1956

Hallucinogens : vistas toward a biochemical concept of schizophrenia

Robert Charles Pfeiler
University of Nebraska Medical Center

HALLUCINOGENS: VISTAS TOWARD A BIOCHEMICAL CONCEPT OF SCHIZOPHRENIA

Robert Charles Pfeiler

Submitted in Partial Fulfillment for the Degree of Doctor of Medicine

College of Medicine, University of Nebraska

April 2, 1956

Omaha, Nebraska

TABLE OF CONTENTS

INTRODUCTION

Schizophrenia of some type is the country's most frequently occurring serious disease. It accounts for 40% of all mental illness and 20% of all hospital beds hold schizophrenics.

The study of schizophrenia, its classification, its signs and symptoms, its therapy, and primarily its etiology is the number one problem in psychiatry and in the general field of mental health today. Towards the unraveling of this mystery many means are providing insight and understanding. The field of experimental psychiatry has with its recent vigorous growth opened up new horizons toward conquering this problem of the ages.

Among the approaches used in experimental psychiatry three prevail. The first attempts to answer - what is a schizophrenic? What are the signs and symptoms, the objective and subjective findings? What physiochemical abnormalities exist in the schizophrenic? The experimental study deals primarily in this instance with schizophrenic humans. By knowing what it is, what can be done about it and what causes it may be more easily answered. The second approach attempts to answer - what is the mechanism by which therapy helps the schizophrenic? By experimentation on both animals and humans an effort is made to discover new therapeutics and to explain in what manner the effective new and "old reliable" ones have their action. In this way enlightenment

into the disease process occurs.

The third approach asks - what is the etiology? What causes and maintains the disease condition? Many etiological theories have been advanced; the most prominent ones have been psychic theories involving psychological and behavioral interrelationships between self and enviornment; biochemical theories involving errors of metabolism, enzyme upsets, endocrine disturbances, and heredity theories of causation.

Much of the experimental work now being done relates to a biochemical concept of schizophrenia; if not to a primary biochemical concept at least to a strongly recognizable biochemical component. Experimental work in this field has been aided by tools called hallucinogens. Hallucinogens are schizophrenic-mimicking drugs and because of their nature are valuable adjuncts in experimental work in man and animals.

This paper deals primarily with a review of the literature pertaining to hallucinogens and their role in the study of schizophrenia. Schizophrenia will be defined and certain findings common to schizophrenics will be discussed. A cursory glance at other theories pertaining to schizophrenia and other experiments relating to an understanding of man and his mental mechanisms will be taken. Following the review certain conclusions and perhaps some hyptheses will be listed.

In a thesis of this type some statements included are common knowledge, and others made are the result of summation integration of knowledge gleaned from the bibliography, so that specific footnotes can not be made for all specific statements. The latter is done, however, where appropos to specific experiments and conclusions. Only those references in foreign languages and those unavailable to the medical library were not seen personally, but several foreign language references were found abstracted in Excerpts Medica. The bibliography is listed alphabetically and numbered in order by alphabet. Referral from the body of the paper is by name year and number.

Appreciation is expressed to the University of Nebraska College of Medicine's library staff headed by Mrs. Hetzner for their cooperation in use of the library and for expeditiously obtaining the necessary references.

SCHIZOPHRENIA

Psychiatric definition and description.

Schizophrenia represents a group of psychotic disorders characterized by fundamental disturbances in reality relationships and concept formations with objective behavioral and intelluctual disturbance in varying degrees and mixtures. The disorders are marked by a strong tendency to retreat from reality, by emotional disharmony, unpredictable disturbances in stream and thought, regressive behavior, and in some by a tendency to deterioration. The predominant symptomology is the determining factor in classifying such patients into the following types: simple, hebephrenic, catatonic, paranoid, acute undifferentiated, chronic undifferentiated, schizo-affective, childhood, and residual. Psychotic disorders may be described as characterized by a varying degree of personality disintegration and failure to test and evaluate correctly external reality in various spheres. In addition, individuals with duch disorders fail in their ability to relate themselves effectively to other people or to their work. (170) (63)

Bleuler (19) feels there are primary and secondary symptoms. He believes the secondary signs are due to normal environmental irritations and to normal psycholog-

(63) Green 1955
(170) Nomenclature 1952

ical and physiological mechanisms built on the structure of the primary lesions. The primary symptoms are: 1) associative disturbance; which include illogical connection of two unrelated ideas, two different ideas combined in a condensation process, abnormal use of symbols, general vague notions replacing concrete thinking, and use of alliterations, and, 2) affective disturbances.

Secondary signs are autism, delusions, illusions of memory, hallucinations usually auditory, negativism, stereotyping, mannerisms and catatonic signs. Perception, memory and intelligence usually are intact.

Kraepelin (95) lists the primary diagnostic symptoms as a peculiar and fundamental want of any strong feelings of the impressions of life with unimpaired ability to understand and to remember, associated with a weakness of judgement and flightiness, mental and emotional infirmity, silly, vacant laughter, face making or grimacing, senseless playing with syllables and words, onanism, flexibilitas cerea, and echopraxia. When hallucinations or confused delusions accompany early states of depression this may preclude a steady progession to schizophrenia, which is synonymous with the older term dementia praecox.

The disease can have an acute or chronic onset with a variable duration. It may die a spontaneous death in late middle life. No correlation with social status, age, body build, economic situation, environment per se exists except there is a definite tendency noted

More frequently in the long, thin people. Osmond 1955 (122)

Some feel schizophrenia is not a disease but a syndrome or collection of symptoms (137) but Bleuler (19) is certain that since his primary symptoms were found in all schizophrenics and not consistently in other diseases, and since several functions are usually found intact in the schizophrenic that are not found in other mental disease that schizophrenia is a single disease entity which can appear in several forms.

Biochemical and physiological findings.

Generally the body chemistry has not been noted to be grossly different from normal people and there has been a paucity of physiological findings specific to schizophrenia. (26) However experimentation has revealed the following findings which, although not of primary diagnostic value, may be of interest secondarily diagnostically and may aid in an understanding of mechanisms involved in the schizophrenic process. Further biological experimentations are vitally necessary in this field. Diagnosis is made currently from the psychodynamics involved in schizophrenia.

The general findings involving;

A. Carbohydrate metabolism abnormalities.. (68) (152) (137) Bellak 1955 (26) Gallaway 1955 (68) Henneman 1955 (152) Shattock 1950

1) lower turnover of adenosine triphosphate (118)
2) increase of phosphoglycolic acid in blood and in turnover (118)
3) glutamic acid metabolism is abnormal in brain, kidney, and muscle tissue (9)
4) carbonic anhydrase is reduced in all organic mental diseases as well as in schizophrenia (8)
5) greater insulin resistance (6)
6) impaired glucose tolerance (6)
7) elevated blood lactate level (6)
8) lowered blood glutathione (6)
9) increased fasting blood sugar (68)

B. Adrenal-pituitary cycle abnormalities.
1) adrenal normal at rest (59) (60) (103), although may have qualitative or decreased quantitative endocrine responses (72) (152)
2) diminished quantitative and qualitative response of adrenals under stress (60) (103)
3) big decrease in urinary excretion of inorganic phosphate (76)
4) increase excretion of 17 keta steroids in urine at rest (5)
5) increase urinary excretion of sodium and potassium ions at rest (75)
6) decrease urinary excretion of corticoids and phosphates at rest (75)

C. Other urinary abnormalities.
1) kidney is normal (4) (76)
2) creatinuria increased (13)
3) possible albuminuria (19)
4) possible ketonuria (152)

D. Bone changes.
1) decalcification (15)

E. Autonomic nervous system changes.
1) sympathetic nervous system less responsive (83)
2) vasomotor changes (19), vasoconstriction of large vessels (152)
3) pupillary changes (19)

F. Blood changes-miscellaneous.
1) mild leucocytosis (19)

(118) Orstrom 1951 (9) Astrup 1955 (8) Ashby 1951
(6) Altschule 1950 (68) Henneman 1955
(59) Gildea 1950 ((60) Gildea 1952 (103) Malamud 1952
(72) Hoagland 1952 (152) Shattock 1950
(76) Hoagland 1955 (75) Hoagland 1953
(4) Altschule 1953 (13) Bellak 1955
(19) Bleuler (15) Beyer 1941 (83) Hoffer 1954

G. Miscellaneous.

1) increased tolerance to histamines (102)
2) change weight, usually a loss (19)
3) decrease in body temperature (152)

Etiology of schizophrenia.

The etiology of schizophrenia is still unknown. Through the years many and varied concepts have been proposed from a gonadal basis to traumatic injury (102) but none as yet have unfolded the mysterious cause or causes of this devitalizing disease. To be sure in recent years much has been added to our library of knowledge but the puzzle is not yet solved. Various prepresentative theories are discussed below.

A. Psychological-behavioral.

While Bleuler (19) felt that the primary etiology is unknown he did feel that the secondary symptoms can be explained by psychological mechanisms. He denies the possiblity that environment or abnormal inborn tendencies have much to do with the basic etiology. His denial is based on extensive studies of schizophrenics and normal humans.

Funkenstein 1951 (51) states that any change is the clinical psychologic status of the mentally ill is accompanied by definite physiological changes, and that without psychologic change there can be no physiologic change. He feels that mental illness is due to the

(102) Lucy 1954 (19) Bleuler
(152) Shattock 1950 (51) Funkenstein 1951

individuals inadequate response to stress but that psychological and physiological mechanisms go hand in hand, since they are both part of the same biologic system.

Another believes that it is a functional psychosis because as yet there is no specific evidence of organic disease of the brain (63). However he concedes that although there is no specific histopathological changes in the brain, there may be histochemical abnormalities. He thinks stress may play an important part in mental disease and feels that conditioning is based upon the application of stress. (63) Hoch 1952 (81) mentioned that some feel there is a correlation between basic personality types and the state and type and severity of the mental illness. It is a question whether the affects of drugs in improving psychiatric illness are due to physiological action of the drugs or due to the alteration in the reality experience or some other psychical change in the patient.

Psychosis is primarily a failure of personality integration, and Hoskins 1946 (85) states that the problem lies in locating the level of defect in the person. He feels that biochemical and heretical factors are important but also feels that schizophrenics operate at a level of reduced awareness and that they fail to retain empathy. He considers a defect in the maturation

(63) Green 1955 (85) Hoskins 1946

process, on either the psychological or biological level, a possibility.

Scope 1955 (173) showed there is a correlation between thought changes and physiological changes accompanying stimulation. They feel it is a possibility that emotional reactions are initiated largely by memory and, that painful emotion triggers illness in man. However they support a neutral reaction within the brain itself with centers in the rhinencephalon as basis for emotional change.

B. Environment.

Callaway 1955 (26) feels that environment plays a part in maintaining normality since the "more stress some people are subjected to; the less environmental stimuli they are free to use; the less of environment they are free to draw upon, the poorer in judgement; poor judgement, less able to avoid stress; and more stress subject to, less of the environment available for future judgements used." A vicious cycle thus ensues. Environment may play a factor in schizophrenia, although not a decisive one or a fundamental one (19) (63) (51)

C. Heredity.

In his studies Kallman 1952 (92) showed a definite heretical to schizophrenia. He demonstrated a recessive

(19) Bleuler
(63) Green 1955
(51) Funkenstein 1951

genotype which he felt might be linked to an endocrinologic determiner. A schizophrenic incidence of 86.2% in monozygotic twins as opposed to an incidence of 14% in full sibling, and in dizygotic twins shown from his studies support his theory.

Hoagland 1953, 1955 (75) (76) feels that genetic factors are responsible for the derangement of enzyme function, the latter being perhaps a causal factor in schizophrenia. He also feels that a genetic factor may have something to do with the fact that young schizophrenics do not react as well to ACTH as older ones.

Shattock 1950 (152) feels that differences of heredity account for clinical varieties while the common feature in the various types is an increasing qualitative loss of critical appraisal, which is probably due to interferences by autistic thought, which the patient can not control since they arise from motives and impulses not accessible to volitional action. Others support possibility of primary heredity importance. (19) (85)

D. Neuronal-brain interrelationships.

Since general irregularities of the electroencephalogram (hereafter referred to as the EEG) have been found, disturbance in this system might be quite important. (63)

Callaway 1955 (26) suggests that procedures which evoke sympathetic activity may create a more limited

(19) Bleuler
(85) Hoskins 1946
(63) Green 1955

sensory environment, and with the development of the latter a psychosis may result since to keep mentally well, one must be in constant sensory contact with the outside world since the validity of thought must be checked to avoid mental illness. An optimum level of stress or alerting for any task is inversely related to the complexity of the task (169). Again stress is postulated as the important factor in the development of mental illness.

A diencephalic-autonomic dysfunction is suggested as underlying mental illness, where those unusually sensitive to stimuli develope a hyperkinetic syndrome. And with the alerted state one has less sensory preception, and with less sensory perception one will easily develope mental illness. Many studies implicate the sympathetic nervous system. (26) Hoskins hypothesizes a hypothalamic failure. (85)

Recent studies by Heath (Whats New 173) in electrode studies of human brains reveals a correlation between thought changes and physiological changes accompanying stimulation of given areas. The same emotional response is shown to accompany stimulation of a specific region each time. Various subjection feelings correspond to specific areas of stimulation. He suggests two hypothetical circuits by which cortical activity dominates behavior.

(169) Yerkes 1908
((85) Hoskins 1946
(26)Callaway 1955

Stimulation of the septal region (prefrontal cortex connected with that area of the rhinencephalon below the corpus callosum) speeds movement and stimulation of the caudate slows movement.

Since removal of the septal area causes changes like that seen in removal of adrenal cortex in cats and monkeys, he feels that pituitaries and adrenals are probably good in mental illness, and that disturbance is probably due to neural reactions rather than to endocrinal mechanisms.

E. Trauma and infection.

These at one time were thought to have caused schizophrenia but are not important theories now. Osmond 1952 (122)

F. Biochemical.

Most of the experimental work currently in progress involves a biochemical search into the etiology of schizophrenia. It is here that the hallucinogens have much to offer as tools. However findings relating to the use of hallucinogens, in addition to discussion of their influence in support of a biochemical concept of schizophrenia, will be discussed further on in this paper. The biochemical and physiologic findings listed in an earlier portion of this paper as prevalent in schizophrenics would lend credence to a biochemical etiological theory. Several biochemical fields have been mentioned as possible areas within which the germ of schizophrenia is nurtured: 1) metabolic-enzymatic errors, either inborn

or outborn; 2) endocrinal disturbances; 3) nutritional and vitamin deficiencies; 4) vascular insufficiencies; 5) toxins-foreign to or developed within the body as through faulty liver action.

1) Metabolic-enzymatic errors.

There has been much supposition that an error in the adrenal pituitary relationship might be the foundation for schizophrenia. This cycle is certainly involved as is demonstrated by the following experiments.

a) Experiments relating to the pituitary-adrenal cycle.

There is a reduced responsivity of schizophrenic patients to experimental stresses and to doses of ACTH. In the normal one sees an increase in 17 ketosteriod urinary excretion following stress but not in the psychotic. Lymphocytopenia in the normal also follows stress but again not in the psychotic. The same results occur with the injection of glucose as a stress agent. So there definitely appears to be hypoadrenalism in psychotic subjects. The converse is not necessarily true since all patients with Addisons disease do not develope bizarre and psychotic behavior, although some do. Further investigation is needed in the adrenocortical-pituitary relationships, Pincus 1949 (130) feels, for perhaps the trouble lies in the pituitary or end organs. Endocrine disturbance may make some people more vulnerable to stress but if they are not subjected to stress they

may lead normal lives. Ibid 1950 (129) He lists two possible explanations for the schizophrenic's abnormal response to stress: 1) exhaustion of the adaptation syndrome, and 2) secretion of adrenal cortices may just differ qualitatively from the normal man.

Hoagland 1952 (72) demonstrated that the schizophrenic in addition to having a subnormal response to stress also finds a subnormal response to the injection of ACTH both qualitative and quantitative, as contrasted to psychoneurotics who elicit normal responses. This response is not improved by a diet rich in protein and vitamins.

Altschule 1950 (6) showed that several of the biochemical findings listed above pertaining to adrenal metabolism are similar to those found following ACTH administration to normal people, except for the retarded water and high sodium excretion at rest. Those patients who respond best to ACTH do the best on electro-convulsive therapy (hereafter referred to as ECT).

Hoagland 1950, 1953, 1955 (74)(75)(76) demonstrated that chronic schizophrenics fail more completely in response to stress than does the acute, but they show a better response to ACTH. The urinary inorganic phosphate level will increase in response to stress, ACTH or cortical extracts if responses are elicited.

Steroids affecting potassium ion excretion seem to be the most affected in the schizophrenic. Pincus 1950 (129)

Although steriod hormones are not effective in most schizophrenics Altschule 1950 (5) showed that they did have some prophylactive effectiveness following remission of schizophrenic symptoms after shock therapy. He thought they helped then, because they kept the adrenal cortex depressed.

ACTH in varying doses given for varying lengths of time seemed to give temporary improvement in Addisons and Cushings diseases as shown by EEG changes and Neuropsychiatric changes. However the disease condition reverted to its original status within one week following discontinuation. (65)(63)

Euphoria, depression, and psychoses are seen in some normals treated with cortisone and ACTH. Rome 1951 (140)

Altschule 1950 (5) found that in schizophrenics following psychotherapy, insulin or ECT that one might find an increase excretion of 17-ketosteroids which was later followed by a decrease in excretion in those responding psychically to therapy. Of course the 17 ketosteroid excretion is directly proportional to the caloric intake but the schizophrenic shows less excretion than could be accounted for on the low caloric intake which is frequently found in them.

A rise in blood glucose and the normal lactic acid level is seen in early psychotics following in-

(63) Green 1955
(65) Haefer 1950

jection of adrenalin but there is a decrease in both blood glucose and lactic acid in chronic psychotics following injection. The later is not a reaction specific to chronic psychotis since this result is found in many chronic diseases. Hennemon 1955 (68)

Funkenstein 1953 (52) in his work on stress showed that anger directed inward accompanied by anxiety lead to physiological illness; while anger directed outward accompanied by anxiety lead to psychological illness. They also observed the relationship of nor-adrenalin and adrenalin to emotional manifestations, and discovered that punitive anger is associated with an abundant release of a nor-adrenalin like substance and that intra punitive anger is associated with over release of an adrenaline like substance. (50) ECT improved patients who excreted adrenalin like substances; but not those excreting nor-adrenalin like substances. The adrenalin-like excreter is usually diagnosed as a manic depressive or involutional psychotic; whilethe excessive nor-adrenalin like excreters areusually diagnosed as schizophrenics.

He theorizes that the adrenal medulla secretion may tie in with mental illness and that response to electric shock follows autonomic typing rather than diagnostic categories.

In 1954 (53) Funkenstein related that intravenous infusion of adrenalin into normals caused an increase in

(50) Funkenstein 1952

blood pressure, an increase in the pulse rate, a decreased peripheral resistance and an increased cardiac output; while an intravenous infusion of nor-adrenalin increased the blood pressure, but decreased the pulse, increased the peripheral resistance, and caused a normal or decreased output. Psychological stress was also found to give these two types of results. This proved that the medulla secretes two substances: adrenalin-like and nor adrenalin like substances.

Schizophrenics show less reaction to adrenalin than the normals although anxiety is produced in the psychoneurotic by it. Mecholyl had little effect on the schizophrenic mental state. The normals showed moderate response to drugs followed by early tendency to reestablish homeostasis. Aggressive agitated patients showed a great increase in blood pressure to adrenalin, and depressed patients showed the greatest decrease in blood pressure with mecholyl. Anxiety precipitated by adrenalin is found to be relieved by insulin coma and increased by electric shock. (51)(49)

b) Experiments relating to carbohydrate metabolism.

Henneman 1955 (68) found that mobilization of liver glycogen after injection of humans with adrenalin was normal or increased in schizophrenia except in the chronic schizophrenics who showed decreased mobilization. There was also noticed a decrease, to point below normal, in

those schizophrenics given insulin.

Nimwich 1952 (71) suggested that the effectiveness of insulin and shock is through the suppression of cerebral metabolism at basic levels by causing anoxia and hypoglycemia leading to a chemical breakdown in energy reserves so that cerebral function is not supported. Following shock therapy there is apparently an increased permeability in brain cells to inorganic substances and to the sodium ion, and a decreased permeability to the potassium ion. He stated that the postassium ion strongly stimulated brain oxidations while enforcing other changes in carbohydrate metabolism. Sodium ion interferes with the fundamental phosphorylation and affects carbohydrate metabolism. The autonomic nervous system is also affected by this. Though the brain is depressed by hypoglycemic shock, in ECT it is stimulated to such a peak that relative hypoglycemia prevails and there ensues such a lack of energy that long activity is impossible. Intensive convulsive attacks are best for affective schizophrenics.

c) Experiments involving other enzymatic processes.

Alpha-(2-piperidyl) benzhydrol hydrochloride demonstrated definite although inconsistent therapeutic effects in schizophrenis dissociation syndromes. Fabing 1955 (42).

A definite although temporary response of catatonics to barbiturates has a definite chemical basis. Formation

of high energy phosphate bonds is inhibited by pentobarbital, thus acetylcholine synthesis and excitability is decreased. This leads to increased activity because of a depression of the inhibitory elements. Hoch 1952 (81)

Chlorpromazine and phenothiazine derivatives have strong CNS and peripheral effects. They interrupt reflex areas at central synapses more than at peripheral ganglion and effector organs. In addition to neural interference they also interfere with cellular metabolism leading to artificial hibernation and an increased hypothermia and general anesthesia. (96) An over dose of chlorpromazine can lead to a Parkinsonian syndrome of muscular rigidity, mask like features, loss of associative movements and salivation. It is presummed to be due to its influence on the paliostriatum. (79) Chlorpromazine although it causes sleepiness gives no characteristic EEG change. (171)

Atropine causes a decrease in blood pressure in the schizophrenic; the greatest decrease in the acute type, and an increase in blood pressure in normals. (83) When the schizophrenic remits there is a reversal of the atropine effect. Atropine potentiates sympathetic action.

Ashby 1951 (8) notes that acetyl phosphatase, the enzyme which catalyzes the reaction which releases the energy stored in energy rich phosphate bonds of acetyl phosphate may play a basic metabolic role in the CNS.

(79) Hoch 1955
(83) Hoffer 1954
(96) Laborit 1954
(171) AAAS 1955

It was noted also that the importance of a region in the CNS to a species is related to the amount of carbonic anhydrase present within that specific region; this being proportionate to the dominance of the area. Various possibilities were cited as to how carbonic anhydrase might increase the speed of conduction and therefore the sensitivity to stimulation in the areas of dominance. Since molecular carbon dioxide depresses conduction rate and therefore sensitivity to stimuli, he puts emphasis on the probability that carbonic anhydrase hastens removal of excess carbon dioxide given off during neural activity, thus decreasing maximum concentration of the gas and increasing the possibility of stimulation.

Bleuler 1950 (18) thought the etiology of schizophrenia might be a metabolic disorder with manifestations in the psyche. Fabing 1955 (42) feels schizophrenia is due to a metabolic error although he feels the psychogenic theories are not disproven yet.

Green 1955 (63) mentions that two major adaptive systems are at fault in schizophrenia; these being the CNS and endocrine system. He believes these two systems are most influenced by enzymatic, nervous, and behavioral disturbances.

The modern conception is that pathological cells and tissue changes represent not merely architectural alterations, but reflect disturbances in the dynamic enzymatic and metabolic activities of functioning units.

Polynucleotide and protein deficits are found in cortical cells in schizophrenia. Normal metabolic-excitability relationships of various brain areas may be upset in the schizophrenic. He feels that the ideal agent for treating the schizophrenic would not be a general metabolic reducer as are those in vogue now, but one that would act by a topographical and selective inhibition of overactive areas.

Hoskins 1946(85) feels the difficulty lies somewhere at the molecular level. He has found a decreased amount of catalytic iron in the brain of the schizophrenic and decreased oxygen uptake, and thus is lead to the conclusion that catalytic and enzymic systems may be at fault. He does concede that vitamin deficiency, fundamental metabolic error, amino acid imbalances in relation to cell processes and functions, maturity failure, endocrine disturbances, all may play a part at the molecular biochemical level..

Pincus 1950 (129) regards all behavior as an interplay of subtle, physiochemical mechanisms which are analyzable with sufficiently developed scientific knowledge and acumen. Schizophrenia should be considered an organic disease involving abnormal mechanisms of action in either, or both, the nervous or endocrine systems. It was felt that a faulty potassium ion metabolism in the face of repeated stresses may be an important cumulative factor in the development of a psychosis since potassium is important in nerve excitability and in generation and

propogation of action currents. The pattern of nerve messages constitutes the physical basis for thought.

That schizophrenia may be another disease of inborn error of metabolism was suggested by Martin 1951 (106), in which might be found metabolically mutated states, some of which might be due to specific naturally occurring metabolic analogues. As an antimetabolite can prevent biosynthesis of an amino acid, in the same manner can enzymes be affected. Psychological normality is based upon hormonal balance. Antagonism between steroids constitute oneof the few known balancing mechanisms which can be directly correlated with psychiatric states. It is probable that stability of human mentality finds its foundation in the interplay of mutually antagonistic molecules. It is in this area that minor modifications produce profound effect.

The theory of biological relativity states that no single molecular structure possesses a function not shared to some degree by structurally related molecules. There exists in nature no example of absolute specificity of anzymes. Biological order is actually based on disorder-antagonism. These competitive phenomena are based upon ordinary short-range forces of chemistry. There are two types of biological antagonists-natural and synthetic.

Biological antagonism is a manifestation of competition between substances for surface positions on proteins.

All proteins under proper conditions are capable of functioning as enzymes. The protein substance is considered the heart of the biologic reaction. All processes of life are fundamentally enzymatic in character. An enzyme is the universal living element. Martin concludes with the concept that biological systems are no more than applications of statistical laws to a system in which biological antagonists are dominant factors. Large numbers of molecules having similar structures to hormones, could upset the delicate balance, thus leading to mental illness.

Phosphoglycolic acid may play an essential role in metabolism. It is increased in schizophrenia as mentioned above, and since there is a decreased turnover of ATP (studies have shown that phosphoglycolic acid is an acceptor of radioactive phosphate rather than ATP), it may play an essential role states Orstrom 1951 (118).

Pope 1952 (132) explained that disturbances of certain cerebral enzymes is revealed in the psychosis of pellagra with its depletion of brain pyridine nucleotide codehydrogeneses. Another example of enzymatic disturbance is demonstrated by the psychotic symptoms which partial inactivation of brain cholinesterase by DEP can cause. Prefrontal cortices of some deeply psychotic patients hydrolyze acetylcholine faster than usual. He hypothesizes that if cholinesterase activity is an index of rate of turnover of the system metabolizing

acetylcholine and if the latter is a compound of critical importance in physical chemistry impulse transmission, initiation, and synaptic transfer, then that might suggest a chronic increase in rate of neuronal discharge into the cortex in question.

2) Endocrinal disturbances.

That endocrinal abnormalities play a part in psychotic and schizophrenic disturbances is already surmised from the discussion of the metabolic-enzyme system described above. Osmond 1952 (122) has in fact suggested that schizophrenia is a specific disorder of the adrenals. There is a close relationship between schizophrenia, anxiety and stress, so when the adrenal is overworked a malfunction of the gland may occur.

Pincus 1950 (129) cited two possibilities as to the failure of the adrenals in stress in the schizophrenic. One is that an exhaustion of adaptation syndrome exists and two that the secretion of cortices is different qualitatively in schizophrenics. Intense stress may break through and evoke secretory reserve. The electrolyte and 17 keto steroids show the greatest differential response between schizophrenics and normal humans. He does not feel that the pituitary is at fault.

However Hoagland 1950 (73) concluded that since electric shock stimulates the pituitary, unresponsiveness of the pituitary may be associated with the chronic phase

of the disorder.

3) Nutritional and vitamin deficiencies.

These may play a part in the development of schizophrenia, but if they do, it is apparently a minor role, since a recent experiment giving protein and vitamins was of no benefit to the patients. (85) (122)

4) Vascular insufficiencies.

Vascular insufficiency is thought to have a part although not a primary one by several people. (152) Shattock 1950. Hoffer 1954 (83) postulated a rigid vascular system for schizphrenia to explain a remarkably high correlation between systolic and diastolic pressures. However this tube-like vascular system is seen in other illnesses associated with stress. Martin 1951 (106)

5) Toxins.

Not many subscribe to a theory of a foreign toxin causation. However many feel as will be discussed in relation with the hallucinogens that there may be a specific substance that arises from within the body which causes schizophrenia. Patsig 1953 (125) felt that a new compound formed in the liver caused mental phenomena. He proposed a biochemical concept with the liver as an important facet. It is of historical interest to note that Jung in 1906 (1936-91) postulated the presence of a toxin "X" in the body which he con-

sidered as the etiologic agent in schizophrenia but he left it to a "more perfect chemistry and anatomy in the future" to demonstrate the metabolic changes in and causes of schizophrenia.

Stocking 1940 (157) considered all psychoses to be variants of the same disease process, and the causative agent to be some type of toxin in the body which has a selective action on the higher centers. The centers attacked and the type of psychosis, he felt, could be determined by a study of the psychophysiologic make-up of the past environmental experiences of the patient.

6) Unified concept.

Bellak 1955 (13) emphasized that schizophrenia must be understood as the final common path of a number of conditions which may lead to severe disturbances of the ego. This ranges from purely psychogenic weakness of the ego to affliction of ego functioning by disturbance of brain by infections, arteriosclerosis, enzymes, toxins, trauma, or genetic (chemogenic, histogenic, genogenic or psychogenic) causes. He felt that contrary to many others that schizophrenia is a syndrome and not a disease. He thought that it is a syndrome of severe ego disturbance and is a result of somatic and psychogenic factors; that it is at one end of a continuum while normality is at at the other end, and in between lie the neuroses, and manics. Schizophrenia is a range on this continuum, not a

point.

Callaway 1955 (26) agreed that since a person is a complex being that no single factor causes mental illness, but that in each patient there are social, physiological, chemical, genetical, cultural, educational and psychological factors which must be considered to fully understand the disease. And as Alexander (51) stated "psychic and somatic phenomena take place in the same biological system and are two aspects of the same process." Many mentioned above feel that although there may exist a basic causative factor in schizophrenia, there are many associative variables that will influence the type, duration and severity of the schizophrenia.

HALLUCINOGENS

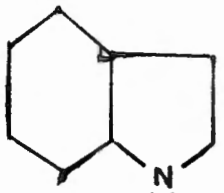
The hallucinogens are schizophrenia-mimicking drugs in that they induce a psychosis in which the subject is left with a clear mind which retains insight to the degree that it is frequently able to understand the transient nature of the experiment and realize that its condition is drug induced. (78) (26) No loss of intelligence usually occurs. (63) The term 'hallucinogen' was coined because most of the drugs bearing that label produce hallucinations of a visual auditory or somatic nature. The term 'model psychosis' is the term used to designate a drug induced psychosis.

Although the model psychoses approximate schizophrenia it is felt that a systematic comparison is invalid since no general acceptable systematic description of schizophrenia has been made.(3) A difference frequently perceived is the synesthesia which is found in the artificially induced patients but not seen in the clinical psychotic. (26) In model psychoses visual hallucinations are commonest and auditory rarest, as contrasted to the reverse which is true in the schizophrenic. (80)

The hallucinogens act in minute quantities leading to belief that they exert some effect on an enzyme system probably in brain metabolism, although this is by no means definitely proven. (79)

(3) Agnew 1955
(26) Callaway 1955
(63) Green 1955
(78) Hoch 1952
(79 Hoch 1955
(80) Hoch 1952

All, with minor exceptions, have either an indole nucleous, or an open chain indole-like structure. (42)



Indole ring.

Hashish is the exception since it has a dibenzopyran structure rather that the indole structure; in fact some would not agree that hashish is a true hallucinogen. (78)

Hallucinogens of vegetable origin, plant alkaloids, include cohaba, amanita pantherina, hashish (marihuana), mescaline, d-lysergic acid diethlyamide (hereafter referred to as LSD), yohimbine, ibogaine, and oliliqui. (84)

Hallucinogens of primarily synthetic origin are amphetamine, methedrine, bufocapnine, and TMP (43).

Hallucinogens of animal origin are tryptamine, bufotenine, adrenochrome and porphobilinogen, and perhaps serotonin (5-hydroxytryptamine, hereafter called 5 HT). (42)

Other drugs may produce psychosis but are not considered hallucinogens since they may affect the sensorium in an "organic way", causing altered consciousness, impaired memory, confusion and unreliability in reporting. Included in this group might be alcohol, DFP (di-iso-propyl flurophosphate), ACTH, pervitin, sodium amytal, cocaine, scopolamine, probably hashish, and others. (78)

The aim in producing a model psychosis has been to create a psychotic disorder in which biochemical, neurophysiological and psycho-dynamic states could be studied

(42) Fabing 1955
(84) Hoffer 1954
(78) Hoch 1952
(43 Fabing 1955

concurrently; thus enabling further investigation of psychotics in general and schizophrenia in particular. The effect of these drugs have been observed on normal humans, the mentally ill including the schizophrenics and in a variety of animals. The drugs have been biologically and biochemically studied although perhaps not too systematically. Hallucinogens have also been used in therapeutic processes with some success. (79)

The results of this experimentation have provided clues in the continuing search for an etiological explanation of mental illness. They have opened definite vistas toward a biochemical explantaion of schizophrenia. Upon the basis of their structure and action various hypotheses have been proposed and studied experimentally, e.g., Hoffer 1954 (84) suggested that a substance in the body having an indole structure like the hallucinogens and which behaved as the hallucinogens might be the etiologic agent of schizophrenia. As a matter of fact work still progresses along this particular line.

The use of hallucinogens and other psychotic producing drugs is found extending for centuries into the past. They were taken as part of religious and ceremonial rights, for sexual prowess and stimulation, for their euphoric effects, by native tribes and peoples of all nationalities and races, both civilized and uncivilized through out the world. Hashish intoxication was described by the Chinese in the 15th century A. D. (2) In 1845 Moreau

(2) Adams 1941 (79) Hoch 1955

de Tours, the father of hallucinogenic experimentation, suggested that hashish be studied by giving it to normal people so that observation of the ensuing mental illness might be done. (93)(94) He was one of the first to intentionally induce himself in order to analyze at first hand the effects of hallucinoggens in the system. DeQuincy in his "Confessions of an Opium Eater" and Davy with his observations on laughing gas are recorded self analyses while under the influence of psychotic producing drugs.

Kraeplin in about 1883 (93) was the first to systematically study drugs for their psychotic-inducing properties. He studied alcohol, coffee, morphine and tea and found them to be unpsychogenic in nature. In his experiments with mescaline, hashish, ether, nitrous oxide, and cocaine he found that the CNS was excited and psychotic like symptoms were produced which he felt were worthy of further study.

Many attempts to produce experimental psychotic symptoms in hope to discover psycho-physicological relationships have been made. Schneideberg produced cataleptic phenomena in rabbits in 1886 by ethyl-urethan. In 1904 Peters (128) discovered the catalyptic action of bulbocapnine. Baruk 1938 (12) and DeJong 1932, 1930 (29) (30) investigated this and other chemicals and demonstrated their catatonic effect on man.

Since then cocaine, scopolamine, hashish, adrenochrome, etc., have been studied in trying to simulate the

(93) Kraeplin 1883 (94) Kraeplin 1925

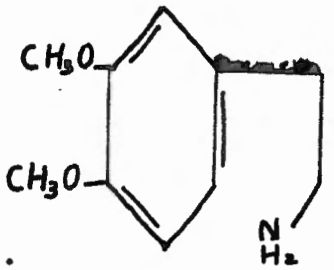
the psychologic changes seen in the mentally ill. All show 1) mood alterations, 2) various perceptual changes, 3) defects of concentrative attention, and of logical process. (14) (69) (87) (112)

Hashish within the last twenty to thirty years has been fully explored and within the last decade lysergic acid diethylamide and adrenochrome have been more and more frequently used as experimental tools.

Mescaline

A. Description.

It is a plant alkaloid having a potential indole nucleus and is the seed of the mescal or peyotl cactus which is of Aztec origin. (84) Mescaline, a phenylalkylamine, may act on the central nervous and sympathetic nervous system. (99) It is thought to be a stimulant physiologically because it is one pharmacologically. Exact sites and modes of action are unknown (63) altho some think the hallucinations are caused by the methoxyl group and the animo acid in the side chain. (142)



Mescaline.

B. History.

Prentiss and Morgan performed the first self induced experiment with mescaline in 1894 and they reported

(84) Hoffer 1954
(63) Green 1955
(142) Salomon 1949
(87) Huxley 1954
(99) Lewis 1954
(14) Beston 1954
(69) Henning 1938
(112) McAuley 1954

colorful visual hallucinations. Mitchell (115) published in 1896 the first classic account of peyotl intoxication. DeJong (28) (30) was the first to use mescaline experimentally to any extent in animals although Kraeplin (94) had studied mescaline around the turn of the century. It is only in recent years that a thorough investigation has been carried out however.

C. Uses.

1) Experimental Psychiatry.

Hoch 1951 (77) reported that mescaline in doses of .4 to .6 grams enhanced schizophrenic symptoms in schizophrenics and caused perceptual psychoses in people suffering from latent schizophrenia. He found 5 to 6 milligrams per kilogram the best dose. No addiction was observed with mescaline.

Mayer-Gross 1951 (110) found similar objective and subjective symptoms in mescaline-induced psychoses and schizophrenia. He thought mescaline might inhibit oxidation in the same manner as narcotics do.

Guttman 1935 (64) found that mescaline improved depersonaliation symptoms to the degree that a change in surroundings (derealization) was elicited, but not of self. He felt that for this reason mescaline could not be used as a model for therapeutic experiments, but might be used as an adjuvant for psycho-therapeutic activity.

(115) Mitchell 1896 (94) Kraeplin 1925
(28) DeJong 1930 (30) DeJong 1930

Hoch 1955 (79) demonstrated that mescaline produced anxiety with an alteration of perception of body sensations and changes of body images which then lead to lowering of the reality control which in turn leads to depression, aggression and paranoid manisfestations. He questioned whether this was due to a physiological action or was the result of a psychological change. He stated mescaline has caused greater disorganization in schizophrenics that in normals; but that there is a difference of degree in response between acute and chronic schizophrenics, for in the former there exists a greater intensity of reaction. Ibid 1951 (77)

Stocking, among many, 1940 (157) felt that if a toxic chemical agent was present in the body it would be an amine with similar chemical and pharmacological properties to mescaline.

a) animals.

DeJong 1945 (31) in poorly controlled experiments with mescaline produced catatonia in small mammals but also discovered that large enough doses of many substances would produce the same result. He was aware of the structural relationship between mescaline and adrenalin but he did not consider this significant nor related to Cannon's stress conception.

Schwartz 1956 (151) found that the injection of mescaline into the cat's ventricle caused violent scratching immediately, and later caused EEG changes which

occurred asymetrical in the brain and spread out. He discovered no antagonism between mescal and 5HT within the ventricles.

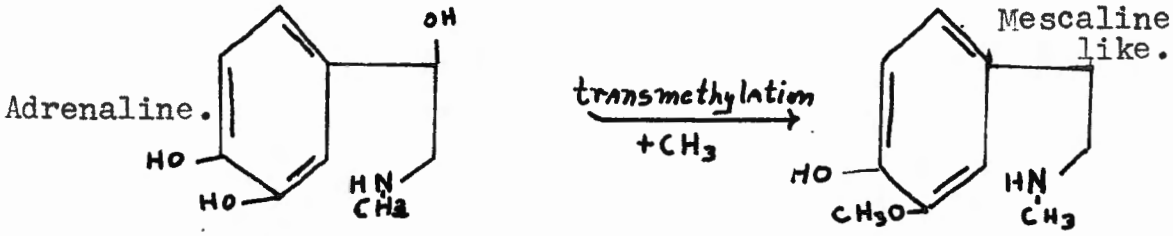
Block 1953, 1954 (21) (20) from his work with radioactive mescaline in mice concluded that mescaline, which was found in the liver and kidney in the greatest concentrations and in secondary amounts in the brain and spinal cord, disappeared from the CNS before psychic symptoms appeared thus establishing the fact that hallucinations are not due to mescaline but to substances formed in its reactions. He assummed mescaline entered into a protein bound combination in the liver.

Lewis 1954 (99) demonstrated that certain cerebral mammalian tissues were not sensitive to mescaline unless they were first stimulated by electric impulse, but then respiration and glycolysis were inhibited by mescaline.

b) man.

Osmond 1952(122) stated that mescaline had long been known for its hallucinogenic qualities and that it produces all major symptoms of acute schizophrenia in the normal man, although in variable degree. These symptoms he listed as sensory disorders (illusions and hallucinations), motor disorder, behavioral disorder, thought disorders, disorders of interpretation, delusions, depersonalizations, mood disorders, splitting, and insight. He also perchance discovered that mescaline and adrenaline have similar structures and hypothesized that if by mistake

methylation of the phenol hydroxy groups occurred a substance "M" similar to mescaline would result which perhaps was the agent for mental illness. He thought this was an error of reaction due to a defect within the adrenals. Mescaline itself was not considered toxic enough to produce the disease. Mott years ago had noticed a peculiarity in the adrenal medulla of schizophrenics but has never pursued the observation further.



Osmond felt that such a hypothesis would account for abnormal adrenecortical activity, vascular change, disturbance of carbohydrate metabolism, overloading of the detoxicating mechanism of liver and pigmentation found in schizophrenics. Mescaline itself he discovered interfered with glucose metabolism of the brain.

Mayer-Gross 1951 (110) reported that mescaline in normal man changed his perceptual color of objects and caused an increase in after image, euphoria, superiority, and joviality. He found his subjects were indifferent to the testers and that they thought in terms of visual images. Many used "witty" remarks which actually were not. Day dreaming was frequent. They did not loose identity although a passive attitude was fully relished.

The main symptoms were 1) predominance of visual

experiences, 2) perceptual distortion of object movement, 3) disorders of time toward the slow side, 4) synaesthesias, 5) variable states of consciousness-euphoria.

Mayer-Gross felt the outward behavior appeared relatively normal although passivity and restfulness present. He catagorized symptoms of mescaline intoxication as belonging to exogenous reactions of which dilerium is a typical form. The differences in effects of the various hallucinogens was felt to be due, in part, to personality traits of the subject but also thought that each drug has its special feature, that of mescaline being its ability to cause derealization and depersonalization, and visual and tactile illusions in a clear sensorium, thus mimicking schizophrenia. Missionaries in foreign lands have had frequent trouble with chronic mescaline intoxication among the natives which leads to lazyness and loss of will power.

Denber 1955 (33) discovered thatintravenous mescaline in epileptics caused EEG changes: a variable effect on alpha wave, decrease of delta wave, and caused disappearance of spike waves. Lethargy, drowsiness and somnolence were the main clinical symptoms produced in epileptics. He theorized that the site of action was the diencephalon.

Hoch 1952 (80) in his experiments on schizophrenic patients found that mexcaline caused more intensive changes than LSD. Physiological and mental content

symtoms were intensely aggravated, in additon to disturbances of perceptual acuity, and emotional alterations. Anxiety was the most frequently found change, followed by hostility, evasiveness, and paranoia. The results were like a condensed psychoanalysis. Sexual material was frequent which he thought quite odd since normals do not verbalize much sexual material under influence of mescaline. Another difference found was that mescaline caused euphoria in normal but not in schizophrenics. The reactions of schizophrenics are more intense, anxiety and disorganization worse. The normals retained more reality control. The drug reenforced schizophrenia but did not cause it in the normal human.

Another oddity noted was that geometrical hallucinationatory forms, while uncommon in both normals and schizophrenics, were found in both normals and schizophrenics.

Denber 1955 (32) was not able in his studies on schizophrenics to duplicate the findings of varied colored hallucinations and paranoia found by the experimenters above. He gave .5 gram mescaline intravenously to schizophrenic patients and found a predominance of emotional over ideational activity, No relationships between clincal phenomena and EEG existed, Psychoses were reactivated in those heretofore improved by ECT, which lead Denber to beleive that ECT gives only quantitative change, but does not effect basic structures. He felt that the acute

anxiety generated by mescaline represented the primary reaction of the organism to imagined danger. He postulated that primary emotional reactions might originate in infracortical areas. Hoch 1951 (77) suggested that perhaps only those with schizoid tendencies will develope schizophrenic-like symptoms with mescaline.

Again in 1955 (34) Denber emphasized that mescaline and LSD not only reactivated psychotic symptons in patients following ECT but also following psychosurgery. He noted that the autonomic nervous system dysfunction is the anlage of the mental charges with LSD and mescaline intoxications. Since hallucinogens of different chemical structure can produce similar disturbances of mood and thought he felt that the clinical picture does not result from peripheral but from central metabolic interference; and that the adrenal cortex may play a part primarily or secondarily was hypothesized. However, if it does, why does mescaline in epileptics cause the opposite symptoms of those found in schizophrenia. It was also noted that adrenalectomies do not improve schizophrenia, so there exists a big question as to whether adrenalin cycle actually involved. He felt that the metabolic disorders that exist, exist in the cellular level in the CNS and not in the glands. In fact we may be even further from the truth than is realized, and are going through a new etiological hypothesizing era. The importance of psycho-

logical environment influences in not questioned, so perhaps no single factor is thought to be responsible.

Mescaline surpresses the high voltage and slow wave activity for about four hours in the post convulsive shock schizophrenic, Merlis 1955 (113) demonstrated. Since this activity arises in the diencephalon he contended that it was there mescaline has at least one site of action.

Mayer-Gross 1953 (111) while he demonstrated psychological change in normal humans with mescaline, he obtained no hexosemonophosphate increase or any change in blood chemistry, yet after giving LSD to schizophrenics he noticed an increase of blood hexosemonophophate associated with minimal psychological effects. However, Jantz 1941 (90) had shown that mescaline caused capillary damage, which caused a loss of protein from the blood, and an increase in nitrogen retention. These findings were not supported.

c) anatagonists.

Frenquel (a gamma isomer of Meratran) given premedically blocks the psychic effect of a mescaline-induced psychosis, as well as alleviates the same manifestations in the full blown artificial psychosis. All ataraxics including reserpine and chlorpromazine have this ability, although the action is not understood. Fabing 1955 (43) (44)

Hoch 1955, 1952 (79) (81) in reviewing the therapeutic research done on mescaline and LSD induced-psychoses related that hypnosis and ECT have had no effect; sodium succinate and glutamic cause some improvement; and that sodium amytal and pervitin are best in neutralizing the effects of the less deteriorated schizophrenics. In returning from an induced psychotic state it is shown that the subject first has increased contact with his environment; then distortions of space and time and visual hallucinations disappear, then tension fades, followed by content abnormalities. This process similates patients who have undergone psychosurgery. Pennes 1954 (126) studied sodium amytal, pervitin, and LSD, and mescaline in schizophrenics and found amytal to be a normalizer agent, while mescaline and LSD intensified the pre-existing symptoms, and pervitin produced an unstable state with normalization first, followed by intensification of response. He felt that the total effects of the drugs depended on secondary or indirect factors in addition to the drug specificity. The secondary response resulted fromthe interaction between the pre-existent status of the individual, the drug, and the particular environment. This upheld the theory that diverse chemicals may produce same effects and that same stimuli may be dealt with by diverse actions. These reactions are at the most complex levels of personality.

Also it has been shown that amytal and pervitin while delaying onset of induced psychoses do not prevent them.

Thorazine in the first injection temporarily improved LSD and mescaline psychoses although this was frequently followed by a relapse which was then permanently reversed by a second injection. With thorazine the anxiety and tension was relieved first, followed by the disappearance of the mental manifestations. Nausea and vomiting were also relieved by thorazine (chlorpromazine). Thorazine has some preventative effects on the induced psychoses, It prevents the autonomic nervous system changes in the LSD psychosis, but no effect on the autonomic changes produced by mescaline, altho it prevents the psychiatric changes of mescaline.

It is felt that thorazine improves the EEG findings of induced psychotics; its action may be to depress the reticular facilitatory region of the brain stem up to and including the diencephalon and most of the mesencephalon represented by the nuclei of the thalamus (thalamic reticular system). There are always two actions to every drug: 1) its specific effect on everyone, 2) those effects it causes in a given patient irregardless of the nature of the drug.

In 1948 Schueler (148) from experiments on rats showed that whereas mescaline had no inhibitory action

on succinate in brain tissue it did cause definite inhibition of lactate, pyruvate and glucose. Sodium succinate decreased the complexity and intensity of visions in humans induced with mescaline and caused more normal conversations. Faster action was observed in vivo studies than in vitro work. The actual action of mescaline remained unexplained.

In his work reported in 1955 Schwarz (150) demonstrated that 25 milligrams of thorazine reverted mescaline and LSD induced psychoses. He demonstrated a different mode of action than with amytal since the EEG is normal with thorazine but with amytal a barbiturate type of EEG results following reversal of the psychoses. There is no direct antagonism between thorazine and the hallucinogens but no definite action of thorazine is known. He hypothesized that it has a neurohumoral action. It may block hypothalamic stimuli. Perhaps mescaline has a cholinergic effect and thorazine an anticholinergic effect; or perhaps LSD and mescaline may cause an adrenergic inhibitory action on the central synapses, and thorazine may have an adrenolytic action.

Since LSD and mescaline reactions are enhanced by stress, maybe this action is produced through increased adrenalin production or by abnormal epinephrine metabolism leading to production of metabolites such as adrenochrome or adrenolutin. There is a wide variation in adrenalin metabolism and this could explain the wide

variations in hallucinogenic effects.

2) Differential diagnosis.

Hoch 1955 (79) states that LSD and mescaline have not shown themselves to be useful in differential diagnosis of mental disorders.

3) Therapeutics.

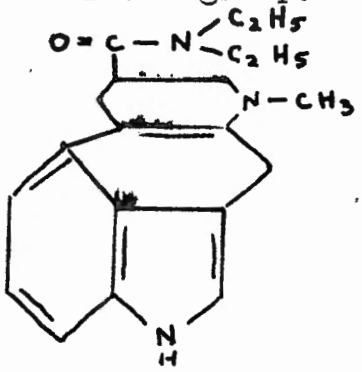
A therapeutic use for mescaline and LSD has been found in psychotherapy by Frederking 1955 (48). He gives mescaline.3 to .5 grams intramuscularly, or LSD 25 to 60 micrograms orally. With these drugs he produces in his paitents dream-like results which contain visual hallucinations and changes in physical perceptions. These have a relationship to the patients psychological background. The dream-like hallucinations reveal: 1) childhood memories, and 2) life situations with psychopathology intertwined. He always gets psycho-catharsis with these drugs. This then enables him to shorten his therapeutic time, break down blocks, and reactivate treatment. Mescaline causes more intense emotional responses, while LSD causes a broader spectrum of recall.

Hoch 1952 (81) agrees that the content of hallucinatory experiences induced by mescaline existed in the previous life of the subject in dreams and free associations. In schizophrenics relieved by lobotomy mescaline caused return of the same symptoms which existed prior to the surgery.

d-lysergic acid diethylamide.

A. Description.

It is an indole, and a synthetic amide of organic d-lysergic acid. Lysergic acid is the base of all lysergic acid alkaloids and it is found in rye rust, Hoffer 1954 (84), and in other infected grain. Natural ergot alkaloids contain d-lysergic acid and are divided into two groups: 1) ergotamine-ergotoxine group, and 2) ergonovine group. In the first group d-lysergic acid is combined with a peptide and in the second are found the monacidamides of d-lysergic acid. Ergonovine (d-lysergic acid iso-proplyanolamide) is the only member of group two, while d-lysergic acid diethlyamide is one of the members of the first group. Forrer 1951 (47)



LSD.

B. History.

Study of the hallucinatory effects of LSD-25 (hereafter LSD) began in 1943 following the accidental discovery by a Swiss chemist named Hoffman who after working all day in the laboratory on a salt of d-lysergic acid, experienced peculiar restlessness and dizziness. He went to bed in a pleasant state of inebriation characterized by an extremely stimulating fantasy associated

with an intense kaleidoscopic play of color which lasted two hours. The next day he took 250 micro grams of the new salt and again experienced more intoxication with the same symptoms. Deshon 1952 (35), Stoll 1947 (158), ibid 1949 (159)

Actually it had been synthesized first in 1938 but its latent qualities were not known at that time. Forrer 1951 (47) The discovery of Hoffman's was later substantiated by Stoll (158) (159). In this country Rinkel and his group were the first to experiment with this drug. Rinkel 1951 (136)

In the middle ages it was this active principle of ergot infected bread that caused thousands of people to go crazy.

C. Uses.

1- Experimental psychiatry.

The drug has been studied in normal and psychotic humans and in animals. It produces effects similar to mescaline psychotic symptoms such as an alteration in perception, bodily sensations, changes in body image and in time sense, which lead to impaired integration and to fragmentive mental processes. Agnew 1955 (3) feels that the depersonalization and derealization are similarities between schizophreniz and LSD psychoses; however short spans of concentration and the visual disturbances of LSD psychoses are not found in schizophrenia.

The value of LSD as well as other hallucinogens

is that the subjects of their intoxications can describe the sensations felt under the drug without loosing clear conscious state and can maintain contact to a certain extent with the examiner. Hoch 1955 (79)

It can produce its effect in doses of 10 to 60 micrograms although some experimenters use up to 6 micrograms per kilogram. Forrer (47) The lethal dose in laboratory animals is 285 micrograms per kilogram, so for that reason it is considered a very safe and non-toxic drug for experimental work. Its use in minute amounts suggest a highly selective action in the CNS. How the mental changes are caused are not clear. A difficult aspect of the problem lies in the fact that all important phenomena are subjective in nature and not varifiable by an observer.

In the search, a relationship to chemicals in the adrenalin cycle has been noted. The similarity of LSD with 5HT, which is itself a metabolic oxidation product of tryptamine, is recognized. It has been considered possible that the antagonism of similar structured chemicals might underlie the psychosis. Whats New felt that the greatest value of these drugs was the interest they have directed toward a biochemical and physiological basis for mental illness. What New 1955 (174)

a) animals.

LSD produced EEG and behavioral alerting in cats that was related to the sympathetic nervous system and

depended upon the ascending reticular system. LSD has been found to be like amphetamine in that it causes low amplitude and diffuse fast EEG waves in the cat, but did not cause response to photic stimulation as seen with amphetamine. The abolishment of the anesthetic EET changes was demonstrated by LSD, although LSD had no effect on anesthesia itself. Amphetamine and LSD are dependent on mesencephalic or spinal connections and they have shown better correlation between behavior and EEg changes than many other drugs tested.

Schwarz 1956 (151) in his study on cat intraventricular injections showed that LSD produced restless states, retching and later drowsiness associated with eome EE^{G} changes, occasional slow EEG waves. He was able to demonstrate no CNS, behavioral or EEG antagonism between 5HT and LSD in the ventricles although he noted that effects of drugs seem to vary with the route given.

In 1951 Witt (165) administered LSD to spiders and discovered that such drugged spiders made more precise although a thinner type webb than the controls, and felt that this demonstrated an effect on the spiders adrenalin supply, since adrenalin is the chief component of spider webbs. This was considered evidence that psychotic like phenomena might be related to adrenalin. A spider given mescaline was not nearly as precise a webb maker, and showed different points of attack in spiders by LSD and

mescaline, although such a difference is hard to distinguish in humans because of the similarity of effects and because of the diffusemess of human reaction.

Evans 1955 (41) demonstrated altered visual reactions in monkeys without loss of muscle power when he gave them a dose of 1 microgram per kilogram. Intra-carotid injection of LSD into the cat produced a block or reduced the post synaptic spike in the lateral geniculate nucleus but did not increase cortical response to optic radiation stimulation. LSD in relatively larger quantities decreased optic tract response to photic stimulation of retina. The thalamic relay station is shown to be sensitive but the cortical response was resistant. Retinal activity was shown to be relatively resistant to depression by LSD. LSD produced no definite blood pressure of respiratory changes.

In his electrophysiological analysis of the psychotogenic effects of LSD on the cat's brain Pupura 1956 (133) showed that the hallucinatory event is associated with an alteration in the recovery cycle of excitability in the primary afferent system. The facilitatory action of LSD on specific projection systems is associated with another mechanism occurring at different synapses.

The differential sensitivity to depression of the auditory projection system at high concentrations of LSD which produced continued facilitation of visual primary responses can not be adequately interpreted. We felt

there may be an existence of discrete biochemical differences in the synaptic mechanism censtituting the two pathways. He felt that the antagonism of LSD by reserpine on the auditory primary response could not be accepted as evidence supporting a competitive action on a specific enzyme system somewhere in the biochemical generator. Since several differently structured chemicals antagonize LSD, then LSD may have multiple biochemical locations for action.

Purpura thought that the disorganization of man under LSD could be explained by the hypothesis that highly integrated processes involving neuronal interrelations is carried on at the axodendritic level. Associated with the inhibition of axodendritic activity is a facilitatory action on specific projection pathways mediating incoming sensory signals.

LSD inhibited the axodendrite system and facilitated the axosomatic synapse of the pyramidal neurons in the optic cortex. Axodendrite synapses are activated by non-apecific thalmocortical system activation. Activation of transcallosal and other corticortical associated pathways involve only dendrites. The duration of dendritic response is longer than axon or cellular response. LSD facilitates axomsomatic activity on specific projection pathways mediating incoming sensory signals when it inhibits axodendrites.

The demonstration of dual action of LSD on different

synaptic patches located on functionally different components of the neuron confirm the existence of dissimilar properties of the bioelectrical generator of neuron potentials.

Dendrites of pyramidal cells remain electrically excitable when they are no longer neurally excitable after LSD.

If the action of LSD on the central neurons is dependent on differences in biochemical properties of post synaptic patches (receptors) located on dendrites or dell bodies, he concluded that there would be no single biochemical mechanism of action of LSD. This should explain why various structural drugs antagonize LSD and also would explain the numerous biochemical alterations of LSD. The dual action of excitability and inhibition of LSD could explain the disorganization and hallucinations from LSD.

Page 1954 (123)stated that LSD has a nor-adrenalin blocking action, causes motor excitation in anesthetized animals and in high doses causes motor rigidity like catatonic states. It inhibits spontaneous rhythmic activity in the EEG but does not prevent response to electric stimulation. It causes slight increase in blood pressure and in the pulse, lacrimation and salivation, dilatation of the pupils, and an increase in the deep reflexes. The mental state is likened to that of the manic depressive or hebephrenic with optical hallucinations.

Its symptoms are those of non-specific exogenous intoxication combined with peculiarities of schizophrenia. He felt it was due to the tryptamine structure in LSD, that LSD was a competitive antagonist to 5HT in his experiments. LSD inhibits 5HT in rats uterus and in the vasoconstriction in the ear. He maintains that 5 HT has some function in brain metabolism so wonders if LSD's mental effect is caused by antagonism to 5 HT. Slater 1955 (155) supports him in this contention.

b) man.

LSD intoxication showed depersonalization, heightened awareness, and fluctuating incongruous effects. Rhythmic photic stimulation enhanced the symptoms. Other signs were distortion of the body, dysarthria, trance-like states, etc. It lead also to unmotivated laughter, crying, bizarre behavior and activation of hallucinatory and delusional material. Elkes 1954 (37)

Sloan 1954 (156) agreed that LSD gave a clinical picture of a hebephrenic while mescaline caused a more paranoid or catatonic like type of schizophrenia. He listed among his findings in people, medicated with 40 to 130 micrograms orally, visual hallucinations, affective blunting, characteristic schizophrenic psychological patterns, increased alpha activity, accentuation of pre-existing affect, lability of mood, retention insight, and no effect on memory of concentration, no perceptual changes and change in the Rorschack. Physiologically noticed leucocytosis, slight increase in pulse and blood pressure,

dilatation of the pupils, slight increase in blood sugar-glucose and hexosemonophosphate, no liver effects, increased respiration, and no abnormal response of blood pressure to painful stress. He found significant changes in the spectroscopic oximetry studies but he questioned the validity. With more discriminative tests he felt that sensitive physiologic recordings would facilitate study of experimental intoxications, and mental disease. He suggested analysis of respiratory function, oximetry, and oscillometry studies.

Rinkel 1955 (138) in his studies with normals on a dose of $\frac{1}{2}$ to 1 microgram per kilogram found among the mood changes the he frequently elicted were effective changes similar to those seen in schizophrenia with or without catatonic features, disturbance of thought processes and perception, misinterpretations, hallucinations, delusions, and depersonalization.

Behavioral changes resulted in subjects having increasing movements "away," "against", and "toward", accompanied by decreased movements "with". He observed a decreasing ability for appropriate social behavior--a greater rigidity of action. An increase in intensity of symptoms were found with stress, but a decrease in supportive situation. He also demonstrated that ectomorphs are intrapunitive and mesoendomorphs are extrapunitive in nature.

Psychological testing revealed significant changes in major personality areas such as in perception, cognition, and emotion. It was of interest to note that each subject maintained his own idiomatic style in functioning even under the strongest intoxication.

A generalized reduction in organization and integration was observed; most frequent in conventional environmental features and experiences. There was an increase of concentration on minute aspects.

Perceptual distortion was prevalent. The loss of emotional control with an increase of self centeredness occurred. Orientation was to the here and now rather than to the past or future. There was a variable anxiety and tension response. However basic personality patterns were maintained.

Autonomic phenomena preceded mental phenomena. Subjective feelings of tremblin, numbness, and hunger and nausea were common.

The pulse increased and the pupils dilated through sympathetic stimulation. In LSD subjects there appeared a decrease in response to adrenaline, but normal responses to nor-adrenalin. Mecholyl did not show much response.

Rinkel wondered if LSD stimulated the pituitary adrenalin axis, although he thought that it just might be a nonspecific stressor. LSD decreases urinary phosphate excretion, while ACTH stimulation of LSD induced patients resulted in increased excretion of urinary phosphates.

This is the same as is found in schizophrenia. It was wondered whether LSD's effect on the adrenals was specific or whether any non-specific stressor could leave the adrenals unresponsive to ACTH.

He felt that LSD and mescaline were definitely not specific in the etiology of psychoses. It was assummed that the causative agent might interfere with the enzyme system or originate a metabolite causing psychosis. Although glucose is the chief substrate of brain tissue and is necessary for normal energy function he was unable to decrease LSD changes by increasing the glucose level.

It was thought that involvement of the adrenalin cycle and the pituitary-adrenocortical adaptation system was likely since the adrenergic autonomic system symptoms preceded mental symptoms. It was also noted that the adrenalin-phenylalanine cycle is related to several clinical diseases which occur as a result of inborn errors of phenylalanine - tyrosine metabolism, among them being albinism, alcaptonuria, and tyrosinosis. Rinkel 1955 (139)

It was concluded that experimental psychiatry, the study of artificial psychoses, is necessary for the advancement of knowledge in psychiatry. LSD is an excellent psychiatric tool for this. He strongly emphasized that clinical psychological, physiological, and biochemical evidence indicated that the adrenalin system is involved in LSD produced emotional psychotic phenomena, and there-

fore theorizes that enzymatic-adrenalin relationships are basic for psychoses.

Condrau 1949 (27) gave 20 to 30 micro grams to normal and psychotic people and although he caused inebriety in all of them he found a higher resistance and better tolerance in the mentally ill. The latter showed less alteration of perception, conscience and personality. Autonomic nervous system symptoms were foremost.

The hostility in LSD induced normals was studied by Hyde 1953 (88) and he revealed that the strongly affective relationships of affiliative or hostile nature were distorted to a greater proportion than impersonal relationships. There appeared disturbances in interplay where the latter was demanding or threatening. Visual hallucinations were seen to provide more "reality" to subjects that were their own thought and feelings. This mechanisms was not projective. The subjects had more keen and more acute realization of interpersonal relationships under LSD, and were more aware of the experimenters attitudes toward them than would have normally been possible.

In his studies with LSD, Forrer 1951 (47), in normals found euphoria, depression, pupillary change, alterations of tendon reflexes and visual hallucinations.

Mayer-Gross 1951 (108) found that vegetative and variable emotional symptoms came first in LSD induced patients followed by the specific illness, hallucinations, and perceptual problems. He feels that a change in the

carbohydrate cycle is responsible for part of the psychological symptoms since an increased metabolism of the glycogen cycle is coupled with a block in catabolism of hexomonophosphate. LSD may have an anti-enzymatic action due to the fact only small amounts are necessary to produce gross results.

Savage 1952 (145) found that 20 micrograms orally produced depersonalization, derealization and hallucinations in normals. Anxiety and euphoria were the prominant reactions. Larger doses were required to get the same effect in psychotics. Insulin requirements were lowered in some diabetes on LSD.

In 1955 Savage (145) stated that LSD caused severe ego disturbances, in which one initially got an increase in ego feeling, which was then followed by a lowering of ego feeling, which in turn was followed by a withdrawal of the ego feeling from the ego boundries with symptoms of estrangement and depersonlization with ultimate regression to previous ego states which were accompanied by the appearance of hallucinations, delusions and projections of bodily processes. LSD apparently acts by altering the perception, and, since continous correct perception is necessary to maintain ego feeling and boundries, this leads to a decrease of ego feeling and then disintegration of senses and to an incoordination of activities.

Psychic energy is called ego libido. Ego libido

is recognized as ego feeling. Thus Savage feels that LSD interferes with the amount of libidinal energy available to the individual. Depersonalization follows when libidinal energy is decreased. In LSD intoxication the subject does not loose interest in the environment but his difficulty is in the fact that he does not have enough energy to maintain object interest. But as to how LSD actually diminishes ego energy is unknown. Savage felt that LSD induced psychoses were good for close study of psychological phenomena, processes and communications. It also presents a good method for study of psychiatric theory.

Gestaut 1953 (58) demonstrated an increased excitability in visual primary system under LSD intoxication in normal man. He felt that the increased alpha rate, and other EEG changes were due to the expression of neuronic hypersensitivity, which caused a decrease in the filtering of impulses from the CNS to the chest.

Hoagland 1955 (76) also showed that LSD decreased excretion of urinary inorganic phosphate. Stress or corticoids caused an increased excretion of inorganic phosphate in LSD induced psychoses. He felt that LSD acts on the enzyme systems to facilitate binding of the phosphate. Adrenocorticoids may release phosphate from the bound form. They consider that endogenous derivatives of adrenaline metabolism may act in schizo-

phrenic patients like LSD does in normals. This hypothetical antimetabloite acts in part via exchanges of the phosphate bond energy. It was wondered how LSD makes the adrenal refractory to ACTH, although it was thought the action may be specific because of LSD's action on phosphates in the urine.

Normal adrenocorticoids release phosphate bound as excess hexosemonophosphate in LSD patients. This is due perhaps to the fact that the equilibrium of several phosphorylating enzyme systems areunder the influence of adrenocortical hormones but they yet are unable to understand the relationships of specific compounds in this equilibrium. It was felt that perhaps adrenoxine may be the chemical agent in schizophrenia. (see Adrenochrome)

Isbell 1955 (89) showed that a tolerance to LSD developes in three to seven days and that once it was developed doses four times as great were not as effective in inducing mental effects. However tolerance is lost within three days after discontinuation. Because of this tolerance LSD is not likely to be the substance causing chronic mental illness.

Liddell 1953 (100) determined the effect of LSD on the plasma adrenalin level and discovered three phases: 1) initial rise of adrenalin, 2) a drop below the startingllevel, and 3) a secondary rise. The second phase

was associated with relaxation and euphoria and the rising phase was associated with tension and anxiety, accompanied by shivering and an increased incidence of schizophrenic symptoms. Rapid mood swings were noted with LSD, Graham 1954 (61) disagreed somewhat by showing that an antagonism between LSD and adrenalin existed both in the inhibitory and stimulating properties.

Mayer-Gross 1952 (109) discussed the influence of LSD on carbohydrate metabolism. He noticed that LSD particularly blocked CHO metabolism at the hexosemonophosphate leve. A slight antagonism was shown toward LSD by an increase in the glucose level. No correlation was shown between LSD behavioral changes and changes in blood chemistry.

Forrer 1951 (47) reported that LSD in schizophrenics caused a slight increase in blood pressure, a slight increase in pulse and no change in respiration, an increase in salivation and lacrimation, dilation of the pupils, an increase in deep reflexes, slight ataxia, leucocytosis, sporadic euphoria, increased accessibility of delusional material and visual hallucination. There were no changes observed in the urine, NPN, EEG, cephalin-flocculation, weight or temperature.

Barbiturates were shown to antagonize the effect of LSD. It was thought that LSD acted on the cortex and produced depression and perhaps released lower

centers from cortical control. So depression of subcorticalcenters then blocks subcortical release which nullifies effects of LSD. The neurological signs of LSD are due to cortical depression. Psychiatric signs are due to fact subcortical activity is uninhibited.

Mayer-Gross 1953 (111) stated that LSD in the schizophrenic caused an accumulation of blood hexosemonophosphate but resulted in minimal psychological effects, perhaps by the sparing action on its metabolism.

Abramson 1955 (1) reported that LSD has its effect on the physiological and perceptual phenomena as follows in order of decreasing frequency; unsteadiness, dream like states, paraesthesias, inner trembling, pressure on ears, difficulty focusing vision, weakness, lightness of limbs, lips drawn up in smiling, dizziness, drowsiness, sensitivity of skin, and a pecular feeling in the limbs.

Callaway 1955 (26) supported various observation of sympathetic nervous system involvement by the hallucinogens. He also got an increase of adrenalin with LSD and found that LSD alerted brain with sympathetic discharges after stimulation by noxious agents, and that emotional changes potentiated LSD effects. LSD may interfere with the adrenalin synthesis. He also noted that Funkenstein related nor-adrenalin and adrenalin effects to extra- and intra-punitive anger and that Witt with his work on

spiders and Hoffer and Osmond with work on adrenoxine all implicated the adrenals in LSD action.

He explained that hallucinations can be induced by psychological methods as well as by drugs. One way is by hypnotic suggestion, and the other way is by decreasing variations in the subjects environment, and since validity of thought must constantly be checked against outside world, a reduction of this whereby thoughts are developed on own without outside influence can lead to psychotic results. The mind that is freed from the mundane demands of reality becomes unrealistic, sick and unreliable. Since Helen Keller is so effective as a person, there must be more that just absence of stimulation.

c) antagonists.

5HT not only did not decrease the effect but intended to increase the inhibitory effect of LSD on respiration and glycolysis of the guinea pig's cerebral cortex in a glucose-saline media. Ergotoxine which is a mixture of lysergic acid derivatives, and hydroergotamine, a derivative of LSD, showed no effect on the guinea pig until the tissue was stimulated electrically, then the chemical became effective and inhibited respiration and glycolysis in the tissue. The effect of dihydroergotamine was not prevented by the simultaneous presence in the tissue of adrenalin. Lewis 1954 (99).

Fabing 1955 (43) stated that frequel (a gamma

isomer of meratran which is a pipradrol) as a premedication blocked the onset of LSD psychoses as well as halted psychoses in process. However it blocked only the psychic effects but not the visceral changes such as nausea, numbness of the limbs, tightening of the jaws, dry mouth, conjunctival injection and sweating. Mescaline was affected the same way.

Nicotinic acid is shown by Agnew 1953 (3) to also have a tranquilizing effect on LSD psychoses, although there remains lack of modification of the affective disturbance. Nicotinic acide as a premedication reduced the disturbances in concentration and vision. It was noticed that in some subjects in which nicotine acid was given as a premedication a psychosis resulted which resembled to a greater degree the primary symptoms of schizophrenia than that resulting from LSD administration. They demonstrated a variable response in disturbances of concentration and power of expression in LSD psychoses. Nicontinic acid was shown not to have a direct antagonism to LSD. Since certain reactions are specific to LSD while other may depend on the situation and personality factors, it is presummed that nictonic acid has its action in a specific way in affecting LSD.

LSD caused normal alerting EEG pattern in conscious cats (low amplitude, diffuse, fast electrical waves) but caused no change in the response to photic stimulation. Large doses of LSD abolished EEG effects of barbiturate anesthesia, although it had no effect on the depth of anesthesia. Different effects in vivo and vitro were observed. Bradley 1953 (23)/ Barbiturates antagonize

LSD. Forrer 1951 (47)

2) Differential diagnosis.

LSD as with mescaline has proven unsatisfactory for differential diagnosis. The responses in humans are so diffuse, complex and overlapping so that specific diagnoses under our present methods can not be made from drug induced toxications. Hoch 1955 (79)

3) Therapeutics.

LSD has a place as an adjunct in psychotherapy as does mescaline. Frederking 1955 (48)

LSD in neurotic patients produces an upsurge of unconscious material into the consciousness. The material from the LSD psychoses are like the dream and fainting material of patients undergoing deep analysis. The material is of personal significance to the patient and should be useful to the therapist. Sandison 1954 (143)

Sandison 1954 (144) proposed that LSD exerts a selective action on the structural seat of repressed memories. It may therefore be useful in therapy of psychoneurotic and neurotics. It was stated that LSD causes a behavior in animals different to that in man. In normals LSD causes psychoses of two types: manic depressive-like, and schizophrenic-like reactions. This classification is based on symptoms rather than correlation with personality, interest and personal

problems. With large doses an exaggeration of the psychotic state is found in psychotics. He felt that LSD and mescaline are alike in their presentation but different in their content.

He felt perhaps that LSD has a selective action on genes. The greatest value therapeutically has been in obsessional-anxiety bound patients having mental tensions.

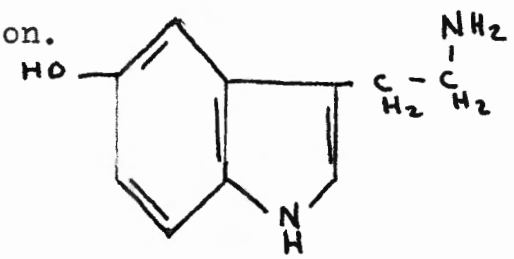
In 1952 Savage (145) agreed with the conclusions listed above that LSD improved patients with depressive reactions, although the improvement was no greater than that which would have been obtained without its use. LSD helps in that it gives the therapist a more rapid insight into the unconscious processes.

Hoff 1954 (82) reported that ataraxics may interfere with LSD and other hallucinogens by inhibiting the latters effect on phosphorylation or on the citric acid cycle in glucose metabolism. Mayer-Gross 1952 (109)

The psychiatric state produced by LSD is not felt to be identical with that in schizophrenia, but there are sufficient similarities to suggest a biochemical factor in schizophrenia. AAAS 1955 (171)

5-Hydroxy Tryptamine (serotonin, enteramine, 5HT).

A. Description.



5 HT.

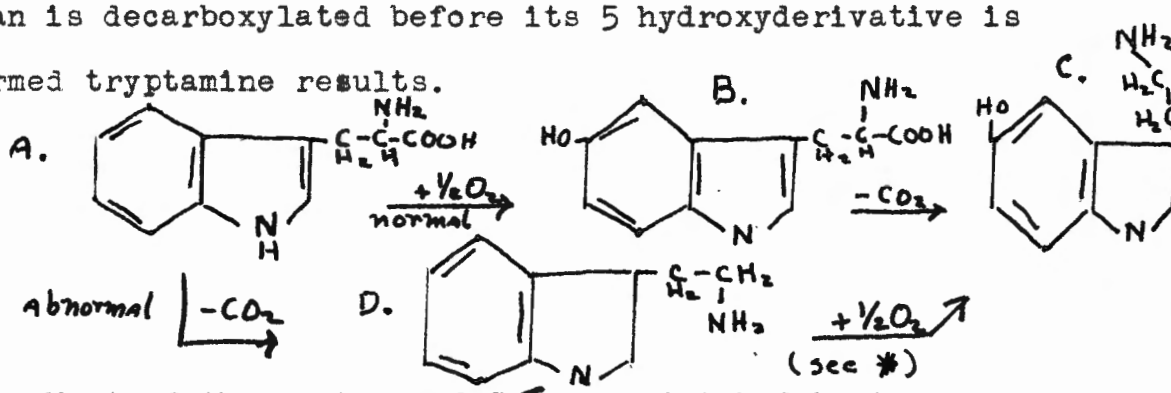
5HT, an indole alkylamine (Evarts 1954-40), arises in the course of tryptophan metabolism in man. Tryptophan, an amino acid, is set free from protein by tryptic digestion and is then converted to 5 hydroxytryptophan by oxidation, which then is decarboxylated to 5 hydroxytrptamine.

5 HT is found in man in all tissues of the enterochromaffin system (gastro-intestinal), blood, spleen, and in the central and peripheral nervous system structures including that of the brain. Erspamer 1954 (39) It is also found in the urine. Pope 1954 (123) It may be a neurohormone. Slater 1955 (155) It was first synthesised by Hamilin 1951 (66).

Actually many do not consider 5HT to be a true hallucinogen, in that it is not shown to cause an induced psychosis in man. However by its position as a normal constituent in the nervous and other tissue and by its relationship to the hallucinogens, it is thought to be closely associated with mental illness perhaps in its deficiency or excess. However credence is lent to the possibility that 5HT may be a hallucingen in that tryptamine which is a metabolic precursor of 5HT is found to have several hallucinogenic properties.

Fabing 1955 (42) listed several errors of metabolism that could be responsible for mental illness, one

being tryptamine formation in the 5HT cycle. If trypophan is decarboxylated before its 5 hydroxyderivative is formed tryptamine results.



Most of the actions of 5HT are mimicked by tryptamine. Reid 1952 (135) Tryptamine causes negativism and catatonia in cats which lasts for days when given intravenously to the cats. Nieuwenhuysen 1936 (117) It was isolated from the urine of patients suffering from pellagra, a disease which can have a psychotic component similar to schizophrenia. The effect of tyramine and other amines on brain tissue has been shown to be not due entirely to the amine but to a product of oxidation of the amine, perhaps 5 HT. Mann 1940 (104).

5HT has been identified as the specific hormone of the enterochromaffinsystem, enteramine, and as the vasocontrictor factor found in platelets. It causes an increase in capillary resistance. Erspamer 1954 (38); Bracco 1954 (33); Evarts 1954 (40)

B. Experimentation.

1) Animals.

Injectionof 5 HT into the lateral ventricles of

* A. Tryptophan B. 5 H-Tryptophan C. 5 HT D. Tryptamine

the cat caused severe behaviorial changes, increased muscular weakness, tachypnoea, and profuse salivation. The inportance of tachypnoea and salivation may not be great since many drugs given in this manner to cats cause vomiting, retching, salivation, swallowing, and tachypnoea. Feldberg 1954 (45) thought that accumulation of 5 HT was the cause of mental illness.

In cats 5 HT causes pulmonary vasoconstriction, and bronchoconstriction by direct effect on the lungs. These actions are antagonized by dihydroergotamine and LSD. Adrenalin given premedically before injection of 5 HT abolished or reduced bronchoconstriction, but no effect was seen b y it on the vasomotor action. Gaddum 1953 (57)

The cats fall in blood pressure is more prominent than the rise in the dual action caused by 5 HT, although the opposite effect is seen in dogs. The fall in blood pressure is abolished by vagotomy or by pharmacological blockard by atropine. 5 HT action in man is similar to that seen in dogs. Page 1954 (123) feels that one of the functions of 5 HT is concerned with nerve metabolism.

He stated in 1953 (124) that the arterial response of 5HT was the result of direct vasoconstriction, transient autonomic ganglion blockard, peripheral inhibition of neurogenic vasoconstriction, and a von Bezold-like

reflex. Adrenalectomy caused no response.

Inhibition of neurogenic vasoconstriction was prominent in animals made hypertensive by section of nerves and resulted in entirely depressor responses to 5HT.

When neurogenic tone is abolished, response of 5 HT is strongly pressor. Inhibition of neurogenic vasoconstriction by 5 HT did not seem to depend on ganglion blockade or upon change of the cerebral vasomotor outflow, but on the peripheral inhibitory or relaxing effect. Its action also does not depend on interference with vasoconstrictive action of nor-adrenalin.

Dogs and hypertensive men respond similarly to 5 HT as mentioned above but different from cats and rabbits. The von Bezold effect and inhibition of neurogenic vasoconstriction may be more prominent in cats and rabbits.

Bufotenine which has a structure similar to 5 HT with the addition of 2 methyl groups has same action as 5 HT except in the cat where it has pressor effects while 5 HT has depressor action. (see Bufotenine)

5 HT liberates adrenalin following the injection of cat arteries thus differing from tryptamine, which mimicked its action in all other instances.

5 HT causes contraction of sheep arteries which action is antagonized by yohimbine. 5 HT is a general

smooth muscle contractive agent. Reid 1952 (135)

After intraventricular injection of 5 HT in cats, muscular weakness, motor immobilization, and salivation occurred without EEG changes. No antagonism in the ventricle was demonstrated by adrenochrome, or adrenolutin with 5 HT, nor between ergotrate and 5 HT. Schwarz 1956 (151)

Amin 1954 (7) felt that 5 HT is the substance P which is the chemical transmitter liberated in the CNS by nerves. He demonstrated that 5 HT in the dog's brain resembled distribution of nor-adrenalin, and this was found mainly in the gray matter. The highest concentration was found in tissues associated with the autonomic system and the area post rema (the area of vascularity containing neuorglia, but no nervous tissue, lying along the lateral border of the caudal end of the fourth ventricle). The heavy concentration in the post rema area was felt to be due to the fact this area contains chemoreceptors. The presence of 5 HT in the brain would be consistent with the theory that LSD acts by antagonizing 5 HT.

Injection of 5 HT into the bloodstream causes a reflex stimulation which results in compensatory vasodilation due to increase in pressure. However if large doses of 5 HT are given, compensation is overcome by much contraction of smooth muscle. Woolley 1954 (168)

Marrazzi 1955 (109) studied the transmission of nerve impulses across neural junctions in cat brains with agents, which were similarly structured hallucinogens, and found qualitative similarity between adrenalin, mescaline, LSD, amphetamine and 5 HT. Synaptic inhibitory action of 5 HT was six to eight times more potent than LSD and twenty-five to thirty times more potent than adrenalin. Since the action of 5 HT was so rapid (acting in a matter of seconds), its action was not considered due to the production of ischemia, which would take a much longer time, but thought probably due to a powerful adrenergic or inhibitory chemical effect.

Mental derarrangements may be caused by an imbalance between adrenergic inhibition and cholinergic excitation in the most susceptible cerebral neural junctions. Hallucinations may be stimulatory phenomena rather that derangements due to partial inhibitors and thusly synaptic inhibition could bring about release from normal restraining influences with consequent stimulation. Thus excess 5 HT instead of deficiency might cause mental disturbances. The importance of chemical substances which act like neural hormones, as 5 HT are great.

Feldberg 1954 (45) noted that adenosine triphosphate resembled adrenalin and 5 HT in effect on the cat after injection into the lateral ventricle. The resultant

signs were muscle weakness associated with ataxia, flushing of the ears and paws and a tendency to fall asleep.

2) Man.

Physiologically 5 HT caused dizziness and peculiar sensations in the head, influenced hemostasis, increased vascular tone and systemic blood pressure, regulated function of the kidneys and perhaps plays a role in maintaining normal mental processes. He disagrees with Woolley that an excess of 5 HT could cause mental disease since 5 HT is so wide spread in nature, but admits that the data referrable to the study of 5 HT in the CNS is scanty. Erspamer 1954 (39)

Page 1954 (123) reported that 5 HT in humans caused a fullness in the chest, tingling and prickling all over, itchy nostrils, difficulty breathing, a desire to empty the bowels, pain in the stomach and bladder, weakness, nausea, desireto sneeze, numbness, ~~etc.,~~ exaggerated respiratory movements, hyperpnea, cough and tachycardia.

Woolley, 1954 (167) suggested that since hallucinogens antagonize 5 HT in smooth muscle and that since 5 HT is present in the brain that the mental changes caused by the drugs are the result of a 5 HT deficiency which they induce. If this is true then natural mental disorders as schizophrenia which are mimicked by these

drugs, may be pictured as a result of cerebral 5 HT deficiency arising from metabolic error rather than by drug action.

He showed 1954 (168) that 1) 5 HT occurs in the brain and some ganglion, 2) stimulation of certain peripheral nerves leads to release in the brain of some substance perhaps 5 HT, which acts on target cells, 3) some specific acting drugs which antagonize 5 HT on smooth muscle cause mental derangements in man and animals, It is possible that this is due to inhibition of 5 HT in the CNS.

There are three classes of natural alkaloids related to 5 HT. The first are the ergot alkaloids which contain ergotamine and LSD. The second are the harmala alkaloids such as harmine. The third class is yohimbine. Although they vary in structure they have a common indole nucleous and a substitued aminoethyl side chain. All act as competitive antagonists of 5 HT on smooth muscle arteries. Another factor in common is that at least one member of each group causes mental aberrations.

If the above discussed thesis is true then other anti 5 HT drugs should cause mental disturbance. Medmain is a drug that does.

However two things rule against mental changes resulting from interference of 5 HT. 1) every antagonist of 5 HT on smooth muscle does not cause mental

change as for example ergotamine, ergotoxine, and l-methyl medmain. 2) 5 HT should reverse the mental effect of the drugs but is unable to do this in mice under the influence of medmain and LSD. This may be due to the fact that 5 HT can not penetrate the blood brain barrier or may be destroyed by amine oxidase in the blood before reaching the brain. Conversely perhaps some anti-metabolite may not be able to penetrate the barrier either, so are unable to provide mental disturbances. This might be checked by injecting 5 HT into the CNS along with an antimetabolite.

Another thesis is based on 5 HT excess. Amine oxidase attacks 5 HT strongly as well as other amines including adrenalin although less vigorously. If amine oxidase was tied up, 5 HT would accumulate in excess. In this instance the antagonistic antimetabolies could compete with 5 HT for the destructive site rather than for the stimulatory site as in smooth muscle. A study of 5 HT in cerebral fluid should be made. Injection of 5 HT into the CNS of normal humans could be revealing, but is now considered too dangerous. A study of amine oxidase and its relationship to all of these drugs should be done so question as to whether amine oxidase is inhibited or whether the receptor for 5 HT is blocked in the brain to cause excess might be answered.

Callaway 1955 (26) does not feel that 5 HT has the important role given it above, but rather feels that LSD

has an effect on carbobydrate metabolism. The latter more closely ties in with his theory of psychological decrease in environmental perception. Hypnogogic hallucinations occur in the tired state, with no accompanying EEG alerting and with a minimal amount of sympathetic activity.

3) Antagonists

The hypertensive effect of 5 HT is weakened by sympatholytic agents like yohimbine; and adrenergic drugs antagonize the antidiuretic effect of 5 HT on rats. Some antiadrenergic drugs seem to possess a true anti 5 HT action. Erspamer 1954 (38) No antagonism was found between adrenochrome and 5 HT in any way. 5 HT inhibits cholinesterase of human serum. Tryptamine and bufotenine have the same action.

Both LSD and 5 HT have an indole ring, both show synaptic inhibition like mescaline and adrenalin, altho 5 HT is more potent. No cerebral antagonism exists between LSD and 5 HT.

Competition between these substances would be expected, but since 5 HT is so more potent than the rest in producing inhibition it would hardly offset the others and its deficiency could not reasonable be expected to lead to the same effects caused by LSD.

5 HT has same potency as acetycholine. It may have natural function in nervous system as an humoral inhibi-

tioner. Inhibition is not due to change of the blood flow or presence of anoxia. 5 HT to be effective must pass the brain barrier.

Disturbance of the adrenergic or related cerebral neurohumoral mechanisms appears to be implicated. Marrazzi 1955 (105)

Mann 1940 (104) noted that amines including tyramine, 5 HT and adrenalin compete with each other for amine oxidase. He feels that aberrant amine metabolism may be a factor in mental disease.

Pope 1954 (123) showed that ergotamine was an antagonist of the pressor action of 5 HT. 5 HT however was antagonized by adrenergic blockade less than were adrenaline or nor-adrenalin. Yohimbine may be an antimetabolie of 5 HT. The theory that 5 HT transiently block the ganglionic transmission and inhibits neurogenic tone seems to have relevance.

Elkes 1954 (37) agreed that nor-adrenalin and 5 HT were found in similar areas of the brain but also found that LSD antagonized 5 HT in the brain tissue of cats.

Gaddum1953 (54) demonstrated that LSD was a potent antagonist of 5 HT's constrictive action. He thought that 5 HT may have role in maintaining sanity and that LSD may have its mental action through its effect on 5 HT. Slater 1955 (155)

He felt that 5 HT acts on two kinds of tryptamine

receptors, one in smooth muscle and the other one in nerve ganglions. The former is inhibited by LSD, the latter is not, but is inhibited by an excess of 5 HT so that the relationship between LSD and 5 HT is similar to the one between acetylcholine and atropine. 5 HT in nervous tissue is inhibited by atropine and cocaine in the same way as nicotinic acid is inhibited. It acts on post ganglionic fibers. Administration of it to schizophrenic patients failed to help them so the conclusion is drawn that the excess theory of 5 HT is likely or that there is a blood brainbarrier to 5 HT. (172)

Active antagonistic compounds which develope antagonism slowly but are irreversible in actionare dibenamine, LSD, and benzyloxygramine. Less active, more rapid, but reversible antagonist include tryptamine. Adrenochrome was only mildly but nonspecifically antagonistic toward 5 HT.

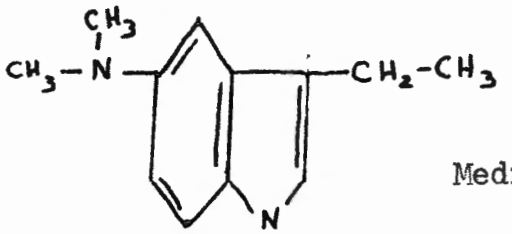
Shaw 1953 (153) reported that 5 HT was antagonized in smooth muscle by medmain. Harmine which is also ananalogue and antagonist ower its pharmacological action to 5 HT. It is felt that the action of 5 HT antagonists is not limited to their antimetabolic antagonism shown toward 5 HT.

Taylor 1951 (163) thought that perhaps 5 HT represented a new series of pressor compounds since it

since it showed different action than adrenalin, arterenal, renin, angiotonin, and pitressin.

Pletscher 1955 (131) showed there existed a similarity in physiological action between reserpine and 5 HT. Both produced sedative effects in mice and potentiated action of hexobarbital by a central mechanism. Both were antagonized by LSD. Reserpine given to dogs causes an increase of urinary excretion of 5-hydroxy indole acetic acid, a metabolite of 5 HT. Reserpine was thought to have a central action mediated thgough the liberation of 5 HT. It was shown that reserpine liberates 5 HT from the intestine in rabbits where it has a major storage depot. It may cause a release of 5 HT in the brain of man leading to beneficial effects. Although LSD antagonized 5 HT and reserpine it had no effect on hexobarbital. Shore 1955 (154)

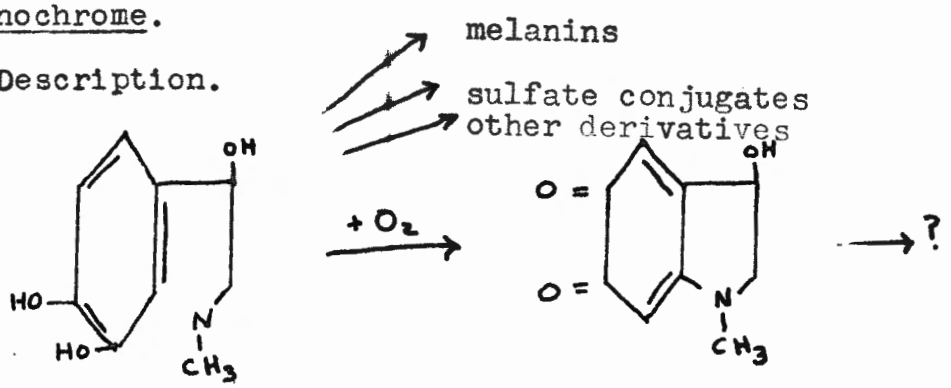
Woolley 1954 (167) reported a study of structure similarly antimetabolites. Among them medmain which has antagonistic effects mentioned above. He felt that the antimetabolite must be able to pass the brain blood barrier to affect the brain 5 HT and medmain met this requirement. In 1954 (168) he agreed with Gaddum that 5 HT plays a part in normal brain function but disagreed with him that mental disease arises from 5 HT excess. He felt that it arises because of a 5 HT deficiency or a suppression of its action.



Medmain.

Adrenochrome.

A. Description.



Adrenalin. Adrenochrome.

In vivo and in vitro adrenalin becomes oxidized to adrenochrome, an indole structure, and perhaps further oxidized to adrenoxine. Adrenochrome is a red pigment which occurs in the body and is an oxidative carrier or respiratory center. It is a basic unstable substance. Adrenalin induces a vigorous oxygen uptake when it is added to the lactic and malic dehydrogenase systems of the heart muscle due to the presence of adrenochrome. Oxidation of adrenalin to adrenochrome is catalyzed by a cyanide insensitive system present inthe heart and skeletal muscle, and by a cytochrome-indophenol oxidase system present in all tissues. Fabing 1955 (42)

B. History.

Adrenochrome was first discovered and described in 1937 by Green D. (62) Hoffer 1954 (84) noted that all

of the hallucinogens except marihuana had an indole nucleus although mescaline had only an indole like structure. They reasoned that if one could find an indole nucleus substance in the body that had the hallucinogenic effects it might be an etiological clue for schizophrenia. This unknown substance he called "M". It was accidentally reported that one of his volunteers had had schizophrenic like symptoms, and an eidetic and hypnogogic imagery associated with a 'strange environmental feeling' whenever he took his adrenalin for chronic asthma. This same experience was found supported in the literature. A hospital anesthesiologist also had noticed that when he used a deteriorated pink solution of adrenalin he obtained psychotic effects in his surgery patients. The solution was found to contain adrenochrome. They continued in their search of the literature for substance "M", a substance that would give schizophrenic effects without loss of consciousness, confusion or gross physiological disturbances. After the accidental discovery of adrenochrome they found that it had an indole nucleus and was readily derived from adrenalin in the body and was related to stress, so they hypothesized that in schizophrenics an increase of stress might cause an increase of adrenochrome. Adrenochrome was the first

naturally occurrin hallucinogen discovered.

C. Experimental psychiatry.

Hoffer 1954 (84) found that he could produce schizophrenic dissociations lasting four days with a synthetic adrenochrome in doses of .1 to 5 milligrams subcutaneously and 10 milligrams intravenously. His main findings in humans were over activity, poor judgement, depression and hallucinatory experiences. It was found that among the common symptoms were preoccupation with inanimated objects, negativism, loosening of the associative process, anxiety and distractibility. Less insight with inability to relate to injections was found in adrenochrome intoxicants than in those under influence of LSD and mescaline. Two of his group took thesdrug themselves and described their experiences in in dramatic self analyses.

Three factors support the presence of adrenochrome in the body of the normal person. 1) Adrenochrome and its oxine (adrenoxyl) are excellent hemostatic substances and have been used as vitamin P factors. 2) Adrenochrome is a quinone and possesses its properties in that it can inhibit activity of many enzymes of the glycolytic cycle and of the tricarboxylic acid cycle and is an antimetoblic factor in stressed mice. 3) When action of tryosinase is inhibited, adrenalin remains with a resultant sympathetic increase and an absent formation of adrenochrome.

Adrenalin may be excreted unchanged in small amounts by kidneys and stored in tissues and red blood cells. Its deamination by amine oxidase, which is found in the liver, intestine, and CNS is unlikely. One important fraction is sulfoconjugated and another fraction is simultaneously oxidized to indole substances. One of these substances being adrenochrome and its derivatives. Bacq 1949 (10)

Hoffer 1954 (84) felt however that amine oxidase may play a role in the sympathetic nervous system as acetylcholine esterase does in the parasympathetic nervous system. Noradrenalin is found to be released at sympathetic nerve endings as acetylcholine is at parasympathetic and ganglion nerve endings. Noradrenalin is destroyed by amine oxidase, while the latter is destroyed by ephedrine and cocaine.

The enzyme amine oxidase is found commonly in the body, particularly in the nervous tissue. All compounds R-C-CH2-NH-CH3 are inhibitors of amine oxidase. These include the ergot alkaloids, cocaine, ephedrine, indoles, indoleaceptic acid, phenylisopropylamine, desoxyyephedrine, pervitin, oxidized derivatives of adrenalin, caffeine, nicotine, methedrine, lysergic acid, and benzedrine. The latter owes its stimulating influence to its ability to compete with amines for amine oxidase in the brain and in other organs, thereby decreasing the the rate of formation of inhibitory aldehyde.

Adrenalin is more slowly destroyed by amine oxidase which disproved the contention of Bacq. Amine oxidase is reduced in the liver by thyroid feeding and is increased by thyroidectomy. So hyperglycemia occurs because of the adrenalin effects in thyroid fed animals. With thyroid, an increase in blood pressure occurs because amine oxidase at blood vessel is reduced. Burn 1952 (25); Mann 1940 (104); Blaschko 1940 (17); Orzechowski 1941 (119)

If amine oxidase does not oxidize adrenalin, phenolase might and then adrenochrome would result. Phenyl propylamines, such as amphetamine, and ephedrine, having amino groups on the terminal carbon are oxidized by amin oxidase, but if OH is present on the ring, the compounds are oxidized by phenolase. If neither condition exists no enzyme works on it. Beyer 1941 (15)

So inactivation of sympathominetic compounds by action of amine oxidase or phenoloxidase is dependent on the molecular configuration. Beyer 1941 (15) supported concept that amine oxidase and phenol oxidase or similar systems determine oral efficacy and the excretion of these chemicals.

Sympathominetic amines having no hydroxyl group on the benzene ring are excreted if the primary or secondary armine group is not on the terminal carbon atom of the side chain; for it is only in that position

is it deaminated by amine oxidase. If the liver function is impaired by carbon tetrachloride or by hydrazine those compounds having a primary or secondary amino group on a terminal carbon atom are also excreted. Oral efficacy and excretion of amines is dependent on whether the compound brought to the liver has its amino acid in a position on the side chain where it can be deaminated by amine oxidase and other systems. Beyer 1942 (16)

There are five ways the body detoxifies large quantities of adrenalin produced by the medulla and other sympathetic ganglion.

1) excretion unchanged in the urine.
2) storage of adrenalin in red blood cells and other tissue cells.
3) deamination of side chain by amine oxidase to form oxidizable aldehydes which have no autonomic properties and are easily metabolized.
4) esterification of phenolic compounds by sulfoesterase which are excreted in the urine.
5) quinone formation to adrenochrome and its derivatives by phenolase which have no pressor properties but other important effects.

If the reactions in 3 or 4 are prevented by blockage of amine oxidase and sulfoesterase, adrenaline is broken down to adrenochrome. Bacq 1949 (11)

Eade 1952 (36) demonstrated that adrenochrome lowers the body temperature by a central effect. It was felt that it could cross blood brain barriers, although adrenalin can not, because following injection of adrenochrome into animals paralysis of the hind legs, dyspnea, apathy and exophthalmia occurred.

Adrenalin injected into the lateral ventricle of the cat caused postural phenomena similar to flexibilitas cerea of the catatonic schizophrenic. It resembled somewhat the effects of a light barbiturate anesthesia. This was preceded by swallowing, retching, and vomiting, and effect noted in all drugs initially after given.

Atropine caused increased liveliness and restlessness, and caused the cats to become unusually affectionate. The appraisal of surroundings was impaired. Acetylcholine caused a high pitched phonation and a state resembling an akinetic seizure, which was followed by a subdued demeanor in which convulsion are produced. Feldberg 1954 (45) in another experiment got an opposite result after injecting atropine into a cat and it became more sleepy. Physostigmine counter acted this last action.

Adrenochrome injected into rat cerebral cells markedly inhibited intermediary metabolism of carbohydrates. The effect was immediate while mescaline required two to three hours. Its action was apparently due to inhibiting glucose and pyruvate aerobic oxidation by inhibition of hexokinase and to blocking of an enzyme below the pyruvate leve. Woodford 1952 (166)

Adrenochrome is an antiomeitotic factor in stressed mice and probably has the same effects in humans. Evidence suggested that the antimitotic action of adrenochrome is due to its inhibition of hexokinase.

Adrenalin is not able to cause this but adrenochrome and perhaps some of its derivatives are powerful enough to do this. Epidermal mitotic activity increases in stress because of the interference in carbohydrate metabolism. Bullough 1952 (24)

Adrenochrome oxidizes sufhydril groups of glutathione proteins and enzymes and is able to inhibit activity of many enzymes of the glycolytic cycle. The inhibition of glycolysis of brain extract by adrenochrome is mainly due to inhibition of hexokinase and phospho - hexokinase. Since it inhibits hexokinase under anerobic conditions the entire oxidative system could be inhibited as is markedly the case in adrenochromic inhibition of glucose and hexosemonophosphate oxidation in the presence of brain enzymes.

O-napthoquinone acts similarly to adrenochrome but is five times as active and inhibits other enzymes of glycolytic cycle.

It should be noted that while adrenochrome inhibits respiration, glycolysis and motility of typanosomes in vitro, there is no appreciable effect in vivo. Meyerhof 1948 (114)

Tyramine, mescaline, benzedrine and other amines of this aromatice type act like typical narcotics in strongly inhibiting oxidation of glucose, sodium lactate, sodium pyruvate and sodium gluconate in the brain.

Tyramine also inhibits sodium succinate. They act by competing with lactic acid for the active surfaces involved.

Many of these amines are produced in normal amino acid break down in the intestines. After absorption into the blood stream they are carried to the liver where detoxification occurs. Disturbance in this mechanism could lead to increased amounts of these substances causing psychological reactions seen in anoxaemia and early stages of narcosis. Disturbance in hepatic function could be a causative element. Quastel 1933 (134)

Adrenochrome given to epileptics intravenously increased cerebral arrhythmias. Epileptic activity occurred in dormant or latent cases and where the EEG had previously been normal, abnormal results became apparent. Adrenochrome can be used in diagnosis of latent epileptics who previously have shown no EEG abnormalities. Osmond 1955 (121)

He theorized that adrenochrome or a similar substance could accumulate under certain circumstances and produce psychological disturbances long before physiological changes would be noted. Such an agent might cause schizophrenia. However should such a single agent exist one could explain the wide variety of clinical pictures by the differences in the cultural

setting, personality patterns, age of onset, rate of production of causative agent, quality of causative agent, exact compounds produced, specific localization of cerebral enzymes inhibited in the nervous system, capacity of the body to store causative agent or to detoxify or destroy it, and in the success with which each patient deals with his psychological disturbances. So the object would be to isolate and identify this substance. Hoffer 1954 (84)

Rinkel 1954 (137) tried to confirm the observations of Hoffer about the hallucinogenic effects of adrenochrome but was unable to do it with a commercial preparation of adrenochrome given in doses orally of 5 milligrams. He also quoted its uneventful use in surgery cases. He concluded that the solution used by Hoffer was unstable and had oxidized even beyond the adrenochrome stage to adrenoxine. He felt that adrenoxine might be the agent in the agent in the adrenalin cycle that interfered with the major enzyme systems that are presummed to have a direct bearing on mental illness. He speculated that at one time in the life of an organism an enzymatic disturbance in synthesis or decomposition of a vital chemical may occur and a metabolite may originate causing a psychosis with its associated physio-chemical changes. He questioned whether psychological distress effects the adrenalin

cycle or whether it is a congenital disturbance. He agrees with Hoffer that adrenochrome or a similar substance is responsible for disease. Rinkel 1955 (138)

Hoagland 1955 (76) pointed out that the commercial adrenochrome used by Rinkel contained a semicarbazone of adrenochrome which he thought could interfere with the true action of adrenochrome and he felt that Hoffer and Osmond may still be right about the effects of adrenochrome. Now Rinkel is carrying out repeat experiments with true adrenochrome.

Adrenoxine, a metabolite axidation product of adrenalin produced by tyrosinase, has the same physiological effects of bradycardia and a slight decrease in blood pressure. Heirman 1937 (67) Hoagland 1955 (76) suggested that it might be the agent in schizophrenis and may act as an antimetabolite to 5 HT, and in excess would then cause schizophrenia. It is felt that deranged adrenalih metabolism may involve modification of some enzyme or co-enzyme system involved in phosphate transfer.

Martin 1942 (107) found that para-aminobenzoic acid inhibited the action of tyrosinase on adrenaline and caused an increase in sympathetic action by adrenalin by blocking its conversion to adrenochrome. Phenolases are also active in vivo destruction of adrenalin. The oxidative destruction of adrenalin, a pressor amine, is

promoted in a tyrosinase-adrenalin system by ortho-substituted phenols and inhibited by aromatic amines and aminobenzoic acids. The effectiveness of tyrosinase in decreasing blood pressure of perinephritic hypertensive dogs is enhanced by the simultaneous administration of catechol.

Schwarz 1956 (151) found that adrenochrome in intraventricular cat injections caused stuporous change with changes in EEG in the occipital region. Adrenolutin, a derivative of adrenochrome, caused the same results but in smaller doses. They concluded that the effects of adrenochrome and adrenolutin is similar to adrenalin and noradrenalin in cats brain.

Szatmari 1955 (162) compared adrenochrome and nicotinic acid, since adrenochrome causes psychological changes in normal people and became nicotinic acid had recently been used in the treatment of schizophrenics. Adrenochrome had also been shown previously to cause a biochemical inhibition of brain respiration by blocking Krebs cycle and the diphosphopyridine nucleotide systems and had induced abnormal EEG's. Adrenochrome in dosages of 10 milligrams caused no change in the EEG of normals but caused an increase of bilateral paroxysmal abnormalities in the EEG of epileptics with little effect on cortical focus.

Nicotinic acid orally or intravenously caused a slight shift in the normal to a fast side. In epileptics the drug considerable decreased bilateral diffuse paroxysmal abnormalities, except in true idiopathic epilepsy, but as with adrenochrome it caused only a little change on the focus.

He theorized that nicotinic acid acts as a coenzyme in Krebs cycle and restores disturbed patterns of carbohydrate metabolism. He noticed that in a schizophrenic that there is a high incidence of paroxysmal bilateral abnormalities of the EEG which he said could be explained in two ways: 1) paroxysmal bilateral activity may represent an increased diencephalic reaction as a homeostatic principle, and 2) adrenochrome or a similar substance plays a part in the genesis of schizophrenia.

Lea 1955 (98) states that if the adrenalin cycle is involved in mental illness, it may be that the abnormality lies with the tyrosine metabolism since adrenalim is derived from tyrosine. If this be the case he would expect the following deductions to hold true:

1) Abnormal pigmentation: One should expect abnormality of pigmentation since metabolic paths of melanin lead through the adrenalin and adrenochrome groups. The type of pigmentation depends on where the interference occurs in the cycle. Since melanin is developed from adrenochrome in the body, one would expect shhizophrenia

to be found in a dark complextioned person.

2) Negative association with allergic states: There occurs a greatly increased tolerance to histamine. Adrenaline best for treating histamine poisoning, so there should be a decreased allergic state in schizophrenia. Adrenochrome antagonizes histaminic action. Hutcheon 1955 (86)

3) Ascorbic acid metabolism: Ascorbic acid prevents oxidation of adrenalin to adrenalone, which is the immedicate precursor of adrenochrome. There is less pigment in Addisons disease following treatment with ascorbic acid. A decreased sodium chloride concentration leads to destruction of ascorbic acid which leads to melanin. So improvement of schizophrenia should be observed in sodium chloride and ascorbic acid treatment.

4) Tyrosine metabolism: A reduction in tyrosine and phenylalanine to a physiological minimum may help the schizophrenic.

5) Abnormal substances in the urine of schizophrenics: There should be some melanuria, or some increase in an indole abnormal body or an excess of normal excretion of such substances in the urine of the schizophrenic.

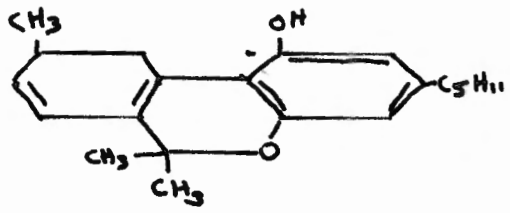
Upon the assumption that schizophrenia is due to intoxication by adrenochrome or a like substance the

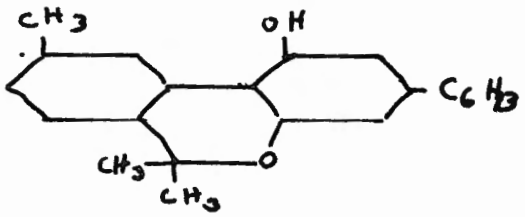
following deductions have been confirmed: 1) Schizophrenics do show an increased dark pigmentation over normals, and 2) schizophrenics show a decreased incidence of allergy.

He then further hypothesized that metabolic fault may be due to hepatic insufficiency and this is due either to heredity or environmental factors or both. This would explain the dark complextions and dark hair, liver damage, abnormal histamine tolerance, and absence of correlation between age of enset and histamine intolerance. He feels that schizophrenia is a single disease, and postulated that the liver trouble might be due to trophopathic hepatitis (necrosis) because of a deprivation of a substance necessary for life.

It was noticed that the dark complextioned schizophrenics all fall into the age group fifteen to nineteen years for which Lea gives two explanation. One is that there are two conditions in the schizophrenic: one condition is due to an adrenochrome, or a similar substance, intoxication at an age younger than twenty, and the other condition is due to unknown causes which allow schizophrenia to make an appearance after the age of thirty. The second explanation is that schizophrenia is a single disease due to a fault in the adrenalin cycle and with an origin in both heredity and environment.

Hashish.





Hemp. (marihuana) Pyrahexyl. (synthetic)

It is a tetra hydrocannibinol which comes from the hemp-Cannabis rativa. Cannibis does not contain an indole structure and has no nitrogen molecule. It is a dibenzopyran structure. Fabing 1955 (42)

The synthetic structure is represented by pyrahexyl, which also has no indole ring but is a dibenzopyran. Adams 1941 (2)

Its pharmacological action is like atropine and alcohol. Physiologically it increases the pulse, increases blood pressure, causes injection of conjunctival vessels, dilatation of pupils, reaction of pupils become sluggish, dryness of mucosal membranes, increased, respirations, ataxia and hyperflexia, diuretic effect leads to concentration of blood and affecting of CHO metabolism.

Psychologically apprehension and anxiety are increased; euphoria, loquaciousness, lessening of inhibitions, hunger and thirst, uncontrollable laughter, and frequently drowsiness are present. Restlessness and movement are prominent. They frequently have choreoathetotic movements and rigidity. Mayer-Gross 1952 (109) There is also a dissociation of thought associated with a hyperkinesis.

Clinical tests are negative, although increased frequency of the alpha waves on the EEG (relaxation) and decreased gastric motility may occur.

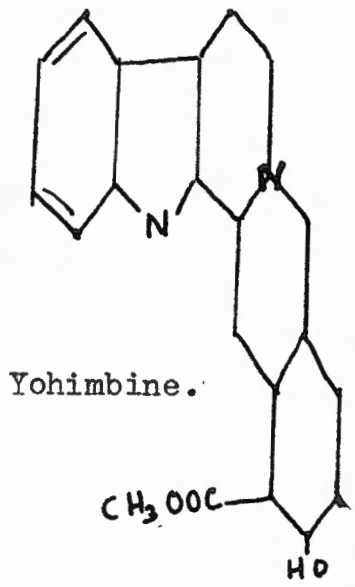
The dose is usually fifteen to forty five milligrams orally and tolerance is produced. There is no addiction noted or is there a craving developed in the user.

Uses may be developed in therapeutics such as to cause euphoria in depressions, appetite stimulants, and as replacement therapy in cases of alchol and opiate addiction.

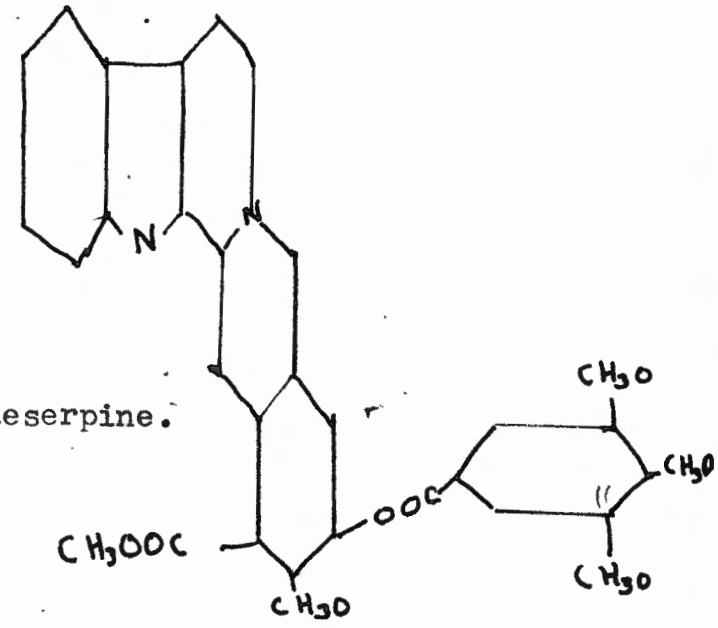
Yohimbine.

It comes from the bark of the yohimshoae tree. Hoffer 1954 (84) It belongs to the natural alkaloidal drugs related to 5 HT and contains amindole nucleus and a substituted amino ethyl side chain. It is a structural analogue of 5 HT and is a highly competitve antimetabolite of it. Shaw 1953 (153)

It causes mental aberrations of an aphrodisiac nature. The dose is .40 milligrams per kilogram. It acts an antagonist to the constrictive action of 5 HT. Evarts 1954 (40). Its chemical structure is similar to that of reserpine which is also an alkaloidal plant product but of opposite effects. Its importance lies generally in its similarity and antagonism to 5 HT. Whats New 1955 (174)

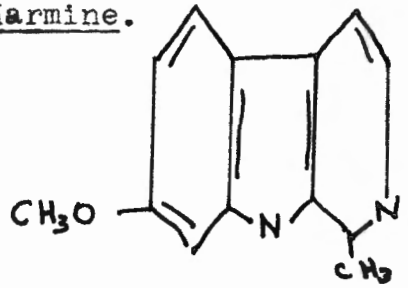


Yohimbine.



Reserpine.

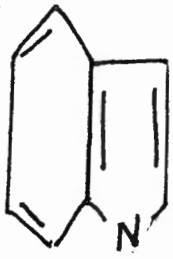
Harmine.



Harmine.

It-is a plant alkloid that comes from the turkish plant Peganum harmala. Hoffer 1953 (84) It has an indole nucleus with a substitued amino ethyl side chain and produces symptoms like LSD. Its dose is .10 milligrams per kilogram. Actually very little is known about the psychological effects although it is known to cause hallucinations and disturbed mental processes. It is an analogue of and an antagonist to 5 HT, to which fact it owes a portion of its pharmacological action. Wooley 1954 (168); Shaw 1953 (153); Osmond 1955 (120); Evarts 1954 (40)

Ibogaine.



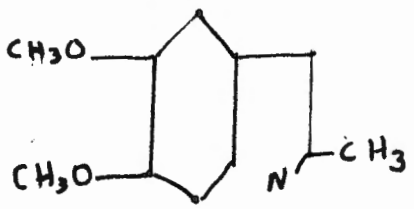
Ibogaine.

This drug with indole nucleus comes from a bean of the iboga plant grown by the Ibo tribe in Central Africa. That it has some hallucinogenic effects is mentioned by Albert Schweitzer. Nothing else is known. Osmond 1955 (120); Hoffer 1953 (84)

Ololiuqui.

This comes from the climbing vein Rivea corynibosa which was used as a narcotic by the Aztecs. Its active narcotic principle was discovered in 1937. As yet its action and structure is not worked out. It causes apathy, loss of interest, decreased verbalization, anergia, heightened visual perception, and increased hypnagogic phenomena. It causes no confusion or alteration of time perception. Apparently after four hours it causes a peried of alertness, calmness, and a state of relaxed well being for many hours. The latter condition is something new in hallucinogenic drugs. Much information as to its history and identification can be found in Schultes 1941 (149) Its action is the reverse of amphetamine. He feels the activities principle should be isolated and the formula compared well as the effect with cerebral enzyme systems. Osmond 1955 (120)

TMP (3,4,5 trimethoxyphenyl) isopropylamine.



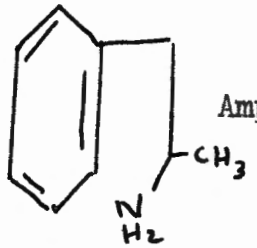
TMP.

This is an open indole structure. The chemical was first synthesized by Hey in 1947 (70). Its causative symptoms and structure is similar to mescaline and amphetamine. There is no increase of blood pressure, a slight increase in pulse rate, and it does not interfere with sleep. It may play a role in psychotherapy.

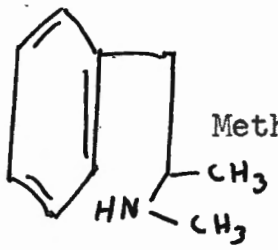
It has a group on the penultimate carbon of the side chain which makes it an inhibiter of amine oxidase. The enzyme of metabolism in higher brain that may be responsible for the phenomena of hallucinogensis may be involved with the inhibition of amine oxidase.

In a dose of .8 to 1.2 milligrams per kilogram it causes euphoria and loosening of emtional restraint in humans. In doses of 1.6 to 2 milligrams per kilogram it causes visual hallucinations. In mice tremors and scratching result, and dogs get catatonic-like conditions. It is excreted in the urine. Peretz 1955 (127)

Amphetamine and Methedrine.



Amphetamine.



Methedrine.

Amphetamine is a CNS stimulant, increases the blood pressure, causes sleeplessness, and produces a cummunicative frame of mind. It does not cause psychologic change in one dose. Methedrine with one more methyl group produces hallucinations in a single dose of 40 to 100

milligrams and has a similarity to LSD in clinical results and blood adrenalin level in mentally disturbed patients. Methedrine does not cause a rapid mood swing as LSD but evokes hallucinations in schizophrenics more rapidly.

Large doses of amphetamine give an alerted EEG rhythm of low amplitude, diffuse and fast waves. Cortical response over visual area is seen in response to photic stimulation. It does not change barbiturate anesthesia, although it increases photic stimulation in the lateral geniculate body. The action of amphetamine is probably on the receptors in the reticular activating system . Elkes 1954 (37) showed that amphetamine is like LSD in producing those EEG and behavior alerting responses in animals. The alerting was related to sympathetic nervous system, and depends on the ascending reticular system, the mesencephalic and spinal connection.

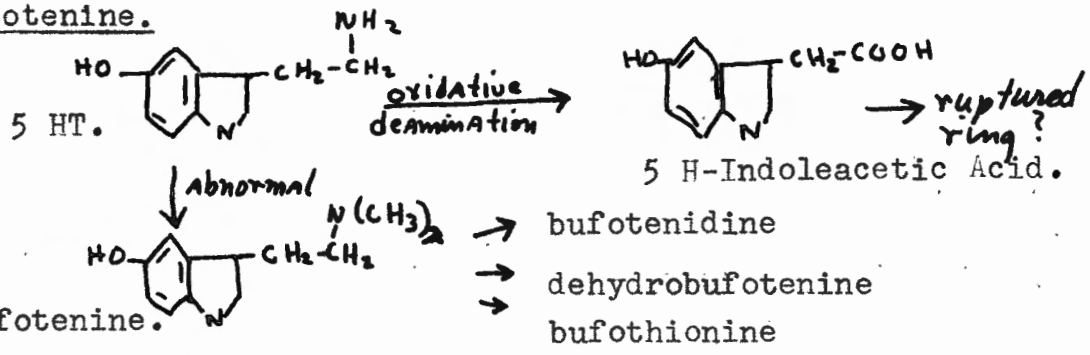
Although amphetamine does not cause hallucination per se and has no effect on barbiturates, it however decreases accessibility of psychosis, while amytal increases accessibility of stupor. This is not understood. Liddell 1953 (100); Peretz 1955 (127); Bradley 1933 (23)

Bulbocapnine.

Its structure and description has not yet been reported. It produces catatonic-like behavior. It may

be produced in hepatic tissue and may implicate in schizophrenia and in drug induced psychoses. Callaway feels that only alteration in fuctions of the liver and intestine are capable of producing signs of experimental catatonia. However he feels that to implicate bulbocapnine may be a mistake since many drugs in large doses will produce hallucingenic effects. Callaway 1955 (26)

Bufotenine.



This is an indole structured drug that can arise out of an error in 5 HT metabolism. Normally 5 HT undergoes oxidation deamination to 5 hydroxy-indoleacetic acid, and it is then decarboxylated. If 5 HT methylates instead of proceeding as above, as happens in amphibians and fungi it becomes n-methyl 5 HT in the first methylation and n-dimethyl 5 Ht (bufotenine) in the secomd methylation. Bufotenine has also been isolated from bean piptadenia peregrenia.

When Evarts 1954 (40) injected bufotenine in the dose of 3 milligrams per kilogram in the monkeys he produced ataxia, motor disturbances, indifference to to tactile stimule, altered sensorium and schizophrenic

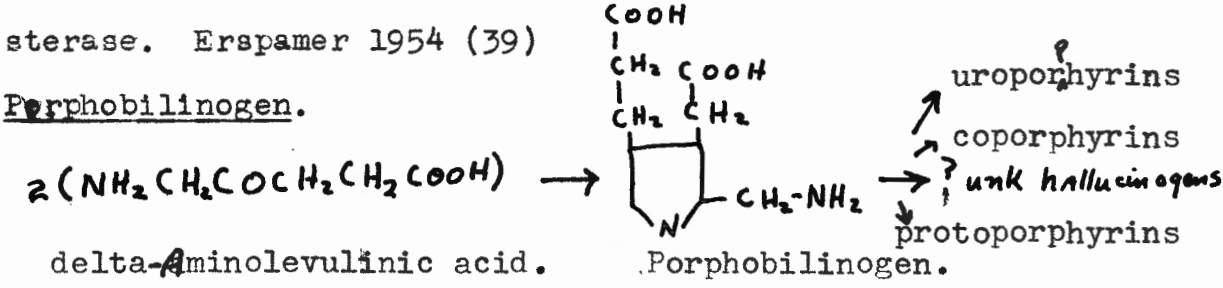
behavior which lasted for several hours. There was similarity noted between it and LSD. He later demonstrated (1955) (41).that it also altered visual response to stimuli in monkeys without causing loss of motor power. The same action was elicited by LSD in a dose of 1 milligram per kilogram intravenously.

It causes LSD-like effects on man, too . Stromberg 1954 (160)

It is about one-half as active as 5 HT but has shown the sameproperties on laboratory animals as 5 HT, except in the cat where it causes a pressor response and 5 HT a depressor one. Page 1953 (124)

Bufoteine as well as tryptamine inhibits cholinesterase. Erspamer 1954 (39)

Porphobilinogen.



delta-Aminolevulinic acid. Porphobilinogen.

It is not an indole, but similar, in that if the chains would close the benzene ring would be formed. It or a derivative is found in aquesous humor, bone marrow and in urine.

Fabing 1955 (42) noticed that twenty-four to thirty-six hours post operatively after prostatectomies, hip pinnings, and eye surgery that there accurred

periodically a dissociation process in the patients. He correlated this with the fact that prophyrin and their precursors are found most commonly in urine, bone marrow, and aqueous humor. Schmid 1954 (147) He theorized that porphobilinogen or an allied derivative was absorbed through the newly incised tissue and caused a schizophrenic-like reaction as seen in acute intermittent porphyria. Watson 1954 (164) Frenquel was found to ameliorate the dissociative state in a short time.

Amanita pantherine (muscaria).

This is a deadly Siberian fungus of which there is not much known, It is a potent hallucinogen, causing euphoria, etc. It is passed through the body as much as five times without losing its effect, as is shown by the custom in Siberian in which the drug is taken and the subject urinates. His urine is then drunk by a friend, and he passes his urine on, and so until five passages of the substance through the body has been made. Osmond 1955 (120); Fabind 1942 (42)

Cohaba.

This also comes from the bean Piptadenia peregrenia. It is a narcotic snuff used in Haiti for necromancy. It was first described by a sailor of Columbus in 1496. Safford 1916 (141) It should be noted that bufotenine has also been isolated from this same bean, Stromberg

1954 (160) Perhaps they are one and the same. Further investigation would bear this out.

Miscellaneous.

A. Hydralazine.

1-hydrazinophthalzaine has caused psychiatric disease in a man given an over dosage in the treatment of essential hypertension. The recovery came in twelve to twenty fours after withdrawal. The psychosis was not related to the blood pressure change or to renal function. It may have resulted from the release of basic personality conflicts after the persons disease state was altered by the drug. Subsequent severe prolonged depressions unrelated to hydralazine substantiated the explantation. There is a similarity between psychotic symptoms here and those that follow cortisone and ACTH withdrawal and consist of hallucinations, delusions, extreme variation of mood and ideational flight and depressive states. This demonstrates that some potent pharmacological agents are capable of altering physiological mecha nisms in the area of psychogenic responses. Moser 1953 (116)

Hydralazine combines with cabonyl and sulfhydryl radicals, and has a strong affinity for metallic ions. It may block enzyme systems and is known to inhibit histaminzse, increase cerebral and renal flow and has

an antipressor effect operating through the mid brain. It can cause CNS effects, headache, nervousness, anxiety, depression, parasthesias, ppsychoses and coma. Visceral effects include an increased pulse, dyspnea, and dryness. Antihistamine, barbiturates, and salicylates are antagonistic. Emotional stress involves the mid brain and is a precipitating and exacerbating factor in essential hypertension ahd rheumatoid arthritis. Lansburg 1955 (97)

B. Fibrous Wool Protein.

Fischer 1954 (46) thinks that the molecule of fibrous wool protein maybe the model of structured surface receptors in drug psychoses. Sorption of drugs onto wool protein may be a model of their action of the CNS structures. He studied mescaline, methamphetamine (methedrine) and LSD and LAE and found an inverse relationship between affinity of these drugs for wool protein and the logarithm of the dose required to produce psychosis. He attributed the increasing affinity of drugs for wool to their different degree of specificity, simulating a reversible inhibition of an equilibrium involved in the production of hallucinations. The increasing absorption of basic (cation action) drugs is accompanied by the following structural features: 1) increase grade of alkylation on the primary amino group, 2) increasing number of amino groups, 3) increase number of carbon stoms between primary amino groups and neighboring

nitrogen of nucleus, 4) presence of two hidden LSD tails, and 5) a molecular weight of about 320.

Thioglycolic acid precipitated a reversible psychosis following a permanent wave. This may be due to an alteration of S-S bonds in the cystein part of the proteins causing an alteration of receptor.

Another problem relates to the adrenergic blocking activity of the compound and a possible relationship of such activity to common structural characteristics concomitant of drugs exerting high affinity for wool protein.

A high affinity for wool protein is associated with a powerful biological activity as is shown by the minute dose required. It is a possibility that stress situations may diminish the amount of drug required to cause a model psychosis; also there may be a decreased intensity of hallucinations if the patient feels psychologically free from anxiety or if he is given drugs which prevent a stress response resulting in adrenergic blockage.

He emphasized that stress and adrenergic blockage are essential for precipitation of model psychoses. A model psychosis may be due to reversible disturbances of integration between diencephalon and cortex leading to lowered reality thresholds. It may act by exerting a sympathetic overtone and an adrenergic blocking activity.

Persisting stress situations might increase dosage of drug required to cause hallucinations at rest. Simultaneous administration of one of the drugs with an adrenergic blocking agent causes psychosis. Certain compounds having high affinity for wool protein, may prevent by competitive inhibition the hallucinations caused by LSD.

That stress can be detrimental on activity is pointed out by Yerkes 1908 (169) who concluded that "an easily acquired habit, that which does not demand difficult sense discrimination or complex associations, may readily be formed under strong stimuli, whereas a difficult habit may be acquired readily only under relatively weak stimulation."

METHODS FOR RESEARCH

Hoskins 1946 (85) stated that there is a mental comfort to theories, but advises against pursuing the "will-o'th-wisp" or working under the semiprojective synthetic artifact of approaching the problem by " considering the patient as a whole." He feels that the subject can be approached by study in: 1) the maturing process in biological laboratories with emphasis on the amino acids, endocrines, vitamins, and enzymes, 2) the value of therapy, how it works, and 3) the teaching for promotion of empathy.

Mayer-Gross 1951 (110) feels there should be a systematic search for drugs with central psychotic effects. Such drugs provide a safe way to study symptoms of mental illness. He cited the need for studies in vivo as well as in animals. He suggested that electro-physiological histopathological and histochemical methods of research be utilized more.

Osmond 1955 (121) describes three ways of attack on schizophrenia: 1) Empirical-- no good because one gets lost in facts-, 2) Systematic theory-- no good because facts trimmed to suit the scientist, 3) Scientific method--approaches goals by planned steps, builds and tests hypotheses. This method is the hand maiden of inspiration. Hallucinogens provide understanding and knowledge required for developing new ones which are important

for the attack on schizophrenia. Those who work with model psychoses should avoid deciding in advance what should happen.

Lindemann 1935 (101) indicted research for lack of scientific procedure. He feels that for good psychopathological examinations one has to go beyond a statistical method and formulate a heuristic hypothesis which is then proved or disproved by experimental sciense. He disagrees with the concept of primary and secondary symptoms in mental disease because he feels that they are only descriptive classifications. It is not considered sufficient to relate any type of physiological or psycological alteration merely to a disease process. The adjustment of the patient at a given time, the relationship of his conflicts, and his resources for relief are important features. The change in adjustment follow the administration of adrenalin. This is determined in measure by the quality of concrete life situations and type of adjustments at the moment of the experiment. The degree of change is related to the process of adjustment.

Under influence of drugs, subjects actions are directed toward inner experiences, toward self. He discovered the significance of the emergency reaction. It is not the result of external alarm but of inner tension. Emergency situation is the imbalance of increased drive

without any corresponding increase in obtainable goals or avenues for direct action by fight or flight.

With adrenalin: 1) self concern out weighs object concern-there is a fear of pain and need of pleasure, 2) immediate discharge of tension in form of direct preventative action is not possible. More frequent changes are protective measures. Therefore anxiety is a signal of dangers, inhibition is useful in prevention of undersirable actions, and frustration and aggravation of symptoms are manifested in increased conflict tension. Adrenalin alone may not cause autonomic disturbances. In concluding he cited need for research into adrenalin and mescaline which has been done.

Green 1956 (63) suggested that the advanced technique of study; micro absorption techniques using ultra violet and soft rays; and biochemical study will lead the way to discovering knowledge of mental disease. He thinks a study of mechanisms used in therapy as to how, and why they work would be very useful.

Evarts 1954 (40) notices two handicaps in the study of mental illness: 1) its really impossible to study a disorder of thinking and feeling in animals, and 2) the lack of objective, measurable indices of these in man. One must depend on verbal report and behavior. He is trying to overcome these deficiences by: 1) developing tests which elicit information of drug induced

psychoses in animals, and 2) developing objective indices of effective psychogenic drugs in humans. He feels further study of indoles in man is greatly warranted, that development of animal preparation for biopsychological assay of drugs is important to research, and that development of objective correlation of mental lesions to the drugs inducing them is necessary.

CONCLUSIONS

1. Schizophrenia is a nebulous complex disease process about which little is known or understood of its pathologic physiology.

2. The true hallucinogens, all of which have an indole or indole-like nucleus, produce a psychosis similar to, but not exactly like, schizophrenia. No hallucinogen has been found to be the causative agent in schizophrenia.

3. The laboratory study of the hallucinogens and of their induced psychoses has given valuable information about the abnormal biochemical, physiological and psychological processes existent in the mentally ill.

4. No definite etiology has been established for schizophrenia, although evidence would seem to rule out a single causative agent.

5. Biochemical imbalance, probably on a metabolic-enzymatic level, must be assumed to play a primary role in the causation or/and maintainence of schizophrenia.

6. The adrenal-pituitary cycle appears to be related to psychosis and schizophrenia.

7. Adrenochrome, and oxidative product of adrenalin, and its oxidative derivatives, shown to be the first natural occurring hallucinogens, could exert a significant causative role in schizophrenia.

8. 5-Hydroxytryptamine, and allied structures,

found normally in nervous and brain tissue, are shown to likely have a vital part in the maintainence of mental health.

9. It is hypothesized that adrenochrome or a potent hallucinogenic oxidative derivative arising out of adrenaline metabolism may, due to some biochemical error, exist in such quantity as to interfere in some way with the normal function of 5 HT, so as to cause or maintain, previously existing, schizophrenia.

10. Psychological mechanisms and environmental interrelationships which lead to loss of external perception and loss of reality contact may have an equally important role in the causation and/or maintainence of schizophrenia.

11. Heretical factors exist in schizophrenia.

12. LSD and mescaline are useful adjuncts in psychotherapy.

13. Continued extensive research is necessary toward answering the question "what is the schizophrenic?", describing not only in terms of psychological mechanisms, bbut in terms of biochemical and physiological pathology.

14, Standardization of descriptive terms is necessary in psychiatric research to adequately classify objective and, particularly, subjective feelings and findings. Indices for evaluating drugs in both man and animal with

reference to this must be developed.

SUMMARY

Following the introduction, the definition and description of schizophrenia as it now is understood is given. A review of the literature as pertains to the schizophrenic-mimicking drugs then follows, into which is incorporated the description, history, man and animal experiments, and theories and conclusions for each drug. A short passage on research methods is next, followed by the writer's conclusions. An extensive bibliography accompanies the thesis.

BIBLIOGRAPHY

1. Abramson, H., Lysergic Acid Diethylamide (LSD-25): 1. Physiological and perceptual responses, J. Psychol. 39:3, 1955 (Neurol., Biochem., & Pharmacol., Excerpta Medica 8: 666, 1955).

2. Adams, Roger, Marihuana, Harvey Lecture Series 37: 168, 1941.

3. Agnew, N. and Hoffer, A., Nicotinic acid modified lysergic acid diethylamide psychosis, J. Ment. Sc. 101: 12, 1955.

4. Altschule, Mark, D., Bodily Physiology in Mental and Emotional Disorder, N. Y., Grune and Stratton, Inc., 1953 (cited Hoagland, et al, 1955).

5. Altschule, M. D. and Parkhurst, B. H., Effect of treatment on excretion of 17-ketosteriods in patients with mental disease, A. M. A. Arch. Neurol. & Psychiat. 64: 516, 1950.

6. Altschule, M. D., Remarks, Proceedings 1st Clinical ACTH Conference, Phila., Blakiston, 1950, p. 553.

7. Amin, A. H., Crawford, T. B. and Gaddum, J. H., The distribution of substance P and 5-hydroxytryptamine in the central nervous system of the dog, J. Physiol. 126: 596, 1954.

8. Ashby, W., Carbonic anhydrase as a factor in the organization of the central nervous system, J. Nerv. & Ment. Dis. 114: 391, 1951.

9. Astrup, P., Gotsche, F. and Ibsen, B., and Munkvad, I., Investigation into glutamic acid metabolism in schizophrenics, J. Ment. Sc. 101: 366, 1955.

10. Bacq, Z. M., (title unknown), J. Pharmacol. & Exp. Therap. 95: 1, 1949 (cited Rinkel 1952).

11. Bacq, Z. M., The metabolism of adrenalin, Pharm. Rev. 1:1, 1949.

12. Baruk, H., Psychiatrie, Medicale, Physiologique et Experimental, Masson et Cie., Paris (VI) 1938 (cited Rinkel, et al, 1952, p. 572).

13. Bellak, Leopold, Toward a unified concept of schizophrenia: an elaboration of the multifactor psychosomatic theory of schizophrenia, J. Nerv. & Ment.

Dis. 121: 60, 1955.

14. Bexton, W. H. and others, Effects of decreased variation in the sensory environment, Canad. J. Psychol. 8: 70, 1954 (cited Callaway 1955).

15. Beyer, K. H., The enzymic inactivation of substituted phenyl-propyl (sympathomimetic) amines, J. Pharmacol. & Exp. Therap. 71: 151, 1942.

16. Beyer, K. H. and Lee, V. W., The fate of certain sympathomimetic amines in the body, J. Pharmacol. & Exp. Therap. 74: 155, 1942.

17. Blaschko, H., (title unknown), Nature 145: 26, 1940 (cited Hoffer, et al, 1955).

18. Bleuler, Eugen, Dementia praecox or the group of schizophrenias, N. Y., Internat. Univ. Press, trans. by Zinkin, J., 1950 (cited Bleuler, M. 1931 and Fabing 1955).

19. Bleuler, Manfred, Schizophrenia, A. M. A. Arch. Neurol. & Psychiat. 26: 610, 1931.

20. Block, W., Block, K., and Patsig, B., Zur physiologie des 14C--radioaktivin mescaline im tierversuch, Hoppe-Seyler's Ztschr. f. physiolog. chem. 290: 160-168, 1952; 290: 230-236, 1952; 291: 119-128, 1952 (cited Rinkel 1955).

21. Block, W., In-vitro-versuche zum einbau von 14C--mescalin and 14C beta-phenyl-athylamin in proteine, Hoppe-Seyler's Ztsche. f. physiolog. chem. 294: 1-12, 1953; 295: 49-56, 1954; 296: 1-10, 1954; 296: 108-121, 1954 (cited Rinkel 1955).

22. Bracco, M. and Curti, P. C., The vasoconstrictor factor of platelets, Experientia 10: 71, 1954(extract Exceprta Medica, Physiol., Biochem. & Pharmacol. 8: 86, 1955).

23. Bradley, P. B. and Elkes, J., Effect of amphetamine and LSD-25 on electrical activity of the brain of the unconscious cat, J. Physiol. 120: 13p, 1953.

24. Bullough, W. S., Stress and epidermal mitotic activity, J. Endocrinol, 8: 265, 1952.

25. Burn, J. H., The enzyme at sympathetic nerve endings, Brit. M. J. 1: 784, 1952.

26. Callaway, Enoch, III. On the production of hallucinated and psychosis-like states, Ann. Int. M. 42: 721, 1955.

27. Condrau, G., Klinische erfahrungen an glisteskranken mit lysergaue-diathylamid, Acta. psychiat. et neurol 24: 9, 1949 (extract Excerpta Medica, Neurol. & Psychiat. 3.2: 549, 1950).

28. DeJong, H., Uber meskalin-katatonie and die experimentalle erzeugung von dementia praecox erscheinungen, Koninklyke Akademie Van Weten Schappen Te Amsterdam, Prodeedings 33: 1076, 1930 (cited Rinkel, et al, 1955).

29. DeJong, H., Die experimentelle katatonie als vielfach vorkommende reaktionsform des zentral nervensystems (Experimental catatonia, as a frequent reaction type of the central nervous system), Ztschr. ges. Neurol. & Psychiat. 139: 468, 1932 (cited Rinkel 1952 p. 572).

30. DeJong, H., and Baruk, H., La catonie experimentale par la bulbocapnine, Paris, Masson et Cie, 1930 (cited Rinkel 1952, p. 572).

31. DeJong, H., Experimental Catatonia, Baltimore, The Williams and Wilkins Co., 1945 (cited Callaway 1955).

32. Denber, H. C. and Merlis, S., Studies on mescaline-1. Action in schizophrenic patients: Clinical observations and brain wave patte ns, showing effects before and after electric convulsive treatment, Psychiat. Q. 29: 421, 1955.

33. Denber, H. C., Studies on mescaline-III. Action in epileptics: Clinical observations and effects on brain wave patterns, Psychiat. Q. 29: 433, 1955.

34. Denber, H. C., Discussional remarks on etiology of schizophrenia, Am. J. Psychiat. 111: 894, 1955.

35. Deshon, H. J., Rinkel, M., and Solomon, H. C., Mental achanges experimentally produced by L.S.D.(d-lysergic acid diethylamide tartrate), Psychiat. Q. 26: 33, 1952.

36. Eade, N. and Hutcheon, D. E., Personal communication to Rinkel 1952 (cited Rinkel, et al, 1955).

37. Elkes, J., Elkes, C. and Bradley, P. B., The effect of some drugs on the electrical activity of the brain, and on behavior, J. Ment. Sc. 100: 125, 1954.

38. Erspamer, V., Pharmacological studies on enteramine (5-hydroxytryptamine) IX. Influence of sympathomimetic and sympatholytic drugs on physiological and pharmacological actions of enteramine, Arch. Internat. Pharmacodyn. et Ther. 93: 293, 1953 (extract Excerpta Medica, Physiol., Biochem. & Pharmacol. 7: 588, 1954).

39. Erspamer, V., Pharmacology of indolealkylamines, Pharmacol. Rev. 6: 425, 1954.

40. Evarts, E., Psychopathological effects of drugs, Symposium of Medicinal Chemistry, Syracuse Univ., June 1954, p. 145.

41. Evarts, E. V., Landau, W., et al, Some effects of LSD and bufotenine on electrical activity in cats visual system, Am. J. Physiol. 182: 594, 1955.

42. Fabing, H. D., The dimensions of neurology, Neurology 5: 603, 1955.

43. Fabing, H. D., New blocking agent aginst the development of LSD-25 psychosis, Science 121: 208, 1955.

44. Fabing, H. D., Frenquel, a blocking agent against LSD-25 and mescaline psychosis, and a preliminary note on its clinical application, Neurology, 5: 319, 1955 (cited Fabing, Neurology 5: 603, 1955).

45. Feldberg, W. and Sherwood, S. L., Injections of drugs into the late al ventricle of the cat, J. Physiol. 123: 148, 1954.

46. Fischer, Roland, Factors involved in drug produced model psychoses, J. Ment. Sc. 100: 623, 1954.

47. Forrer, G. R.& Goldner, R. D., Experimental physiological studies with lysergic acid diethylamide (LSD-25), A. M. A. Arch. Neurol. & Psychiat. 65: 581, 1951.

48. Frederking, Walter, Intoxicant drugs (mescaline and lysergic acid diethylamide) in psychotherapy, J. Nerv. & Ment. Dis. 121: 262, 1955.

49. Funkenstein, D. H. and others, Psychophysiologic study of mentally ill patients. Part 1. The status of the peripheral autonomic nervous system as determined by reaction to epinephrine and mecholyl, Am. J. Psychiat. 106: 16, 1949.

50. Funkenstein, D. H., Greenblatt, M. and Solomon, H. C., Nor-epinephrine-like andepinephrine-like sub-

stances in psychotic and psychoneurotic patients, Am. J. Psychiat. 108: 652, 1952.

51. Funkenstein, ibid, Autonomic changes paralleling psychologic changes in mentally ill patients, J. Nerv. & Ment. Dis. 114: 1, 1951.

52. Funkenstein, D. H., King, S. H. and Dnolette, M., The experimental evaluation of stress, Symposium on Stress, National Research Council and Army Medical Service, Graduate School, Walter Reed Army Medical Center, Washington, D. C. 1953, p. 303-322.

53. Funkenstein, D. H. and Mead, L. W., Nor-epinephrine like and epinephrine like substances and the elevation of blood pressure during acute stress, J. Nerv. & Ment. Dis. 119: 380, 1954.

54. Gaddum, J. H., Antagonism between LSD-25 and 5-hydroxytryptamine, J. Physiol. 121: 15p, 1953.

55. Gaddum, J. H. and Hameed, K. A., Drugs which antagonize 5-hydroxytryptamine, Brit. J. Pharmacol. 9: 240, 1954.

56. Gaddum, J. H. and others, Quantitative studies of antagonists for 5-hydroxytryptamine, Q. J. Exp. Physiol. 40: 49, 1955.

57. Gaddum, J. H., Hebb, C. O., Silver, A., Swan, A. A., 5-Hydroxytryptamine. Pharmacological action and destruction in perfused lungs, Q. J. Exp. Physiol. 38: 255, 1953.

58. Gestaut, H., Ferrer, S. and Castells, C., Action de la diethylamide de l'acide d-lysergique (LSD-25) Sur les fonctions psychiques at l'electroencephalogramme, Confinia neurol. 13: 102, 1953 (extract Excerpta Medica, Neurol. & Psychiat. 711: 363, 1954).

59. Gildea, E. F., Discussion, Proceedings of the 1st Clinical ACTH Conference, Phila., Blakiston Co., 1950, p. 553.

60. Gildea, E. F., et al, Results from the use of ACTH and cortisone in psychosis, The Biology of Mental Health and Disease, The 27th Clinical Conference of the Milbank Memorial Fund, N. Y., Paul B. Hoeber, Inc., Harper, 1952, p. 600-613.

61. Graham, J. D. P. and Alaa iddeen, Khalida, The actions of d-lysergic acid diethylamide (LSD-25), J. Faculty of Medicine, Baghdad, Iraq 18:1, 1954 (cited Rinkel 1955).

62. Green, D. E. and Richter, D., Adrenaline and adrenochrome, Biochem. J. 31: 596, 1937.

63. Green, Joseph B., Biological aspect of schizophrenia, J. Stud. A. M. A. 8: 19, 1955.

64. Guttman, E. and Maclay, W. S., Mescaline and depersonalization, J. Neurol. & Psychopath. 16: 193, 1935.

65. Haefer, F. A. and Glaser, H. G., Electroencephalographic and neuropsychiatric changes in patients treated with ACTH, Proceedings of the 1st Clinical ACTH Conference, Phila., Blakiston Co., 1950, p. 536-544.

66. Hamlin, K. E. and Fischer, F. E., The synthesis of 5-hydroxytryptamine, J. Am. Chem. Soc. 73: 5007, 1951 (cited by No. 174).

67. Heirman, P., L'adrenoxine, adrenaline oxydie inhibitrice, Compt. rend. soc. de biol. 126: 1264, 1937 (cited Rinkel 1955).

68. Henneman, D. H., Altschule, M. D., Goncz, R. M., and Davis, P., Carbohydrate metabolism in brain disease. V. Effect of epinephrine on intermediary carbohydrate metabolism in schizophrenic and manic depressive psychoses, A. M. A. Arch. Int. M. 95: 594, 1955.

69. Henning, J., The Witnesses, London, 1938 (cited Osmond, et al, 1952).

70. Hey, P., The synthesis of a new homologue of mescaline, Q. J. Pharmacol. 20: 129, 1947.

71. Himwich, H. E., Effect of shock therapies upon the brain, The biology of Mental Health and Disease, The 27th Clinical Conference of the Milbank Memorial Fund, N. Y., Paul B. Hoeber, Inc., Harper, 1952, p. 548-559.

72. Hoagland, H., Metabolic and physiologic disturbances in the psychoses, The Biology of Mental Health and Disease, The 27th Clinical Conference of the Milbank Memorial Fund, N. Y., Paul B. Hoeber, Inc., Harper, 1952, p. 434-447.

73. Hoagland, H., et al, Adrenal cortical responsivity of psychotic patients in relation to electroshock treatments, Psychosom. Med. 12: 73, 1950.

74. Hoagland, H. and Pincus, G., Pituitary-Adrenocortical function in patients with severe personality disorders, Proceedings of the 1st Clinical ACTH Conferen Phila., Blakiston Co., 1950, p. 544.

75. Hoagland, H., et al, Study of adrenocortical physiology in normal and schizophrenic men, A. M. A. Arch. Neurol. & Psychiat. 69: 470, 1953.

76. Hoagland, H., Rinkel, M., Hyde, R. W., Adrenocortical function and urinary phosphate excretion, A. M. A. Arch. Neurol. & Psychiat. 73: 100, 1955.

77. Hoch, P. H., Experimentally produced psychoses, Am. J. Psychiat. 107: 607, 1951.

78. Hoch, P. H., Experimental induction ofpsychoses, The Biology of Mental Health and Disease, The 27th Clinical Conference of the Milbank Memorial Fund, N. Y., Paul B. Hoeber, Inc., Harper, 1952, p. 539-546.

79. Hoch, P. H., Editorial comments on experimental psychiatry, Am. J. Psychiat. 111: 787, 1955.

80. Hoch, P. H., Cattell, J. P. and Pennes, H. H., Effects of mescaline and lysergic acid (d-LSD-25), Am. J. Psychiat. 108: 579, 1952.

81. Hoch, P. H., Cattell, J. P. and Pennes, H. H., Effects of drugs, Am. J. Psychiat. 108: 585, 1952.

82. Hoff, H. and Arnold, O. H., Die therapie der schizophrenic, Wien. Klin. Wshr. 66: 345, 1954 (cited Fabing 1955).

83. Hoffer, A., Effect of atropine on blood pressure of patients with mental and emotional disease, A. M. A. Arch. Neurol. & Psychiat. 71: 80, 1954.

84. Hoffer, A., Osmond, H. and Smythies, J., Schizophrenia, a new approach, II. Results of a years research, J. Ment. Sc. 100: 29, 1954.

85. Hoskins, R. G., Biology of Schizophrenia, 1st Ed., N. Y., W. W. Norton & Co., 1946, p. 1-173.

86. Hutcheon, D. E., Personal communication to Lea (cited Lea 1955).

87. Huxley, Aldous, The doors of perception, N. Y., Harper & Bros., 1954 (cited in 1955 Fabing).

88. Hyde, R. W., Von Mering, O. and Morimoto, K., Hostility in the lysergic psychosis, J. Nerv. & Ment. Dis. 118: 266, 1953.

89. Isbell, H., et al, Tolerance to diethylamide of lysergic acid (LSD-25), Fed. Proc. 14: 354, 1955.

90. Jantz, H. M., (title unknown), Z. ges. Neurol. Psychiat. 171: 28, 1941 (cited Mayer-Gross 1951).

91. Jung, C. G., Psychology of dementia praecox, trans. A. A. Brill, monograph Nerv. & Ment. Dis., N. Y., 1936, p. 32, 62, 88-89.

92. Kallman, F. J., The genetic aspects of psychoses, The Biology of Mental Health and Disease, The 27th Annual Conference of the Milbank Memorial Fund, N. Y., Paul B. Hoeber, Inc. Harper, 1952, p. 283-298.

93. Kraeplin, E., (title unknown), Philos. Studier. 1: 573, 1883 (cited Mayer-Gross 1951).

94. Kraeplin, E., (title unknown), Psychol. Arb. 8: 181, 1925 (cited Mayer-Gross 1951).

95. Kraeplin, E., Dementia Praecox, Clinical Psychiatry, William Wood & Co., N. Y. C., 1917, p. 1-10.

96. Laborit, H. and Benitte, A., Potenzierte narkose and kunstlicher winter-schlaf, Arch. Exp. Path. Pharmok. 222: 20, 1954 (extract Excerpta Medica, Physiol., Biochem. & Pharmacol. 8: 497, 1955).

97. Lansbury, John and Rogers, F. B., The hydralazine syndrome, Bulletin on Rheumatic Disease 5: 85, 1955.

98. Lea, A. J., Adrenochrome as the cause of schizophrenia. Investigation of some deductions for this hypothesis, J. Ment. Sc. 101: 538, 1955.

99. Lewis, J. L. and McIlwain, H., The action of some ergot derivatives, mescaline, and dibenamine on the metabolism of separated mammalian cerebral tissues, Biochem. J. 57: 680, 1954.

100. Liddell, D. W. and Weil-Malherbe, H., The effects of methedrine and of LSD-25 on mental processes and on blood adrenalin level, J. Neurol., Neurosurg. & Psychiat. 16: 7, 1953.

101. Lindemann, E., Psychopathological effect of drugs affecting the vegetative nervous system: 1. Adrenalin, Am. J. Psychiat. 91: 983, 1935.

102. Lucy, J. D., Histamine tolerance in schizophrenia, A. M. A. Arch. Neurol. & Psychiat. 71: 629, 1954.

103. Malamud, William, Hypophyseal-adrenocortical dysfunction in Mental disease, The Biology of Mental Health & Disease, The 27th Clinical Conference of the Milbank Memorial Fund, N. Y., Paul B. Hoeber, Inc., Harper, 1952, p. 613-617.

104. Mann, P. J.& Quastel, J. H., Benzedrine (beta-phenylisopropylamine) and brain metabolism, Biochem. J. 34: 414, 1940.

105. Marrazzi, A. S. and Hart, E., Relationship of Hallucinogens to adrenergic cerbral neurohumors, Science 121: 365, 1955.

106. Martin, G. J., Biological antagonism, Phila., Blakiston, 1951, pp. 37-38, 140, 171-179.

107. Martin, G. J., Ichniowski, C. T., Wisansky, W. A. and Ansbacher, S., Oxidases, Pressor amines and hypertension, Am. J. Physiol. 136: 66, 1942.

108. Mayer-Gross W., McAdams, W.& Walker, J. W., Psychological and biochemical effects of LSD, Nature 168: 827, 1951.

109. Mayer-Gross, W., et al, Lysergsaure-diathylamid und kohlenezdrats toff-wuchsel, Nervenarzt 23: 30, 1952 (cited Rinkel 1955).

110. Mayer-Gross, W., Experimental psychoses and other mental abnormalities produced by drugs, Brit. M. J. 2: 317, 1951.

111. Mayer-Gross, W., et al, Further observations on effects of LSD, J. Ment. Sc. 99: 804, 1953.

112. McAuley, W. F., Concept of schizophrenia, N. Y., Philosophical Library Publ., 1954 (cited Fabing 1955).

113. Merlis, S., Studies on mescaline II. Electroencephalogram in schizophrenics: Effects of administration after electric convulsive treatment of schizophrenic patients, Psychiat. Q. 29: 430, 1955.

114. Meyerhof, O. and Randall, L. O., The inhibitory effects of adrenochrome on cell metabolism, Arch. Biochem 17: 171, 1948.

115. Mitchell, S., Remarks on the effects of anhalonium Lewinii (The Mescal Button), Brit. M. J. 2: 1625, 1896.

116. Moser, M., Syner, J., et al, Acute psychosis as a complication of hydralazine therapy in essential hypertension, J.A. M. A. 152: 1329, 1953.

117. Nieuwenhuysen, F. J., Chronic experimental catatonia produced by intermediate products of metabolism, Proc. Roy. Acad. Amsterdam 39: 1151, 1936 (cited Fabing 1955).

118. Orstrom, Ake, Isolation of phosphoglycolic acid from human erythrocytes, Arch. Biochem. 33: 484, 1951.

119. Orzechowski, G., (title unknown), Arch. exper. Path. u. Pharmakol. 198: 27, 1941 (cited Woolley, et al, 1954 No. 168).

120. Osmond, Humphrey, Ololiuqui: The ancient Aztec narcotic, J. Ment. Sc. 101: 526, 1955.

121. Osmond, H., Inspiration and methodin schizophrenia research, Dis. Nerv. Syst. 16: 101, 1955.

122. Osmond, H. and Smythies, J., Schizophrenia: A new approach, J. Ment. Sc. 98: 309, 1952.

123. Page, I. H., Serotonin (5-hydroxytryptamine), Physiol. Rev. 34: 563, 1954.

124. Page, I. H., and McCubbine, J. W., The variable arterial pressure response to serotonin in laboratory animals and man, Circulation Res. 1: 354, 1953.

125. Patzig, B. and Block W., Zur auffassung des schizophrenen prozessgeschehens nach tierversuchen mit 14 C radioaktivem meskalin, die naturwissenschaften, 1: 13-17, 1953 (cited Rinkel 1955).

126. Pennes, H. H., Clinical reactions of schizophrenics to sodium amytal, perviting hydrochloride, mescaline, sulfate, and d-lysergic acid diethylamide (LSD-25), J. Nerv. & Ment. Dis. 119: 95, 1954.

127. Peretz, D. J., Smythies, J. K. andGibson, W. C., A new hallucinogen : 3,4,5,-trimethoxyphenyl-beta-aminopropane with notes on the stroboscopic phenomena, (TMA), J. Ment. Sc. 101: 317, 1955.

128. Peters, F., Pharmacologische untersuchungen uber corydalisalkaloide (Pharmacological investigation of corydalisalkaloids), Arch. f. Exper. Patholog. 51: 130, 1904 (cited Rinkel 1952, p. 572.)

129. Pincus, G., Hoagland, H., Adrenal cortical responses to stress in normal men and in those with personality disorders. Part 1-Some stress responses in normal and psychotic subjects, Am. J. Psychiat. 106: 641, 1950.

130. Pincus, G., Hoagland, H., Freeman, H., et al, A study of pituitary-adrenocortical function in normal and psychotic men, Psychosom. Med. 11: 74, 1949.

131. Pletscher, Alfred, Shore, Parkhursta and Brodie, Bernard, Serotonin release as a possible mechanism of reserpine action, Science 122: 374, 1955 and 284, 1955.

132. Pope, A., Coenzymaatic changes in mental disease, The Biology of Mental Health and Disease, The 27th Clinical conference of the Milbank Memorial Fund, N. Y., Paul B. Hoeber, Inc., Harper, 1952, p. 457-466.

133. Purpura, D. P., Electrophysiological analysis of psychotogenic drug action. I. & II., A. M. A. Arch. Neurol., & Psychiat. 75: 122, 1956.

134. Quastel, J. H. and Wheatley, A. H. M., The effects of amines on oxidations of the brain, Biochem. J. 27: 1609, 1933.

135. Reid, G. and Rand, M., Pharmacological actions of synthetic 5-hydroxytryptamine(Serotonin, thrombocytine, Nature 169: 801, 1952.

136. Rinkel, M., et al, Experimental schizophrenic-like symptoms, Am. J. Psychiat. 108, 572, 1952.

137. Rinkel, M., Hyde, R. W. andSolomon, H. C., Experimental psychiatry. III. A chemical concept of psychosis, Dis. Nerv. Syst. 15: 259, 1954.

138. Rinkel, M., Hyde, Robert W., Solomon, H. C., and Hoagland, Hudson, Experimental psychiatry II. Clinical and physiochemical observations in experimental psychosis, Am J. Psychiat. 111: 8881, 1955.

139. Rinkel, M., Hyde, R. W. & Solomon, H. C., Experimental psychiatry. IV. Hallucinogens: tools in experimental psychiatry, Dis. Nerv. Syst. 16: 229, 1955.

140. Rome, H. P. and Braceland, F. J., The psychological response to ACTH, cortisone, hydrocortisone, and related steriod substances, Am. J. Psychiat. 108: 641, 1951.

141. Safford, W. E., (title unknown), J. Wash. Acad. Sc. 6: 547, 1916 (cited Evarts 1955).

142. Salomon, Kurt, Gabrio, B. W. and Thale, Thomas, A study on mescaline in human subjects, J. Pharmacol. and Exper. Therap. 95: 455, 1949.

143. Sandison, R. A., Psychological aspects of the LSD treatment of the neuroses, J. Ment. Sc. 100: 508, 1954.

144. Sandsion, R. A., Spencer, A. M. and Whitelaw, J. D., The therapeutic value of lysergic acid diethylamide in mental illness, J. Ment. Sc. 100: 491, 1954.

145. Savage, C., Lysergic acid diethylamide (LSD-25), Am. J. Psychiat. 108: 896, 1952.

146. Savage, C., Variations in ego feeling induced by d-lysergic acid diethylamide (LSD-25), Psychoanal. Rev. 42: 1, 1955.

147. Schmid, R., Schwartz, S., and Watson, C. J., Porphyrin content of bone marrow and liver in various forms of porphyria, A. M. A. Arch. Int. M. 93: 167, 1954.

148. Schueler, F. W., The effect of succinate in mescaline hallucination, J. Lab. & Clinic. Med. 33: 1297, 1948.

149. Schultes, R. E., A contribution to our knowledge of Rivea Coryribosa, Botanical Museum of Harvard Univ., 1941 (cited Osmond 1955).

150. Schwarz, B. E., Bickford, R. G. and Rome, H. D., Reversibility of induced psychosis with chlorpromazine, Proc. Mayo. Clin. 30: 407, 1955.

151. Schwarz, B. E., Wakim, K. G., Bickford, R. B. and Lichtenheld, R. R., Behavorial and electroencephalographic effects of hallucinogenic drugs, A. M. A. Arch. Neurol. & Psychiat. 75: 83, 1956.

152. Shattock, F. M., Somatic Manifestations of schizophenia, J. Ment Sc. 96: 32, 1950.

153. Shaw, E. and Woolley, D. W., Yohimbine and ergot alkaloids as naturally occurring anti-metabolites of serotonin, J. Biol. Chem. 203: 979,1953.

154. Shore, P. A., Silver, S. L. and Brodie, B. B., Interaction of reserpine, serotonin and lysergic acid diethylamide in the brain, Science 122: 284, 1955.

155. Slater, I. M., et al, The action of serotonin and lysergic acid diethylamide on spinal reflexes, Pharmacol. & Exper. Therap. 113: 48, 1955.

156. Sloan, B. and Doust, J. W. L., Psycho-physiological investigations in experimental psychoses: Results of the inhibition of e-lysergic acid diethylamide to psychiatric patients, J. Ment. Sc. 100: 129, 1954.

157. Stockings, G. T., A clinical study of the mescaline psychosis with special reference to the mechanism of the genesis of schizophrenia and other psychotic states, J. Ment. Sc. 86: 29, 1940.

158. Stoll, W. A., Lysergsaure-diathylamid, ein phantastikum aus der mutterkorngruppe, Schweiz. Archiv. f. Neurol. & Psychiat. 60: 279, 1947 (cited by Forrer 1951).

159. Stoll, W. A., (title unknown), Schweiz. med. Wchnsches. 79: 110, 1949 (cited by Forrer 1951 and Rinkel 1955).

160. Stromberg, V. L., The isolationof bufotenine from piptadenia peregraina, J. Am. Chem. Soc. 76: 1707, 1954.

161. Sullivan, M., Indolethylamine in urine of pellagrine, J. Biol. Chem. 50: xxxix, 1922.

162. Szatmari, A., Hoffer, A., and Schneider, R., The effect of adrenochrome and macin on the elctroencephalogram of epileptics, Am. J. Psychiat. 11: 603, 1955.

163. Taylor, R. D., Page, I. H., and Corcoran, A. C., A hormonal neurogenic vasopressor mechanism, A. M. A. Arch. Int. M. 88: 1, 1951.

164. Watson, C. J., Porphyria, Advance, Int. M. 6: 235, 1954.

165. Witt, P. N., d-Lysergsaure-diathylamid (LSD-25) im spinnentest, Experientia 7: 310, 1951 (extract Excerpta Medica, Physiol., Biochem. & Pharmacol. 5.1: 1749, 1952).

166. Woodford, V., Personal communication to Hoffer, (cited Hoffer 1952).

167. Woolley, D. W. and Shaw, E., A biochemical and pharmacological suggestion about certain mental disorders, Proc. Nat. Acad. Sc. 40: 228, 1954.

168. Woolley, D. W. and Shaw, E., Some neurophysiological aspects of serotonin, Brit. M. J. 2: 122, 1954.

169. Yerkes, R. M. and Dodson, J. D., The relation of strength of stimulus to rapidity of habit formation, J. Comp. Neurol. 18: 459, 1908.

170. Diagnostic Nomenclature and Definitions of Mental Disorders, Nebraska Psychiatric Unit, 1952.

171. AAAS, Reports of Sections and Societies, Berkley Meeting, Science 121: 262, 1955.

172. May Cure Mental Disease, Science News Letters 67: 179, 1955 (cited Altschule, et al 1950).

173. Physiology and Pharmacology of Emotion, Scope 4: 1, 1955.

174. Chemical Concept of Psychoses, Whats New, No. 189, 1955.