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Etiology of schizophrenia

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ETIOLOGY OF SCHIZOPHRENIA

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INTRODUCTION

Every year, in practically every country of the world, the burden of caring for the mentally ill increases. Schizophrenia or dementia praecox is the most vicious offender in causing increase in the population of our mental hospitals year after year. In 1922 the Federal Census (52) showed that there were 15,526 first admissions of patients suffering from dementia praecox to mental hospitals in the United States, 8,950 of these were males and 6,576 females. This represented, in 1922, a first admission rate of 16.7 males and 12.8 females per 100,000 population. In 1924, Alford (1) estimated that half of the inmates of state asylums suffered from dementia praecox, an estimated economic loss for the nation of 124 million dollars. Because of the relatively early onset of schizophrenia, the economic stress is increased, for it takes away the capacity of relatively young individuals to earn their own livelihood. Only two other psychotic conditions have an average earlier onset than dementia praecox. The average age of onset of psychoses with psychopathis personality is 31.2 years and in psychoses with mental deficiency 31.7 years. Schizophrenia is next with an average age onset of 32.2 years.

The need for intensive study of the schizophrenia problem at once becomes apparent. Research in this branch of psychiatry has not been lacking. Many investigations have been undertaken and many observations have been recorded, many of which are contradictory. This is not altogether the fault of the various

investigators. Even yet there is considerable doubt as just to what constitutes schizophrenia.

Kraepelin's conception was that dementia praecox was a progressive dementing condition which was not recoverable and that any psychotic condition which resembled schizophrenia was not if recovery took place. At the present many psychiatrists classify all psychoses which resemble the schizophrenic reaction type as schizophrenia whether they recover or not. Kamman (27) suggests that the schizophrenic psychoses terminating in a dementing process be classified as "dementia praecox" and the recoverable cases as "schizophrenic reactions".

Progress in the study of genetic factors has been difficult because of the long length of time needed for the development of a new generation. Family histories are often times not accurate because people are ashamed of having insanity in their family and sometimes deny it when it exists. Man is the most perfectly crossbred animal, which further complicates Mendelian studies.

Considerable investigation on the endocrine system of dementia praecox patients as well as blood studies and histopathological studies of the brain, to mention only a few, has been done. However, it does not seem that these have been adequately controlled by comparisons on normal humans of the same age and approximate physical status, and therefore, perhaps many

of the variations noted are not beyond those of normal individuals.

However, we see in the more recent literature observations which have been quite adequately controlled, so that results obtained are of more value than those of years past.

Alford (1) believes that "after the nature of dementia praecox has been elucidated, manic-depressive, the next most frequent psychosis, and others of this group will long remain obscure".

It must be admitted that at the present therapeutic attempts in the treatment of schizophrenia, on the whole, have been rather unsuccessful. It is not likely that a satisfactory method of treatment will be developed until more is known of the etiology.

It is not the purpose of this paper to decide the cause of schizophrenia, but only to review a small portion of the literature to show what the trends in research have been and some of the results and conclusions which have been drawn from them.

HISTORY

The history of dementia praecox is almost the history of psychiatry (18). This condition was first described in 1674 by Willis (De Anima Brutorum), who recognized a progressive descent into hebetude dating from adolescence. Pinel described similar cases and called them "idiotism". Esquirol used the term "accidental or acquired idiocy" (Des Maladies Mentales). Later idiocy became limited to early and congenital defects while dementia became limited to acquired deteriorations. These non-organic deteriorations began to be divided into partial and total insanities, into which were incorporated mania, melancholia, and confusion.

About the middle of the nineteenth century Morel first used the term "Demence Precoce", and described it as a "stupidite", making his concept the picture of familial degeneracy.

Later the term "vesania" or total insanity was used by Sauvages and Cullen. Under this heading were included melancholia, mania, confusion or paranoia and dementia, to which was later added neurasthenia as a prodromal sympton, the term being used as descriptive of a fatigue syndrome.

At this time there appeared, described by Magnan, "Delire Chronique a Evolution Systematique", the equivalent of a paranoid type of dementia praecox in which degeneration was not marked.

Meantime in Austria and Germany there was a sorting out whereby the affective psychoses, the manias and melancholias were separated as recoverable from a group, the prognosis of which was less clear.

Morel, in his formulation of the "demence precoce" entity had in mind unity of cause, course and outcome in cases of this disease; and in 1863 Kahlbaum made a considerable advance along these lines. He attempted a much more complete attitude to the patient, in which there was both comprehensiveness and comprehension. In his conception the general clinical findings of whatever kind were given equal value with the psychic symptoms and it is here that we find the first frank and declared attempt to regard the patient's illness as a dysfunction of a psycho-biological unit, that is to say, a disorder of the entire organism. He described four groups of disorder.

1. Vesania, equivalent to dementia praecox, but including in it a progress of the type already mentioned.
2. Vercordias (wrong-heartedness), the affective psychoses of the manic-depressive type.
3. The dysphrenias, equal to our toxic exhaustive reactions.
4. The paraphrenias, psychoses determined

by age: neophrenia, in infancy; hebephrenia, in youth; presbyophrenia, in old age.

Hecker described as hebephrenia one of Kahlbaum's paraphrenias, the age-bound disorder. At about the same time Kahlbaum described katatonia as a vesania similar to paresis with motor symptoms. In this way the grouping he had set up became less firm.

Thereafter, for some time Kahlbaum was lost sight of in what Meyer calls a "paranoification of psychiatry" by Westphal, Krafft-Ebing and Schule, during which paranoias of various types came to occupy the place of dementia praecox. This was in response to a psychology of emotion which tended to create a separation between affective and intellectual disorder. The manic-depressive group was in the affective series, and under the paranoias were included part of the older vesanias with paranoia as a primary state. At the same time in America, Spitzka, Hammond and Pick began to describe a progressive primary dementia.

In 1893 Kraepelin described dementia praecox as synonymous with the hebephrenia of Hecker and also included katatonia and dementia paranoides, and in a review of Zieman's work, which was full of a series of paranoias, he grouped all primary and secondary dementias in a progressive, deteriorative dementing process, thus dementia praecox made its debut at the hands of Kraepelin in 1898. Kraepelin's work still dominates the thought of European psychiatrists.

In 1896 Meyer developed a general analytic-synthetic principle which gradually expanded into "a conception of dementia praecox as depending on a special personality and constitution, on habit disorganization; leaving the internal working and development of the functional and structural defect as possibly incidental, still to be worked out. Meyer's work has had considerable influence on American psychiatry.

In 1907 Jung developed the determination of symptoms by complexes and hinted at special personality types. Also in 1907 Bleuler looked to a disease process, generalized as a toxemia or localized as a gliosis, causing associative disorders, but later he abandoned this narrow view and stated, "The term schizoid designates a type of mental nature and reaction which is more or less present in everybody and in its morbid exaggerations constitutes schizophrenia."

Stransky developed the conception of an "intrapsychic ataxia" as an explanation of affective dysharmony. In 1914 Berze suggested a primary insuffiency of mental activity--a constitutional defect.

Kempf in 1920 introduced a classification based on the etiological process, problems of repression and regression to more primitive thought processes and fixation. At the same time Kretschmer developed the constitutional factor and Kahn developed the hereditary to the point of postulating two inheritable factors,

first a predisposition to the disease and second, an actual degenerative process. Mott has done considerable work in trying to establish schizophrenia as a hereditary degeneration. His views are prevalent in English psychiatry.

Psychiatrists hold two basic concepts of the etiological factors in schizophrenia. One group believes that psychic stresses and strains are the chief causes and that the reactions of the individual in evading these situations or in making an attempt to meet them build up a mental pattern that we recognize as schizophrenia. These psychogenic factors are many in number and will be discussed later.

The other group of psychiatrists are of the opinion that organic changes within the nervous system, probably of the higher centers of mentation, are responsible for the abnormal mental processes seen in schizophrenia. Here, too, many structures of the body have been investigated both histologically and chemically in search for this basic lesion.

The present concepts of organic causes can be grouped into the following:

1. Hereditary defects or degenerations.

2. Toxic-infectious factors.

3. Endocrinopathies.

As in many phases of medicine there is much controversy, and psychiatry is no exception. Much illuminating research has

been done in schizophrenia, but also much work has been done and false conclusions drawn from inadequate study.

Many investigators have let their personal opinions reflect in their work, thus rendering their conclusions erroneous.

As was stated previously, it is not the purpose of this paper to decide the cause of schizophrenia but only to review a portion of the literature and to show what concepts are being held and which of these at the present seem to have the most support.

For clarity and ease of discussion the various etiological factors will be discussed separately, in so far as possible. However, when contrary evidence is at hand this will be correlated in the discussion.

THE PSYCHOGENIC CONCEPT

Psychogenic Factors:

In 1910 Adolph Meyer (45) made the following statement. "We are, I believe, justified in directing our attention to the factors which we see at work in the life history of the cases of so-called dementia praecox. We are justified in emphasizing the process of a crowding out of normal reactions, of a substitution of inferior reactions, some of which determine a cleavage along distinctly psychobiological lines incompatible with reintegration. Psychobiological analysis and reconstruction furnish us with the essential material, and progress is to be expected from a frank and unprejudiced weighing and use of this material, including its non-mental components rather than from the stereotyped lesion-pathology and the dogmatic nosological principles when they become intolerant."

Hoch (19) holds beliefs similar to those of Meyer. In his concept, physical causes may play a part in the precipitation of the psychoses, but mental causes are much more important.

In a study of 777 cases of insanity including all psychoses except imbecility, epilepsy, alcoholic psychoses, paresis, and certain organic conditions, Rosanoff (56) found that in 66.9 per cent of cases no cause could be found and that erroneous causes were present in 4.0 per cent. Insanity in 7.1 per cent was attributed to alcohol. In 2.6 per cent physical

causes as pregnancy, lactation, trauma, surgery and acute infectious disease seemed to be the exciting factor. Psychical stresses as business trouble, failure in love, and death of relatives were prominent in 16.6 per cent. Combined psychical and physical conditions were present in 2.8 per cent. From this he concludes that "the exciting causes of the forms of insanity here considered appear to be invariably of a psychical nature".

Strecker (69) compared the precipitating factors in 100 cases of manic-depressive psychosis with the precipitating factors in 100 cases of schizophrenia. In the manic-depressives, 32 patients showed serious and sometimes overwhelming prepsychotic mental and physical problems; 20 schizophrenics showed mental and physical problems. In the manic-depressive group mental and physical causes were doubtful in 37 cases and insignificant in 29. In the schizophrenics this was 44 and 24 respectively. He found the most difference in those groups of patients in which no exciting cause either mental or physical could be found. No causes could be illicited in only 2 cases of manic-depressive and neither of these were initial attacks. However, in the schizophrenic group no causitive factor could be found in 12 cases. Of the 32 cases of manic-depressive in which there were significant and important precipitating factors, organic disease was more emphatic than mental insult in 21 instances. This was also true for 17 of the 20 schizophrenic cases. In the doubtful

and insignificant groups there was a sharp decline in the significance and frequency of somatic factors. Of the manic-depressives in this group 26 were psychic and 11 somatic. In the schizophrenics 27 were psychic and 17 somatic. In the insignificant group of the manic-depressives 20 were psychic and 9 somatic and in the schizophrenics 17 were psychic and 7 somatic.

In summarizing these results we see that in 52 instances somatic and psychic influences were important in precipitation of the psychosis. In 81 cases these influences were doubtful and in 53 were insignificant. In 14 cases no cause could be found. In 107 cases there was a combination of psychic and organic factors, the former predominating in 65 and the latter in 42. In 40 cases the psychosis seemingly followed somatic disturbances alone and in 39 the pre-psychotic circumstances were solely psychic. In conclusion Strecker says, "the concrete situations in which the psychic element either stood alone or was emphasized were, of course, very numerous and represented all the difficulties and troubles which ordinarily fall to the lot of humanity. Thus we had to consider the mental effect of cruelty, poverty, marital infidelity, sexual assualt, illegitimate pregnancy, undue responsibility, illness and death of husband, parents, children, other relatives or friends, unhappy marriage, illicit sexual relations and pregnancy, financial reverses and failure in the struggle for success, love affairs, jealousy, self-induced

abortion, neglect, fright and fear precipitated by various agencies. Of the somatic factors influenza, overwork, the menopause, and complicated childbirth were most important. In this group taking into consideration the important, the doubtful and insignificant groups, psychic stresses were more prevalent than somatic conditions. Of these psychic stresses, cruelty, poverty, illness and death of relatives, and unhappy love affairs were the most frequent."

In a subsequent study of 25 cases of recoverable dementia praecox, Strecker and Willey (70) found that 14 patients or 66 per cent were subjected to life situations which were adequate to precipitate the psychosis.

Many authorities believe sexual maladjustments and abberations are largely responsible for precipitation of the schizophrenic psychosis. Hutchings, Cheney, and Wright (24) describe two types of precipitating causes. The first are sexual causes which are plain and definite as betrothal, marriage or other sexual experiences; the second type by occurrences which seem to act by arousing strong unconscious wishes or wishes which may have been repressed from conscious acceptance, as for example, a wish for incestuous relations with brother or the death of a husband or mother and that schizophrenia develops as an eccentric or malignant reaction of the personality to a threatened or actual appearance in the consciousness of a repressed and long

forgotten infantile incestuous attachment to the parent of the opposite sex, a mechanism which is recognized as the Oedipus Complex. The precipitating cause is the agent which brings to the surface the previously submerged cravings and the psychosis is the attempt of the individual to solve the conflict between these cravings and the standard adult life. Boltz (9) holds similar views and believes that a homosexual environment (as in the navy) or an advance by a homosexual offers gratification in a passive form to the unconscious or even suppressed homosexual impulses of the patient and thereby serves as the precipitating factor. Situations which refer to incest, castration or other elements of the Oedipus Complex seem to precipitate the psychosis less frequently. He cites many cases, one of which will be given briefly to illustrate the mechanism. A schizophrenic homosexual had a son. The father, being homosexual, had no affection for his wife. The wife, therefore, casts her affection upon her son who may be stimulated to incest. This precipitates the psychoses in the father and may cause a homosexual complex in the son so that he too will become schizophrenic.

Zilboorg (78) states that 50 per cent of post partum psychoses are schizophrenic. These usually appear in women who have reached the third decade of life. They show schizoid characteristics and appear to have carried over into adult life anal libidinous attitudes and to have never reached the so-called

vaginal stage of development. They seem to have arrested their growth on what Freud terms the phallic stage, hence they are all masturbators and sexually frigid and potentially homosexual. Their unconscious clinging to the Oedipus Complex is intimately interwoven with the unconscious desire to belong to the male rather than the female species, hence they appear in part to identify themselves with their fathers and in part to harbor revengeful feelings because they are not males. They labor under the pressure of a penis envy which makes them seek little or no contact with men and they marry late, usually under compulsion of society.

This type of woman begets a penis by becoming pregnant; the unconscious equation of child-penis appears to become a predominant factor. Her narcissism achieves sufficient gratification, a gratification reinforced by cultural approval (motherhood) that she finds it possible to proceed through pregnancy without any difficulty. However, when labor sets in the child (penis) is forcefully expelled from within her body. Her reaction is to hold that which is her most cherished narcissistic possession. A substantial part of her ego, thus through childbirth, becomes a part of the outer world; on the other hand it is something foreign and the woman finds it impossible to attach any love to it. The patient already feels punished (castrated), the phallus child has become separated, a foreign object and at the same time

a testimony to the patient's anatomical femininity and she then denies it is her child. She says it is her husband's, her obstetrician's, or it is the infant Jesus immaculately conceived ("I can do it alone"--male desire). The whole reaction is characterized by a turning away, by the denial of reality, or by a return to the masculine role and psychotic or transparently sublimated homosexuality.

Kilpatrick and Tiebout (30), however, do not find dementia praecox as prevalent among psychoses precipitated by childbirth as does Zilboorg. In 72 cases they found 32 per cent were dileria, 50 per cent manic depressive, 14 per cent dementia praecox and 4 per cent psychoneuroses. They are of the opinion that child bearing presents many problems of physical and psychical nature which play a definite role in the precipitation of a psychosis, but that no psychosis is peculiar to child bearing.

Gardner (16) made a study of 50 cases of male and 50 cases of female dementia praecox to determine precipitating factors.

In the 50 female cases he found -

1. Conflicts of a sexual nature in 28 cases.
2. Conflicts arising from a failure in occupation or life's plans in 6 cases.
3. Long continued vague feelings of guilt,

inadequacy and fear in 12 cases.

In 4 cases there was no data.

Of the sexual situations there were 6 cases of homosexuality, 6 cases of uncontrollable sex impulses, 5 cases of faithlessness or desertion by husband, 4 cases of guilt arising from illicit sexual intercourse, 4 cases of unfortunate love affairs, and 3 cases of guilt arising from excessive masturbation.

In the group classed as conflicts arising from failure in occupation or life's plans, the schizophrenic syndrome represented the effect of continual frustration and thwarting of desires--desires inculcated in the girl by her parents and associates but which were far in excess of the girl's capability. The desire of the girl's parents to live her life for her regardless of her likes or dislikes, a situation to which the girl never entirely acquiesces nor openly rebels that keeps her in a continual state of unhappiness and mental conflict which may precipitate the psychosis.

General feelings of inadequacy cause the individual to shun the harsh and painful experiences of life. These people are usually frail and over-sensitive creatures. They turn aside from life's problems and satisfy their desires to be successful by day dreaming.

Of the 50 cases of schizophrenia in males in which a study similar to the one above was made, it was found conflicts

of a sexual nature were prominent in 18 cases. Homosexuality was present in 7 cases; feelings of guilt arising from excessive masturbation in 6 cases; feelings of guilt arising from excessive illicit sexual intercourse in 3 cases and unfortunate termination of love affairs in 2 cases. Occupational failure was thought to be the precipitating factor in 18 cases and feelings of guilt, fear and inadequacy in 12 cases. Summarizing we find in the 100 cases sexual maladjustment was present in 46 cases. 24 patients were struggling against economic insufficiency and failure. Gardner, however, does not believe sexual maladjustment should be given the major role in the precipitation of schizophrenia. It is his opinion that deep feelings of guilt, inadequacy, and incompetency arising in connection with any of our multi-varied contacts with our fellow man--our "social relations"--are the most general mental states concomitant with the onset of a schizophrenic disorder.

Lampron (36) made a survey of the children of 75 schizophrenic patients, paying particular attention to their environment. Of these 75 schizophrenic parents there were 244 offspring but only 186 could be contacted.

The environment, economically speaking, was favorable. 34 of the homes were marginal, 29 comfortable, and 4 wealthy. 173 of the children were reared in private homes and 13 in institutions. The homes were classed as good and bad in regard

to mental hygiene. A home in which there was immorality on the part of a non-psychotic mother or father, the presence of a psychotic parent, no opportunity for normal home life or no recreational outlet, the parents were emotionally unstable constituted a bad home for good mental hygiene.

Of the 186 offspring, 56 or 30 per cent were maladjusted. 36 or nearly 65 per cent apparently owed their maladjustment to endogenous factors, viz., 3 psychotics, 7 mental deficients, 7 potential psychotics, 10 emotionally unstable, 1 suffering from recurrent depression, 2 suicides, 4 seclusive individuals, and 2 neurotics. The remaining 20 apparently owed their condition to exogenous factors, viz., 7 wayward individuals, 1 in prison for murder, 12 worried about heredity but emotionally controlled. The economic factor and the physical condition of the home had little effect upon the offspring in the way of determining adjustments.

However, 19 of the bad homes (as to mental hygiene) furnished 60 per cent of the maladjusted. Of all the siblings of bad homes, 70 per cent were maladjusted.

The 56 maladjusted offspring occurred in 38 of 75 families. In these 38 families there were 48 other children, thus out of 104 children, 54 percent were maladjusted.

31 of the offspring reacted to fear of heredity of mental disease to the extent it was a disturbing factor in

their lives.

There was a greater tendency toward maladjustment of offspring from female than from male schizophrenic parents. This is probably due to the closer contact of mother and child.

Lampron concludes that instability resulting from the schizophrenic parent is a factor to be considered.

Cannon (11) sums up the views of the psychogenic school in the following statements. "A living organism preserves its integrity only by the operation of an intricate series of adaptive mechanisms. When any stress is imposed upon the organism this tends automatically to set into operation to counteract the impinging stress and preserve the internal milieu in a 'steady state'". "The adaptive mechanisms possessed by the schizophrenic to preserve this 'steady state' are defective, and hence he swings like a physiologic pendulum from one extreme to the other, whereas the adaptive swing of the normal individual is a much shorter and slower one."

THE ORGANIC CONCEPTS

Why do some individuals react abnormally to their surroundings? Are there pathologic processes or anatomical aberrations in these people who develop insanity? Such questions as these have occupied the minds of medical men interested in psychiatry for several generations, and in the search for the answer to these questions many approaches to the problem have been made.

Hereditary Factors:

One of the first attempts to catalog schizophrenia as an organic disorder was to establish it as a hereditary defect. In 1911 Rosanoff and Orr(59) concluded that insanity is transmitted as a recessive Mendelian character. Two years later Rosanoff (57) stated that a hereditary relationship existed between various neuropathic conditions which were clinically sharply distinguishable one from the other. He mentioned epilepsy, dementia praecox, manic-depressive, imbecility, involutional melancholia, paranoia, alcoholic hallucinosis, and some allied psychoses as particularly being so related. These neuropathic conditions possess in common the property of behaving as recessive Mendelian traits.

Myerson (50) made a study of the families of 10 cases of paranoid insanity. Two generations were investigated in each case. He found that following paranoid disease in the immediate

ancestors, dementia praecox or a paranoid condition followed in the descendants. The disease in the descendants usually commenced earlier and was generally worse in the ancestors. From these observations he concluded that paranoid conditions in the ancestors breeds dementia praecox in the descendants.

A similar study of 20 families of two and three generations with dementia praecox in the ancestors was made, and he found that dementia praecox tended to breed true, for it was followed in a great majority of those cases, where insanity occurred in the next generation, by dementia praecox. In two cases moral imbecility followed. Epilepsy in conjunction with the praecox reaction was observed twice. Many of the descendants were of lower mentality than their ancestors and there was a great downward trend as far as intellectual ability was concerned. In ancestors with manic-depressive psychoses, studies similar to the above showed manic-depressive usually appeared in the offspring. However, in a series of 62 cases of manic-depressive collected by Luther (40) from Vorster, Kraus, Kreuger, Jolly, and Luther, manic depressive was seen in only 43 of the 77 descendants. Dementia praecox was present in 22, idiocy and imbecility in 6, paranoid conditions in 2, epilepsy in 2, amentia in 1, and hysteria in 1. Myerson is of the opinion that the clearly uncomplicated cases of manic-depressive are followed by manic-depressive in the descendants and that difficulty in distinguishing

some catatonic attacks and some transitory depressions of other diseases from the excitement and depression of manic-depressive is an important factor in the discrepancy seen.

In the 9 cases of involutional melancholia that Myerson studied, most of the insane descendants were schizophrenics. He believes that some involutional psychoses are nothing more than late dementia praecox. From his studies Myerson concluded that "all roads seem to lead to dementia praecox and from thence to imbecility".

Kraepelin (32) suggested that many feebleminded are really dementia praecox reaction types with dementia as the prominent symptom.

Alford (2) (3) considers schizophrenia as a group of hereditary degenerations. He (1) classes it with progressive muscular atrophy and dystrophy, amyotrophic lateral sclerosis, Friedreich's ataxia, Huntington's chorea, otosclerosis, and familial optic atrophy, and to this group gives the name "heredofamilial degeneration". Further he says "the appearance of progression in dementia praecox, it may be said, is looked upon by some psychiatrists as being in the nature of a psychic process, as consisting of an increasing withdrawal of interest from external things. Against this contention may be urged the invariable chronicity of the condition which would appear to be inconsistent with a purely psychic process. Furthermore, the appearance of

progression is not found in other mental deviations whether psychic or not, such as psychoneurosis, mental deficiency and psychopathic personality wherein there should be an equally severe psychic stress and a similar excuse for avoiding external conflicts.

Krabbe (31) reports a family in which three sisters have schizophrenia and myoclonus. The family tree shows three members with dementia praecox out of the twelve in the second generation and six schizophrenics out of the 24 members of the third generation, including the three sisters with myoclonus in addition. The fourth generation has 27 members and all seem normal. The founder of the family married his cousin and his wife's mother also belonged to the same family. In this family dementia praecox seemed to be a recessive character.

Barrett (5) made an extensive study of the families of 150 schizophrenic patients. Only the nearest tainting factors were considered. He found hereditary tainting in 78.01 per cent of cases of schizophrenia. The frequency of the various types of tainting factors were as follows:

Psychoses	32.67 per cent
Nervous diseases	2.66 " "
Alcoholism	12.67 " "
Apoplexy	11.33 " "
Abnormal behavior	17.67 " "

Suicide	1.34 per cent
Senile dementia	.67 " "

Tainting factors were present in the father in 24.66 per cent of cases and in the mother in 10.00 per cent, furnishing a direct taint in 34.66 per cent. Tainting factors were present in collaterals in 15.34 per cent and in atavistic lines in 23.34 per cent, giving an indirect tainting in 38.68 per cent of cases.

Jerrell (25) made a study of 760 cases of schizophrenia similar to the method of Barrett. Of the 760 cases reviewed, 247 were rejected because of inadequate family history. However, in the 463 cases which were considered complete enough for study, in only 160 cases was there complete information of the maternal and paternal grandparents. His results are tabulated below along with those of Barrett for comparison.

	150 Cases of Barrett Percentage	463 Cases Present Series Percentage	166 Selected Cases Percentage
Psychoses	32.67	34.09	30.11
Nervous Disease	2.66	1.29	-----
Alcoholism	12.67	13.57	9.03
Apoplexy	11.33	6.02	6.01
Senile Dementia	.67	-----	-----
Abnormal Character	16.67	6.67	8.41
Suicide	1.34	3.43	4.80
Total	78.01	65.07	58.36

	150 Cases of Barrett Percentage	463 Cases Present Series Percentage	166 Selected Cases Percentage
Direct Tainting	34.66	32.97	21.07
Indirect Tainting	38.68	18.73	28.28
Collateral Line	15.34	10.99	12.64
Siblings	4.64	6.67	9.01
Grandparents	23.34	7.74	15.64

We see a close agreement between Jerrell and Barrett's percentages. We would expect some discrepancy on the basis of the difficulty in obtaining satisfactory family histories and the variations in personal judgment as to whether the relatives were mentally abnormal or not. These men from their results conclude that heredity is an important factor in schizophrenia; and that indirect hereditary tainting is greater than direct. This is especially emphasized in Jerrell's statistics. In his group of 463 cases in which a complete history of the maternal and paternal grandparents was not obtained, he found a direct tainting of 32.97 per cent and an indirect tainting of only 18.73 per cent, while in the 166 cases in which information concerning the grandparents was complete, direct tainting was present in only 21.07 percent while along the indirect lines it was 28.28 per cent. Also from this study we see that psychoses are the most frequent tainting factors, which again makes us become cognizant of Myerson's statement that "all roads seem to lead to dementia

praecox and from thence to imbecility".

Rudin (60) found schizophrenia to behave as a recessive Mendelian character. Of 81 children of 20 old schizophrenics, not more than 2 or 3 developed schizophrenia. He believes that the continuous occurrence of schizophrenia over two generations is extremely rare. He does not believe the rule of dominence that a family once free from the schizophrenic characteristic is always free hold for schizophrenia, for collateral heredity may have an influence. He believes that schizophrenia is transmitted as a complex rather than a simple Mendelian character. From a study of proportional frequency with which schizophrenia occurs among children of non-schizophrenic parents, he found only 1/16 of the total number children developed schizophrenia. If it were a monohybrid crossing 1/4 of the children would be expected to be schizophrenic. The fact that the percentage obtained is near 1/16 makes it possible that the mode of crossing is dihybrid.

Hoffman (21) sums up the results of his observations in the formulations of the following thesis.

1. Schizoid character anomalies occur among the children of a schizophrenic parent, even if the other parent is not schizoid.
2. The crossing of a schizophrenic parent with a schizoid may give descendants

among whom, although it is not exclusively so, schizoid types tend to predominate.

3. The combination of schizoid disposition with circular phenomena among children of schizophrenic parents occurs only when the non-schizophrenic mate furnishes a reason for this.

Kraepelin (33), Bleuler (6) and Mott (47, 49) from their statistics conclude that heredity plays an important part in the etiology of dementia praecox.

Several investigators, in trying to establish schizophrenia on a hereditary basis, report cases of the disorder appearing in twins. Frantz (15) and Johnston (26) each report one case of dementia praecox occurring in identical twins. The psychosis came on at approximately the same time in each set of twins and the symptomatology in each pair of twins was very much alike. Richmond (54) reports a case of dementia praecox in female identical twins. These two individuals were married and living apart from one another yet each had similar domestic troubles and each was admitted to the hospital within a few days of each other and each had similar mental symptoms. Parker (51) reports a similar case and expresses the belief that germinal inheritance is far more important than environment. He says,

"This (germinal inheritance)it is that is chiefly responsible for that similarity in identical twins that makes them often indistinguishable even to their close associates. That they should dress alike is without doubt chiefly due to the environment, but that their countenances should be indistinguishable is germinal. The simultaneous occurrence in identical twins of children's diseases such as chicken pox and the like is probably quite as much an environmental affair as a germinal one, but with the occurrence of dementia praecox in such twins, the evidence is strongly in favor of a germinal source, for as far as I am aware, this disease has never been attributed to an infection. It appears to arise from a germinal taint, a maladjustment in the egg cell, or the sperm cell, or both, and its simultaneous occurrence in identical twins is strongly in favor of its germinal origin."

These authors define identical or monozygotic twins as twins springing from the same egg, and possessing the same germinal composition.

In these instances, however, the number of cases studied is too small to conclude that in identical twins insanity in one will be associated with insanity in the other; that the age of onset in each will be approximately the same or that each will show the same symptomatology. Rosanoff, Handy, Plesset, and Brush (58) have made a comprehensive statistical study of 142 pairs of

twins with schizophrenia in one or both twins of each pair; 41 pair of twins were monozygotic; 53 pair were same sex dizygotic; and 48 pair were opposite sex dizygotic. There was a marked contrast between monozygotic and dizygotic twins with respect to the proportion of cases both twins affected. These proportions are, respectively, 68.3 per cent to 14.9 per cent. Here, too, hereditary factors seem to play an important part. This is revealed especially by the contrast in the findings among monozygotic and dizygotic twins: The monozygotic twin-brothers and twin-sisters of schizophrenic patients are also affected with schizophrenia in 61.0 per cent of cases and in dizygotic twins in but 9.9 per cent of cases. However, hereditary factors alone are inadequate as is shown by the high percentage of cases in which but one pair of monozygotic twins is affected--31.7 per cent. The pathogenic effect of hereditary factors is not highly specific. Identicalness of psychoses in monozygotes is the exception rather than the rule. In 17.1 per cent there was marked quantitative dissimilarities and in 7.3 per cent qualitative ones. Even among the 43.9 per cent listed as "similarly affected" there was dissimilarity in time of onset, symptomatology and duration. These investigators believe a large proportion of such psychoses originate in a cerebral trauma at birth or in childhood; that such cases are more prevalent in the male than in the female, probably because males are larger at birth, and in young subjects than those over 30 years of age;

that the type of injury is often asymptomatic, or almost so, at the time of its occurrence; that it probably consists in subarachnoid and subpial hemorrhage upon the cerebral convexity in the frontal and parietal regions; and that it results in partial avulsion or detachment of the pia-arachnoid from the top and side surfaces of the gyri causing interference with the blood supply and slow atrophy, and progressive impairment of mental function.

Shaw (62, 63) points out the high incidence of schizophrenia in the insane of the Parsee population of Bombay. This tribe is strongly interbred. In a series of 150 consecutive admissions of Parsees to a mental hospital he found 76 dementia praecox, 20 manic-depressive, 6 cases of insanity with epilepsy, 28 secondary dementia, 2 paranoids, 3 paretics, 14 idiots and imbeciles, and 1 case due to Cannabis indica. Schizophrenia in the Hindus and Mohammedans who make up the bulk of the population in this region is rare. Shaw classes schizophrenia as a degenerative process and believes it to be inborn in the individual. Its frequency among the Parsee is due to their interbreeding of defective mental stock.

Bleuler (8), in his study of the families of 100 schizophrenic patients, did not find heredity an important factor. In 351 siblings he found only 9 known cases of schizophrenia and 3 which were doubtful. He does not find it permissable, from his material, to assume a tendency to dementia praecox from an

appearance of it within the family. In his cases with a schizophrenic heredity, he found that the course they ran was on the average somewhat lighter and in no case more severe than in those cases which had no schizophrenic history.

Many investigators have tried to demonstrate degenerative changes in various body structures by studies on gross specimens from autopsy, comparing them with accepted normals and by histiopathological methods.

Mott (48) in 1922 thought that mental affections termed puerperal manias and lactational manias were due to a disentegration of the psychic unity. He said this failure was due generally either to a physiological or a psychic stress, but it might be due to microbial toxic agencies causing suspension or suppression of function of the highest centers of psychic function. The patient might, as a result of one or more of these exciting causes, suffer from an exhaustion psychosis from which she might or might not recover. If she did recover, then it could be assumed that there was only suspension of neuronic function. If, however, she progressed into dementia, the neuronic changes were not reversible. Since similar nuclear changes were found in the brains of adolescent dementia praecox patients dying of some acute disease lasting only a few days, or from some chronic disease process, he thought the neuronic changes seen in these puerperal manias (dementia praecox) could not be ascribed

as secondary to the prolonged effect of toxins and therefore must be due to other causes.

In 1925 Mott (49) reported that he found, in 27 cases of dementia praecox dying from intercurrent disease, partial or complete primary regressive atrophy of the testicles as evidenced by morphological and microchemical changes in the spermatogenic epithelial cells and interstitial cells with a corresponding thickening of the basement membrane and overgrowth of interstitial connective tissue. In all but a few exceptions these testes showed less active spermatogenesis than those of an old man 81 years old at death. He then ran a control series of 108 cases of individuals with normal mentality dying at different ages from sepsis, natural causes, and shock from injury. In all cases he found active spermatogenesis from active puberty to old age except in several cases of prolonged suppuration and cancer.

Matsumato (41), in a study similar to Mott's, made histological examinations on 20 cases of dementia praecox post mortem. He found similar testicular changes.

Mott (49) then examined the brains of dementia praecox patients histologically and found an "inherent defect" of the vita propria of the neurons, especially those developed from the telencephalon. This portion of the neural tube is the latest to develop phylogenetically and ontogenetically and is the seat of highest mentation. In explanation, he says there may be varying

amounts of prenatal complete arrest of neuronic development, especially those neurons of the highest level which are of evolutionary latest development, namely, the supragranular layers of the pyramids, and various grades of amentia may be the result. There may be various degrees of partial arrest of growth and extension of the dendrons by which there is only incomplete synaptic junction of many neurons of the highest evolutional level of control without much morphological evidence of a mental defect. Lastly, there may be an inherent lack of durability of the neurons by which they are incapable of performing their functions of storage and transformation of energy during the life of the individual. Through this inherent defect they are apt to fail to function at the critical periods of life, namely, adolescence, the menopause, and senescence; physiological conditions of stress as gestation, parturition and lactation.

Mott has also noticed histological changes in the nuclei of the brain. They show swelling, often with irregular infolding of the nuclear membrane, and a deficiency or absence of the basophil staining of the intranuclear network by Nissl stain. The nucleus of the neuron probably plays an important part in the function of transformation and discharge of energy from the cell, and although Nissl granules are artefacts and do not exist in the living cell, yet their presence in the body of the cell and dendrons, and the microchemical reactions they give

indicate that there is between the surface of the granules and the nucleus a continuous interaction mediated by the cytoplasm. If there is nuclear failure, this may account for the neurons being unable to transform and discharge energy along the axon. The neuron is still able to live and its axon is not wasting, therefore, the brain does not waste.

From these observations Mott concludes that in schizophrenia there is a hereditary biochemical deficiency of nuclear material in the two structures essential for the preservation of the individual and the species, namely, the cortex cerebri and the reproductive organs.

Levine (38) says the evolution of the cerebrum is manifested in the following ways. There is increasing versatility of the cerebrum. i. e., its cells can enter into more complex and more numerous combinations, with a corresponding effect on the richness and complexity of concept formation. There is increasing autonomy of parts of the cerebrum, permitting these parts to act independently of each other; there is increasing capacity for "splitting of attention". In schizophrenia these trends are reversed. There is a loss of cerebral "versatility", resulting in fewer and less complex concepts and in diminished capacity to differentiate concepts. Levine does not say what causes this loss of cerebral "versatility".

Alpers (4) made histological studies on the brains of

three patients dying of Little's disease. These patients were 4 months, 8 months, and 19 years of age. The anatomic substratum in each case consisted of a marked demyelinization of the cortex, due probably to a failure of development and a similar though less marked absence of fibers in the basal ganglia. The cortex showed a diffuse loss of ganglion cells in the third lamina. If we consider this as one of the abiotrophies and follow Alford's view that dementia praecox is an abiotrophy, then perhaps the lesions described in Little's disease may throw some light upon the pathology of schizophrenia.

Southard (66) made an intensive study of four brains of dementia praecox patients. These brains appeared normal grossly. On microscopic examination he found no marked suprastellate lesions in one case of paranoid type, but there was some lesions in the infrastellate region. The other cases had lesions in both suprastellate and infrastellate regions, sometimes numerous and sometimes isolated and apparently capricious in distribution. No good examples of lesions confined chiefly to the suprastellate regions were found. The lesions seen in these cases were both parenchymatous (neuronic) and interstitial (neuroglia) changes and were in the nature of atrophies and scleroses.

Later, Southard (67) in reinvestigation of the brains described above postulated that lesions could be localized in relation to the symptoms they produced. He described lesions in

cases of catatonia which were in infracortical parts of the post-central gyrus and parietal regions. These lesions were bilateral and no similar lesions were found in the frontal, precentral, occipital, lower temporal, or small regions. In cases with auditory hallucinations he found lesions in the temporal region. In one case with severe temporal lesions there were no hallucinations of hearing, but in this case there was severe supracortical disease of the temporal region so Southard thought there may have to be some congress between the activities of the supra and infra-cortex in order to have auditory hallucinations. From these four cases he believes there is nothing inconsistent in the findings with the hypothesis that ordinary delusions are correlated with frontal situated lesions; but the supracortical type of delusion found in certain long standing paranoiacs whose fine mental processes run in a quasi-normal manner, find no special correlation in any region.

It is interesting to note that three of the four cases described had severe pulmonary tuberculosis. The one case which did not have tuberculosis (the paranoid) did not show marked brain changes. This at once brings up the problem of these lesions being secondary to the tuberculosis and not related to the dementia praecox.

Winkelman (74) has described two types of tissue reaction in the brain.

1. Change in small blood vessels, whereby the cells become swollen and so narrow the lumina of the blood vessels concerned, that an anoxemia of varying degrees results.
2. Angiospasm of the cerebral vessels with anoxemia of the brain.

He believes that the mental symptoms are explicable on the basis of brain destruction just as mental symptoms in dementia paralytica occur from brain changes due to syphiletic endarteritis.

He has found these changes in patients dying from toxic infectious conditions as typhoid fever and lead poisoning, in which cases there were mental symptoms.

He says, "In order to completely evaluate changes in the brain, they must be studied in conjunction with the personality of the individual from whence they came. Just as different mental reactions can occur in dementia paralytica, depending on the basic personality of the individual, so in other mental diseases the same variability prevails for the same reason."

Davidson (13) also explains the cause of schizophrenia on vascular changes within the brain resulting in cerebral anoxemia and cortex destruction, by a mechanism called the "capillary theory".

Menstruation, pregnancy, childbirth, and involution which engage the organism to its utmost shows remarkably well the role played by the capillary system. Menstruation produces changes in the distribution of the blood volume of the body. Abnormal opening or closure of visceral and glandular capillaries may cause under or over nutrition of given parts with consequent changes in secretion and function. It may result in disturbance of the neurohumeral equilibrium. During menstruation one often notices psychic manifestations of varying degrees. On account of the critical state of disequilibrium psychobiological conflicts of the individual may gain considerable ground, resulting in a deepening of the process, since psychic factors, through their influence upon the vegetative nervous system may produce further disfunction. Post mortems upon schizophrenics dying in which no demonstrable physical disease was present showed that there was an enormous opening of visceral capillaries which leads to arterial oligemia. Very little blood is left to be driven toward the heart and gives a clinical appearance of heart failure, the cause of death being given as exhaustion following excitement. This is apparently a capillary toxicosis.

The cerebral capillaries undergo similar changes and perhaps such capillary dystonia may be responsible for the non-specific findings demonstrated in schizophrenic brains. It is through these capillaries that the tissue exchange is accomplished

and capillary changes may alter the cellular metabolism and colloidal state of the protoplasm. Consequently, reflex mechanisms will suffer, since, as Pavlov says, the intensity of any reflex and its very presence depends upon the irritability of centers which in turn depends upon the physiochemical properties of the blood and interaction of reflexes.

External and internal stimuli not finding proper colloidal state of the protoplasm, will not be able to extend, absorb or reflect, and at the same time the state of organized cerebration will lose its capacity of control over lower levels.

The organism and function compose the human "constitution", while the organism, function, and personality compose the "total personality" or "constitution" plus "experience". Under "experience" we understand are included all possible influences exercised by exteroceptive and interoceptive stimuli upon the constitution which will construct, reflect, influence, modify, and condition its synthesis and reactions. "Experience" will include all environmental data with reference to time and space, such as intrauterine life, birth, infancy, etc., including meteorological, alimentary conditions, and disease.

In the light of the foregoing statements schizophrenia is not a constitutional disease or a psychogenic reaction, but a disorder of the total personality resulting in dissociation of function up to complete dissolution, and, on the other hand,

capable of showing remissions. While the causes are undoubtedly multiple, we may say that the constitutional element (somatic) responsible for the production of the disorder is to seek at the nivean of the reticulo-endothelial system, particularly at the level of the capillary endothel.

"Experience" will furnish the exciting or precipitating (relatively causitive) factors. It may also be responsible for quickening the individual's predisposition, such as heredity.

Kure and Shimoda (34) studied grossly 106 dementia praecox brains. They found the average weight of the male praecox brains was 1,322 grams which was 56 grams below normal. The female praecox brains weighed on the average 1,170 grams, 69 grams below normal. The brains of the male patients weighed mostly less than 1,300 grams whereas the brains of normal individuals weighed, in the larger per cent, more than 1,300 grams. Brains weighing more than 1,500 grams were decidedly rarer in dementia praecox patients than in normal. In the female praecox cases no brain weighed more than 1,300 grams which is often the case in normal female brains.

The average brain weight of the male dementia praecox was 29 grams more than that of the general paralytic, whereas the average female praecox brain weighed 24 grams less than that of the female general paralytic.

The average brain of dementia praecox weighed 28 grams

in the male and 37 grams in the female more than that of idiots.

The cerebral hemispheres of dementia praecox weighed, on the average, 1,142 grams in the male and 1,000 grams in the female. The dementia praecox rhombencephalon weighed 174 grams in the male and 115 grams in the female.

The average brain weight in dementia praecox decreases when dementia praecox develops. In cases of terminal dementia the brain weighed, on the average, 90 grams less than that of the normal Japanese.

The cerebral hemispheres of dementia praecox show a decrease in weight when the dementia advances, while the rhombencephalon stays the same.

In dementia praecox the cerebral hemispheres were found to be equal in weight in 65 per cent of the cases and unequal in 45 per cent, showing a disparity of more than 10 grams in 55 per cent; more than 20 grams in 14 per cent; and more than 30 grams in 7.6 per cent.

Atrophy of the gyri was noticed in 88.6 per cent of praecox brains. The distribution of the involvements occurred in the following order: frontal plus parietal 26 per cent; frontal and frontal plus parietal plus temporal 17 per cent; parietal 7.9 per cent.

The frequency of involvements in each lobe came in the following order: frontal 79.5 per cent; parietal 65.9 per cent;

temporal 31.8 per cent; cerebellum and occipital rare.

Kure and Shimoda conclude that brains of dementia praecox often times show alterations. However, they believe these changes are not directly related to the schizophrenic process but are to be regarded as residuals of certain diseases previous to mental involvement.

Kure and Shimoda (35) then made a further study, taking into consideration the history of these praecox patients with the hope of finding some explanation for the changes seen in these brains. They studied 388 cases of which 246 were males and 142 females. Insane heredity, alcoholism in family, diseases, and head trauma were taken into consideration. 47.2 per cent showed insane heredity, of which 23.6 per cent was in direct lines and 39.6 per cent in collateral lines. 46.2 per cent had a history of alcoholic ancestors. 8.4 per cent had convulsions in childhood. In all, 80 per cent of the dementia praecox patients were the least number which showed abnormalities previous to the onset of schizophrenia. To these investigators this seemed more than a mere coincidence but they did not feel that their study was extensive enough to determine or make any conclusions as to what this relationship might be.

Taft and Strecker (71) reported a case in which an infant sustained a head injury and later developed a psychosis resembling schizophrenia. It was found, however, that the

psychotic symptoms were due to a dural tumor.

Spielmeyer (68) finds there are three sources of error in interpreting the brain changes seen in dementia praecox as being due to the dementia praecox. These are:

1. Bodily disease can produce brain changes.
2. We see small areas of nerve cell-free zones in normal brains of executed individuals or those who have met a sudden accidental death. These have been described as cellular loss in cases of dementia praecox. Copious fatty substances in glial cells and blood vessel walls is often considered as signs of pathological disentegration and only in older individuals is it said that such fatty substances occur physiologically in connection with senility. However, we see these changes in young, healthy people 20 to 25 years old.
3. Mistaking organic brain disease for dementia praecox.

Spielmeyer believes the findings which have been described are sufficient to establish schizophrenia as an organic

disease, but are not specific enough to be considered as the exact pathologic anatomy.

Dunlap (14) examined the brains of 31 cases of dementia praecox. The following prerequisites were set up.

1. The clinical diagnosis must have been free from doubt.
2. The patient must not have been over 40 years of age to exclude senile changes.
3. They must have died of some acute process, sudden death from suicide or accident preferred, and not from any wasting disease such as tuberculosis.
4. The autopsy must have been done immediately after death.

After these requirements were set up, only 8 cases were found satisfactory for study. From his results he makes the following conclusion.

"It would seem, judging from our findings, that dementia praecox is even less of a structural brain disease than pellagra or alcoholism. In both of the latter conditions changes if present in the brain are not primary but are secondary, not so much to varying somatic conditions as to fairly specific somatic conditions; but our study of dementia praecox, as far as it has gone, strongly indicates that it is a condition completely

lacking in any fundamental or constant alteration of nerve cells, though dementia praecox shows at times within the brain the presence of nerve-cell changes secondary to those varying somatic states of which we now have little knowledge, but which we find operating in so-called normal control cases."

Research has not been confined to brain studies, but many other systems have been investigated.

Lewis (39) made post mortem studies on 4,800 cases of mental disease, 601 cases of which were either catatonic or hebephrenic schizophrenia. Studies were made regarding age, color, sex, lethal lesions, and general condition of the circulatory system with the weight of the heart.

Generally a small circulatory system was discovered to be characteristic of the dementia praecox group; this constitutional feature being independent of age, color, sex, duration of psychosis or associated diseases.

Lewis says the circulatory system has not only been arrested in growth but lacks the ability to react by a satisfactory hypertrophy when occasion demands, and often remains below the average size after developing valvular insufficiencies. Ordinarily, in the normal subject, the heart under usual conditions gets larger as age advances, but this does not occur to any extent with the constitutionally small heart; it is small throughout life. The small heart is not a feature of the other major psychoses

although the average heart weight in general paresis is the nearest approach. The various larger organs of the body, as compared with those of the other major psychoses, are not diminished in size in keeping with the small size of the heart. With the exception of the heart, the organs from all cases of mental disease average somewhat below normal in weight, as would be expected from secondary atrophy.

Lewis believes that it is this type of inherited constitution, the inadequate underdeveloped circulatory system and the deficient "tissue stuff" composing some of the endocrine glands (see under endocrine factors for Lewis' discussion of changes), and, allowing for early aplasias, multiple glandular sclerosis, and disfunction which renders an individual in danger of developing the "praecox" psychosis at puberty or, if then escaped, at some subsequent period of more severe physical, chemical, psychic or social stress.

Yorshis and Gottlieb (75) studied the genetic relationship of blood groups and schizophrenia. The study was made on 31 intact families of two generations. Of these, 21 families were selected which contained one or more schizophrenic siblings. They found there was no typical distribution of blood groups except a problamatic increase in group III (Jansky) for the schizophrenics. The distribution of blood groups according to sex showed no significant differences. There was a trend indicating

a higher incidence of schizophrenic sons following the blood group of the father and schizophrenic daughters following the blood group of the mother than in normal sons and daughters of the same families.

Raphael, Searle, and Schulton (53) studied the blood groups in manic-depressive psychoses and dementia praecox. They found the distribution for the two psychotic series showed no essential differences between themselves and likewise conformed very closely to the general average or normal blood group formula which has been determined by American workers.

Conn (12) has reviewed the work that has been done in trying to establish schizophrenia as a specific disease process and to demonstrate organic lesions. He makes the following conclusions.

1. There are many contradictory opinions expressed on the topic of a uniform anatomical basis to this disorder. There has been no satisfactory correlation made between the so-called classical groups of dementia praecox and specific anatomical findings.
2. The same histological findings which are reported as being specific for these groups are also reported as being present

in a variety of organic and toxic conditions.

3. There is no uniformity to be found in the various clinical constitutions as to what constitutes a dementia praecox reaction.

TOXIC-INFECTIOUS FACTORS

It has been noted that many cases of schizophrenia have had toxic and infectious processes at work before the onset of the mental symptoms. This fact has led to considerable effort to establish schizophrenia as secondary to these toxic conditions.

Holmes (22) said that dementia praecox patients suffer from constipation which is obstinate and chronic. There is caecal statis and decomposition of food residue into amine derrivatives of histidine. B. coli breaks histidine down into histamine-like substances which are absorbed into the portal circulation. Part of these toxic substances are detoxified by the liver, but the process is so prolonged and the amount of toxin so great that the liver is unable to render all the toxins innocuous and they get into the general circulation, causing a gradual selective degeneration which includes the cerebral tissue and possibly the choroid plexus.

He substantiates this view by several facts.

1. The blood pressure in dementia praecox patients is always low and an injection of adrenalin, instead of producing a marked rise as in normal individuals, usually causes the pressure to drop lower. The peculiar behavior of persons to whom ergot has been given is suggestive in this connection. Ergot contains histamine. Its administration produces a marked fall in blood pressure which cannot be elevated by adrenaline.

2. Extremities of dementia praecox patients are often cold, cyanotic, edematous, and occasionally ecchymotic and necrotic--marked resemblance to ergotism.

3. Excessive salivation in dementia praecox patients. Histamine is a powerful salivary stimulant.

4. At the acute onset of dementia praecox, patients have an acetone breath showing acidosis. Under these conditions one would expect the intestinal contents to have a high H-ion concentration which is favorable to the production of histamine from the histidine by the colon bacillus.

Kanner (28) noted, in 34 cases of dementia praecox selected to exclude physical disease that might alter the epinephrin reaction, that he invariably obtained a vagatonic blood pressure curve irrespective of the type of schizophrenia after administration of adrenalin. This might add some support to Holmes' histamine intoxication theory.

Holmes admits, however, that he has been unable to produce brain lesions with histamine and has been unable to cure schizophrenia by colostomy and caecal irrigation.

Robertson (55) is also of the opinion that chronic bacterial infection, especially of the intestinal tract, is important in the causation of schizophrenia. The mechanism he describes is entirely different than that of Holmes.

He included in his study 32 cases of dementia praecox,

30 cases of other acquired insanity, and 300 cases of nervous and other disorders in the general population.

In every case of dementia praecox he found severe bacterial infection. This infection was due either to an anerobic streptococcus, pneumococcus, or neurotoxic diphtheroid bacilli. Of the 32 cases he found

7 cases with pneumococci,

13 cases with anerobic streptococci,

9 cases with neurotoxic diphtheroid bacilli,

3 cases unclassified.

He believes that these chronic bacterial infections are the most important of several factors that determine the mental disorder; that they are the direct cause of the morbid process in the brain that destroys its efficiency as a mechanism and leaves it incapable of many normal motor, sensory, and psychical reactions.

All people do not develop schizophrenia from infections of this type because there must be an inherent defective resistance to the action of bacterial toxins. This defective resistance would appear to be especially on the part of the nerve cells of the most highly developed areas of the brain, namely, the association centers. These people, who develop mental disorder, have a predisposition to fix certain toxins in their higher cortical nerve cells, and when they suffer from severe neurotoxic infections their association centers quickly become damaged.

Robertson claims to have had a few cases of dementia praecox improve after immunization against the causitive agent, but on the whole his results were very disappointing. Improvement in these few cases may have been merely coincidental with the giving of the vaccine.

Keyes (29) considers dementia praecox and manic-depressive psychosis as moniliases. He claims to have cultured moniliae from the stools of these patients and that these moniliae are specific for the disorder they produce as shown by their morphology and cultural characteristics. He believes these moniliae are transmitted in utero and this accounts for the hereditary aspect of these psychotic conditions. He also says that extra-uterine contact-infection is important, and that the reason that some mental defectives at times give birth to normal children is because the children are early isolated from the parents' moniliae.

It seems to me, if this were true, that there would be a greater incidence of schizophrenia in a single generation of a given family in which one member is schizophrenic than our statistics show is the actual case. On this basis how could we explain the tendency for schizophrenia to behave as a recessive Mendelian character? Perhaps some of the moniliae are transmitted by carriers who themselves are not infected!

Hodges (20) reports 25 cases of hebephrenic type of dementia praecox in which there was dental infection. All showed

physical improvement after this was cleared up and 14 showed improvement in their mental condition. Hodges seems to think, however, that the psychosis may have caused the poor dental hygiene due to lack of interest in personal up-keep.

Skliar (64) found psychoses followed in 35 of 109 cases of typhus fever; 9 of the 35 were schizophrenia, 10 were manic-depressive, and 6 were hysterias.

In 41 cases of recurrent fever reported by the same author there were 9 cases which terminated in psychoses; 4 were schizophrenia, 3 were manic-depressive, and 2 were hysterias.

Similarly, 7 cases of typhoid was followed by psychoses in 5 instances; 3 were schizophrenia.

Of 4 cases of malaria followed by psychoses, there was no schizophrenia.

Of 4 cases of post-influenzal psychoses, 2 were schizophrenia.

Skliar found that in nearly all these cases there was hereditary taint.

In 175 cases of psychoses following influenza, Menninger (43) found 60 which were diagnosed as schizophrenia. 50 cases were traced for study: 35 cases were recovered; 5 were improved; 5 were unimproved; and 5 were worse, five years after the influenzal infection.

In the 35 cases that recovered, the diagnosis of schizo-

phrenia was confirmed in 9 cases, unconfirmed in 12 cases, and contradicted in 14. In the improved group, 3 were confirmed, 1 unconfirmed, and 1 contradicted. All 5 of the unimproved group were confirmed and in the group considered as worse the diagnosis was confirmed in 4 and contradicted in 1. Of the 50 cases, 21 cases were confirmed as being dementia praecox.

Menninger found that schizophrenia was the most frequent psychiatric syndrome following influenza and that it occurred with and without evidence of hereditary taint or predisposition.

In a later communication, Menninger (44) makes the following statement. "Infectious disease, not to mention other exogenous agents, in certain persons breaks the integrative fabric of consciousness and releases a psychologic regression of various degrees and types. These regressive pictures include all of the recognized 'reaction types', but apparently most frequently the delerious and the schizophrenic. The syndromes formerly designated 'dementia praecox', 'toxic-infectious psychosis', 'amentia', and 'confusional psychosis' are all included, the differentiation being in many cases neither possible nor useful. The particular type of psychotic picture revealed in any particular case by a toxic attack on the encephalon probably depends on the kind of mental substructure preexisting and not demonstrably on the kind of toxin."

Kamman (27) closely agrees with Menninger. He too says that the schizophrenic reaction is not a specific entity but can

have "varied and cooperative etiologies", some endogenous and some exogenous. He finds that the schizophrenic reaction is the most frequent mental reaction caused by influenza.

Whitemire (73) reports a case in which Parkinsonism and the hebephrenic type of schizophrenia appeared after an influenzal infection. The symptoms were still present four years after the onset.

Smith (65) made a survey of 1,212 cases of schizophrenia to determine the incidence of tertiary syphilis. He found 28 cases. After intensive anti-luetic therapy these cases did not show any improvement in their mental condition, which probably means that the syphilis had no relation to the schizophrenia in a causitive way, although it is interesting to note that in 3 cases the syphiletic infection preceeded the onset of the psychoses.

ENDOCRINE FACTORS

With the increasing advances in endocrinology in the past two decades, it is not surprising that this field has been searched, in so far as our present knowledge permits, for some clue into the yet unsolved mystery of schizophrenia.

Gibbs (17) made a rather extensive study of the secondary sex characters in 325 male schizophrenics. He found that those patients first admitted between the ages of 16 and 20 years had testicles which compared favorably in size with those patients first admitted between the ages of 21 and 40 years. Pubic hair of feminine distribution was present in 13 per cent of patients between 16 and 20 years and was still present in 13.4 per cent after they were 21 years old, but was present in only 2.6 per cent of those first admitted between 21 and 40 years. Deficiency of beard after 21 years of age was present in 34.6 per cent of patients admitted between 12 and 20 years of age and in 21 per cent of patients first admitted between 21 and 25 years of age.

The marriage rate of males developing dementia praecox was definitely lower than for males of the general population. Adult sexual relations with the opposite sex had never been accomplished in 64.1 per cent of 120 praecox patients. Only 20.5 per cent of patients had reached an adult level of sexual behavior and maintained it for even a short time, either married or single.

Deficient development of secondary sexual hair did not

depend on size of testicles, being associated with rather large testicles.

Gibbs was inclined to believe there was a polyglandular deficiency rather than just testicular deficiency.

Sears, Morter, Simonsen, and Williams (61) made blood-estrin studies on 186 female schizophrenics between the ages of 15 and 45 years and on 50 controls of normal menstruating women according to the method of Frank Goldberger. The tests were done one to four days before the onset of the menstrual period. 129 patients or 69.35 per cent showed a negative reaction or no demonstrable quantity of blood-estrin. In the control series only 4 cases or 8 per cent showed no demonstrable quantity of estrin.

These results were borne out clinically by the fact that many of the schizophrenic women showed evidence of sex-hormone deficiency manifested by hypertrichosis, amenorrhea, genital hypoplasia, and weakness of libido as evidenced by lack of sex interest, loss of object libido, and narcissism.

These workers concluded that in female dementia praecox patients there is a definite imbalance of the gonadotropic and gonad stimulating hormones.

In post mortem study of 22 cases of dementia praecox for changes in the endocrine glands by Lewis (39) histopathologic changes in the thyroid, adrenals and gonads were found to be as universally present as the mental symptoms were. The various aplasias, atrophies,

scleroses, and patchy hyperplasias of these glands apparently did not depend upon age, duration of the psychosis, or the incidence of associated physical diseases. He concluded that these structures have suffered in the course of the development of the personality so that their respective functions are subsequently imperfectly and aberrantly performed.

Morse (46) made a study on the gonads, thyroid, and adrenals in 12 male and 15 female schizophrenics dying under the age of 45 years. Controls consisted of non-psychotics dying of the same disease at approximately the same age.

He found very little evidence of primary atrophy of the gonads in dementia praecox. He said the atrophy when present could be accounted for by the somatic disease from which the patients suffered. We see this is directly contradictory to the results of Mott (49), Matsumato (41), and Lewis (39). Further, Morse says he found no specific changes in the adrenals or thyroid. He concludes there is no one uniform condition of the gonads in dementia praecox, dependent on the disease process. The main factors which determine the condition of the glands at autopsy are the nature and duration of the terminal disease, the state of nutrition, and in some instances an underlying defect of development which is expressed in feeblemindedness or the hypoplastic constitution.

A study of 24 cases of schizophrenia was made by Bowman (10) using tests which would have special reference to the endocrine

function as complete x-ray studies on the skull, teeth, phalanges for bone age, chest, gastro-intestinal system, and gall bladder; basal metabolic rate; blood sugar curve; galactose tolerance test; blood non protein nitrogen, urea, creatine, sugar, animo acid, and nitrogen; Koltman test; spinal fluid examination; gastric analysis; renal function; and cardio-ocular reflex.

An abnormally low basal metabolic rate was seen in one-half of the cases with a tendency toward low or minus readings in nearly all the other cases. Nearly one-half showed abnormal sugar curves, all but one being of the sustained type. Over one-third showed a positive galactose tolerance test. X-ray and gastric analyses showed definite functional disorder of the gastro-intestinal tract in about one-half of cases and questionable functional disorders in all but two cases. X-ray showed infected teeth in 40 per cent and questionable infection in 10 per cent. X-ray showed dropped hearts in 30 per cent.

The findings are not consistent with the constant presence of any definite endocrine disorder, and do not suggest that a simple glandular disfunction of a constant type is an etiological factor. The most constant finding appears to be a metabolic disorder of varying degree manifested in gastro-intestinal disorder and a tendency toward a low basal metabolic rate.

Hoskins (23) found low basal metabolic rates on 43 or 54 per cent in a series of 80 cases; 37 cases or 46 per cent were

within normal limits. On the whole he figured there was approximately a 10 per cent reduction in the basal metabolic rate.

Lazell and Prince (37) have demonstrated, to their satisfaction, a soluble substance in the blood of schizophrenic patients which is toxic to embryonic cells and which, they believe, is endocrine in origin.

They found that defibrinated blood serum of normal males was lethal for tadpoles in dilutions of 1:500. They adopted a dilution of 1:1000 as safe. In this dilution the tadpoles lived and grew during the entire period of the experiment, which was one month.

However, when tadpoles of the same species and age were put into 1:1000 dilutions of blood serum from schizophrenic males they all died within three days and most of them lived only a short time. It is from these observations that they draw their conclusions.

In 1938 McFarland and Goldstein (42) made an extensive review of the biochemical studies made on dementia praecox patients. They found that blood sugar, acid and alkalie reserve, carbon dioxide, oxygen, calcium and phosphorus, nitrogenous substances, and lipoidal substances have all been found to be average normals. They found greater fluctuations in the schizophrenic group than in the normal group and a greater fluctuation in the schizophrenic individual than in the normal individual. But they found no evidence had been brought forth to show that dementia praecox was based upon the

disfunction of a single gland. Errors arise because the physical condition and mental activity are uncontrolled variables.

Some work has been done on the relation of vitamins to schizophrenia. By determining the hemoclastic crisis Thomas (72) found a positive hemoclastic crisis in 94 per cent of the schizophrenics he examined, 85 per cent of the melancholias, 75 per cent of the chronic manias, and 60 per cent of early psychotics and neurotics. In 360 controls on non-psychotics he obtained negative hemoclastic crises in all but one instance. Irradiated ergosterol caused a reversal of this abnormal blood reaction known as the hemoclastic crisis. He suggested a possible relation between Vitamin D and schizophrenia or mental disease.

SUMMARY and CONCLUSION

Schizophrenia is a very common condition, in fact, it is one of the most frequent of the major psychoses. It may occur from puberty to senescence, but has a relatively early age of onset.

The condition was first described by Willis in 1674. Morel first used the term "Demence Precoce" to describe the condition in about 1850. In 1898 Kraepelin gave the disease the name "Schizophrenia" and described the condition as we now know it.

There are two concepts as to the cause of schizophrenia, the psychogenic and the organic.

Environmental stresses ans strains and difficulty in meeting problems of every day life, in other words, psychic trauma, have been emphasized by the psychogenic school as being the most important causitive factors.

The organic school has sought the etiological factors in definite pathologic changes within various body structures. They have tried to show that hereditary transmission of defects which predispose to schozophrenia is important. They have looked for and described various atrophies and scleroses of the cerebral cortex, especially in the supra-granular layers. Many have described pathologic changes in the endocrine glands, testes, adrenals, and thyroid. Some men believe toxic-infectious conditions are important.

Practically in all the work that has been done there are contradictory opinions. For every bit of positive evidence some

one else has obtained contrary results.

Personal feelings often color the results obtained and conclusions.

Many workers agree that probably the cause of schizophrenia is to be found in several rather than a single factor.

The etiology of schizophrenia is not known.

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