stress and presumably is antagonistic to insulin (119). However, adrenochrome is antagonistic to insulinase activity and thus would cause insulin levels to be raised, accounting for the negative correlation of diabetes mellitus and schizophrenia (16). The patient's condition would determine whether insulin levels were abnormally high or low. In a relatively constant environment the insulin level would be expected to be relatively high and hypoglycemia present. In remission insulin levels should fall to normal. Increased stress and increased adrenalin levels should also cause insulin levels to fall.
The workers at the Lafayette Clinic have noted that schizophrenics may have difficulty in the control mechanisms of carbohydrate metabolism in response to insulin stress (71,72). Foszormenyi-Nagy and Gerty have reported low phosphorous values in schizophrenics, although wide variation throughout the range of values was evident. This fact indicates a possible dysfunction in the energy transfer of phosphate bonds (76). The adrenochrome theory might explain this evidence, since adrenochrome is known to uncouple oxidative phosphorylation in hamster liver mitochondria (16). Hoffer and Osmond suggest that adrenochrome also inhibits hexokinase and phosphohexokinase activity in vivo. These facts may also explain, in part, the abnormal growth factors which are apparent in schizophrenia (81).

The Saskatchewan group has noted that schizophrenic patients, in which the disease had an early age of onset, commonly suffer from growth abnormalities. This is not apparent in patients whose illness occurred after maturation processes were complete. Adrenochrome is toxic to L-strain fibroblasts and inhibits the growth of rat epidermis. Therefore, a positive correlation between abnormal growth and an early age of onset in schizophrenia might be expected. Further, the antimitotic effects of adrenochrome might also explain the abnormally high frequency in which tuberculosis occurs in schizophrenics (83).

In the acute stages of schizophrenia a state of physical excitement is commonly present. In the chronic stages this excitement is less common and a generally apathetic condition
prevails. A decrease in the level of the mild brain inhibitor gamma amino butyric acid (GABA), formed by the decarboxylation of glutamic acid, can cause an excitatory state. Adrenochrome is an inhibitor to decarboxylase activity. Thus adrenochrome might induce a state of excitement by increasing the levels of glutamic acid and proportionately decreasing the levels of GABA (16). Some evidence has indicated that the glutamic acid-glutamine relationship is disturbed (30).

Adrenolution, in contrast, is known to reduce anxiety levels. Therefore, the accumulation of adrenolutin, as a breakdown product of unstable adrenochrome, accounts for the lowered anxiety levels of chronic schizophrenics and perhaps the increased stability of the disease once chronicity has been reached.

In summary, the adrenochrome theory has explained on theoretical grounds the various biochemical and physiological abnormalities which have been observed. Adrenochrome’s psychotomimetic activity accounts for the behavioral changes in schizophrenia and it is significant that these changes are "functional", rather than toxic in nature. Adrenochrome is anti-histaminic and an antagonist to thyroxin, explaining the negative correlation of allergies and schizophrenia and the observed abnormality in thyroxin distribution respectively. Adrenochrome would be expected to lower glutathione and ascorbic acid levels, interfere with oxidative phosphorylation, and inhibit insulinase activity, all of which have been indicated. Finally, it would be expected that if the adrenochrome theory
Physiological and Biochemical Properties of Adrenochrome and Resulting Clinical Properties if Present in Schizophrenia.

(16, p.226)
were valid, there would be a rise in the concentration of indolic compounds in schizophrenic urine. This condition has been reported in the literature. The effects of the adrenochrome theory are summarized in figure seven.

The main criticism to the adrenochrome theory lies in the fact that adrenochrome has not yet been isolated in humans. Thus, all the evidence for its presence in vivo must be considered essentially indirect, although a good deal of the data support the theory. Adrenochrome, as indicated, is extremely unstable in any biological system, and consequently its isolation from the blood becomes correspondingly difficult. Nevertheless, in 1959, Payza and Mahon claimed to have developed a test by which adrenochrome levels could be accurately determined in vivo. This test was based upon the conversion of adrenochrome to adrenolutin and then reacting this product with a zinc acetate-ascorbic acid reagent. The resulting solution exhibited a fluorescence which was measurable, specific, and directly related to adrenolutin levels in the blood. The experimental solution was compared with an acetone blank and the difference in terms of fluorimetric units converted into concentration values, based on a comparison with a solution of known adrenolutin concentration (85).

A number of criticisms have been brought forth concerning the values which Horfer and Payza found in schizophrenics, using this test. Feldstein concluded that this method was unreliable, since the spectrophotometric values obtained could have been the result of the zinc-ascorbic acid reaction (63).
Szara and Axelrod, in their own investigations, concluded that the method of Hoffer and Payza resulted in high adrenochrome values because of the high fluorimetric values of the blanks. Since precision is markedly reduced when high blank values are used, the measurement of small amounts of adrenochrome can not be accurately measured. Using lower blank values and a modified experimental set up, these workers found that adrenochrome levels were far below those previously indicated (85). Randrup and Munkvad reached the same conclusion in independent studies (107).

Hoffer and Payza answered these criticisms by comparing the Szara and Payza methods in schizophrenics injected with a known amount of adrenochrome. They found that after fluorimetric analysis, the Szara method yielded only 76μg/l liter. These workers then concluded that both tests were equally specific, but that the Payza method was considerably more sensitive (85). In view of the conflicting data, it should be considered that the fluorimetric determination of adrenochrome in blood plasma is still of indeterminate accuracy.

The effects of the adrenochrome theory can be interestingly correlated with the effects noted in the taraxein theory, thus encompassing the genetic evidence which has been compiled. The effects of adrenochrome and taraxein are not readily predictable in humans, but may vary in accordance with cultural setting, personality, and the capacity of the individual to deal with psychological disturbances. Naturally, the rates of production and destruction of adrenochrome, as well as the capacity of the individual for storing the chemical,
have an effect on the psychological changes which occur (78,84). This provides some evidence to indicate that schizophrenia is a unified concept and not a catch-all for a variety of fundamentally different conditions.

The taraxein theory provides evidence for an enzyme system which may oxidize epinephrine and its related compounds to hallucinogenic metabolites. Ceruloplasmin, in contrast, does not oxidize epinephrine in vivo, although copper ion may do so. Adrenolutin is bound to ceruloplasmin. This may explain why some chronic schizophrenic women undergo a period of remission during pregnancy (16). Melander and Martens observed that taraxein potentiates the activity of adrenolutin in cats and humans (103). Since the normal adrenal medulla produces approximately 5mg. of adrenalin per day, this would seem to be insufficient to cause the behavioral changes occurring in schizophrenia (16). The observations of the Swedish workers tend to allay this difficulty.

Hoffer and Osmond have suggested these relationships between the taraxein and adrenochrome adrenolutin theories:

1. The septal region in schizophrenics is abnormally sensitive to certain substances in the blood, especially taraxein and adrenolutin.

2. Ceruloplasmin adsorbs adrenolutin as so protects the brain. It does not oxidize epinephrine.

3. Taraxein may both sensitize the brain to adrenolutin and decrease the adsorption of adrenolutin upon ceruloplasmin, if it is correct that it can displace adrenolutin (16).

If the adrenochrome theory is correct it would suggest several possibilities in regard to new treatments. Under the chemical properties of adrenochrome several reductants were
noted, among them glutathione, ascorbic acid, and penicillamine. The injection of any one of these should lower adrenochrome levels and thus inhibit its action. If ceruloplasmin binds adrenolutin, then raising the ceruloplasmin level should be therapeutically beneficial in chronic schizophrenics (63).

If adrenochrome is the main component responsible for schizophrenia, then presumably adrenalectomy should be therapeutically beneficial. Although some paranoids do respond to this treatment, on the whole it is of little value (21, 24). However, adrenalin may not be produced solely in the adrenal medulla. It is found generated at synapses and distributed in the brain.

In all, the theory offers a number of interesting possibilities which should be carefully weighed and evaluated. The final proof of its accuracy will come after adrenochrome itself has been clearly isolated from schizophrenic blood and methods of treatment are found to successfully combat schizophrenia.
CONCLUSION

Throughout the entirety of this paper there has been one assumption made that may be questionable, namely, the belief that schizophrenia is a unified concept which can be differentiated from other forms of mental illness by some criterion or criteria. It may seem that a belated attempt is being made to define the problem with which this paper is concerned. On the contrary, it was the purpose of this paper to define the problem as clearly as possible, using the functional devices available to gain some mastery of the difficulties inherent in such a definition. This conclusion will deal with the definition of schizophrenia.

It was mentioned earlier in the paper that the human being may be studied on three interrelated levels, the genetic, biochemical-physiological, and psychological levels. The process of genetic transmission manufactures the body-building units, proteins. Inclusive in the substances created by this process are the various enzyme systems which occur in vivo. In schizophrenia, due to a genetic abnormality, similar, perhaps, to that occurring in hemophilia, a specific enzyme is produced which is qualitatively different from the comparable enzyme which occurs in normal persons.

On the biochemical level, this aberrant enzyme catalyzes some system, one associated, perhaps, with stress, which produces a substance which is not found in normals. This substance, then, exerts its own far-reaching biochemical effects on various other physiological systems, including those which
are situated in the brain.

Psychologically, the effects of this substance are reflected in the behavioral adjustments of the organism. Possibly a mildly stressful situation produces excess amounts of this aberrant chemical, which, in turn, raises anxiety levels, so that an internal stress, which is self-propagating, results. Environmental factors may be such that, in a limited number of cases, the onset of the disease is inhibited.

In consideration of the methods of treatment which may be useful in schizophrenia the following statements can be derived from the definition. Psychological methods can not cure schizophrenia. They can, however, lower the levels of the anxiety-producing substance by reducing the internal stress, lowering thereby the stability level of the syndrome. Drug therapy is also useful as an independent, rather than an adjunctive tool. Tranquilizers also suffer the limitations of psychotherapy in that they do not act directly on the aberrant substance.

Therefore, the biochemical level offers a means of treating schizophrenia directly. First the aberrant substance must be determined and isolated. Finally, methods must be devised for destroying or inhibiting this substance. This process should result in the eventual cure of schizophrenia.
ABSTRACT

Schizophrenia is a disease whose physical cause is unknown despite the attempts of several research teams to discover a physical basis for it. Some success has been gained in genetic studies which indicate that schizophrenia is an inherited disability. However, since research tools are at present so sadly inadequate, the value of pursuing a genetic line of reasoning is questionable.

To compensate for the lack of biochemical certainties in treating mental illness, psychological theories have been constructed to explain the schizophrenic syndrome. Normal personality is seen as the resultant of environmental and inherited influences. Involved in the formation of personality are the processes of differentiation and integration, maturation of inherited traits, and the learning processes. As personality develops, consciousness of the self, inferiority feelings, and compensatory mechanisms, and the transformation of interests into drives exert a decided influence upon personality growth. Finally, in the mature personality, an integrating philosophy of life, a large variety of interests, and the possibility of self-objectification become evident.

The abnormal personality is shown to be the result of an early isolation from the learning experiences of social adjustment, usually characterized by painful rejection in childhood learning experiences. Typical schizophrenic withdrawal and indifference, manifested in a variety of ways, reflect the compensating mechanisms for this social isolation. The genetic theories are examined in the light of the somatotype considerations of some workers. The latter may provide a partial explanation for the genetic evidence.
The genogentic theories are examined in the light of the somato­type considerations of some workers. The latter may provide a partial explanation for the genetic evidence. Anxiety and defense are seen as central to the problem of neurosis and psychosis, and schizophrenia itself is considered as a misinterpretation of the concept of self, resulting in a disintegration of personality characteristics.

Psychotherapy, at present, offers the most important means of treating psychological maladjustments. Three methods are possible for treating neurotics, the non-directive method, the standard psychoanalytic method, and an abbreviated form of the latter, termed "briefer psychoanalysis". The therapeutic relationship is deemed most important in encouraging the patient to lower his defensive mechanisms. The expression of feelings is encouraged by the process of free association and the recognition of defenses and the emotional content of thought eventually leads to abreaction, the corrective emotional experience necessary to allay the anxiety generated by the core of the neurosis.

In schizophrenia, the therapeutic relationship itself is difficult to establish because of the schizophrenic's rejection of the external world. In mental institutions social contact is greatly encouraged in order to gain therapeutic rapport. Recently chemical agents have been helpful in establishing this rapport.

Drug therapy, in its early years, was considered a pan­acea for schizophrenia. More recent studies have indicated that the drugs are no better than adjunctive tools to psychotherapy,
although their use in this regard is of the highest value. The drugs of the tranquilizing variety can be classified into five classes, the phenothiazines, the Rauwolfia alkaloids, the substituted amides, the diphenylmethanes, and the substituted propanediols. Each of these classes has found some use in the treatment of schizophrenia, in general, lowering anxiety levels without disturbing the intellectual capacities or the power of motility in normal doses. Four regions of the brain are of particular importance in determining the effect of the drugs, the cortex, the hypothalamus, the limbic system, and the reticular formation. The stimulating drugs, the analeptics, the MAO inhibitors, and the acetylcholine precursors, are briefly considered, being useful in some depressive conditions. The action of these drugs may be involved with effects on the hypophyseal-adrenal axis.

Statistics provide the basic means by which differences may be established between schizophrenic and normal groups. The various elements of statistical techniques are reviewed. The measures of central tendency, the methods of scaling, the normal curve, and the differentiation of parametric and non-parametric statistics are explained. The null hypothesis is formulated and defined and its importance to research emphasized. Some methods which increase the efficiency of an experiment are reviewed. Included in this group are special designs, physical manipulation of error sources, and such techniques as covariance analysis. Emphasis is laid upon the fact that caution must be used in accepting the assumptions
which these methods of efficiency dictate.

The psychedelic drugs have played an important part in the history of several cultures. The historical aspects of these drugs are mentioned and the effects of some of the drugs, as indicated by non-scientific observers, elaborated. The psychedelics today offer a means by which the mechanisms of psychosis may be profitably studied under controlled conditions. The objections to the use of the model, that the psychedelics produce a toxic, not a functional disorder and that visual hallucinations, rare in schizophrenia, predominate in experimental psychosis, are answered in detail. The drugs are then divided into three categories, those structurally related to epinephrine, those interfering with acetylcholine function, and those structurally related to adrenochrome, an indole metabolite of adrenaline. Their actions are considered with respect to these classifications.

The biochemical abnormalities which have been elicited in schizophrenia are reviewed. Much of the data exhibits wide variation and its value is questionable on this account. The most predominant findings include the possibilities that schizophrenics have a defect in control mechanisms involving carbohydrate metabolism under stress conditions, there is an abnormal tolerance for histamine, schizophrenia somehow involves the pituitary-adrenocortical axis, and indolic compounds are excessively present in schizophrenic urine. The difficulties inherent in a biochemical analysis are elaborated.

Three biochemical theories have been suggested and have
gained a large number of supporters. The serotonin theory finds its basis in three major points: It is naturally occurring in the brain, it is antagonistic to several psychedelic drugs, and its precursor causes mental aberrations. Criticisms of the theory are entered and it is concluded that at present the available evidence is too weak to consider accepting the serotonin theory.

The historical foundation for the taraxin theory is elaborated. Taraxin, isolated by Robert Heath at Tulane University, is considered an aberrant protein in the bodies of schizophrenics. Its psychological effects are noted. It is concluded that this is the first step on the road to a biochemical theory of schizophrenia.

The adrenochrome theory was first proposed on theoretical considerations. Adrenochrome is a psychotomimetic substance and a metabolite of adrenalin, which has long been indicated as a factor in stress. Adrenolutin is a breakdown product of adrenochrome. These two chemicals explain, to a degree, the biochemical abnormalities considered above. They also explain the stages of acute and chronic schizophrenia. Adrenochrome has not been isolated from the blood as yet, and this difficulty is a major block to its acceptance. Possible treatments are derived from this theory.

Finally, it is concluded that schizophrenia is a disease which is manifested through the three levels of biological organization, the genetic, biochemical-physiological, and psychological levels. The interrelation of the three levels
is illustrated. An attempt is made to define schizophrenia as a manifestation of each of these three levels.
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