

Chronological Parameters, Twin Studies, and Mental Diseases

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SUMMARY

Genetics deals with ordered and directed biological change in time; psychiatry with the development or the breakdown over the human life span of thought, feeling, and social adaptation. With the growing acknowledgement of the contribution of the genotype to mental and emotional uniqueness, it is appropriate to consider chronological parameters of mental disease in a genetic framework. These parameters include age of onset of illness (in turn affecting clinical characteristics), sequence of morbid signs and symptoms, length of illness, periodicity of illness, and temporal relation of clinical episodes to other biological events. Data are reviewed from twin and family studies, retrospective and ongoing, that relate such time phenomena to genetic factors in psychiatric disorder. Among the conditions to be considered are schizophrenia, manic-depressive psychosis, Huntington's chorea, karyotype abnormalities, presenile and senile disease, and the psychobiological ageing process itself.

Mental disorders at any stage of life, as well as the emotional and intellectual concomitants of normal growth and aging, may be characterized clinically in terms of their signs, their symptoms, and their effects on human adaptation. There is increasing evidence — from pedigree, family prevalence, and twin studies, from demographic and population-genetic considerations, and from biochemical and cytogenetic findings — that heredity plays a necessary role in the etiology of, or vulnerability to, most aberrations of mental health. It is not the task here to review this evidence *in toto*, but to consider rather a special aspect of the genetic contribution to psychiatric disorders, namely the extent of specification by the genome of some of their chronological characteristics.

Genetics has to do with ordered and directed biological growth and change in time; psychiatry with the temporal development of human thought, feeling, and human adaptation, ordered and disordered. With the growing acknowledgement of the relation of the genotype to mental and emotional uniqueness, it is indeed appropriate to consider the chronological parameters of mental disease and development in a genetic framework. Among these parameters are age of onset of illness, clinical characteristics as affected by age of onset, sequence of morbid signs and symptoms, length of illness, periodicity of illness, and temporal relation of clinical episodes to other biological events.

Schizophrenia

In the case of schizophrenia, there is convincing evidence extending over fifty years of research that a genetically transmitted factor is involved in the vulnerability to this most prevalent psychosis. Whether this factor is transmitted as a single gene, whether its consequences are modified by other genes or by various prenatal, perinatal and postnatal environmental factors, or whether the polygenic or heterogeneous theory of transmission is to be favored, are questions which have not yet been definitively answered. Nevertheless, family studies, twin studies, adoption studies, and longitudinal observations have built up a body of data most convincing as to the genetic role in schizophrenia.

Now, schizophrenia ever since its earliest description is a psychosis which has been characterized in its generality as well as in its particular manifestations according to the age of the affected individual in relation to its clinical course. Kraepelin's original term "dementia praecox" referred respectively to its unfavorable outcome and its onset in youth or in early adulthood. With reference to the age of onset in respect to clinical characteristics, schizophrenic psychoses coming on in childhood are often marked by symptoms resembling mental retardation or severe neurological defect. At one time the term "pifropschizophrenia" was given to a concurrence of catatonic symptoms in severe early mental defectives, the implication being that the schizophrenic process starting so early in life halted mental development at a very primitive stage. In childhood schizophrenia there has been described maturational lag, a disturbance in the chronology of development and maturation of the central nervous system (Bender, 1969). Both in children who later became schizophrenic as well as infants born to schizophrenic mothers, deviations in muscle tone, homeostasis and posture have been observed as early as the first day of life. As described by Bender, "Childhood schizophrenia is ... a maturational lag caused by an inherited factor, with a pattern of behavioral disturbance in all areas of central nervous system functions characteristically plastic at an embryonic level." She felt that this plasticity appeared to be characteristic of those brain functions specifically human and last in evolutionary development (Bender, 1966). Other investigators have considered soft neurological signs to be characteristic of schizophrenic or pre-schizophrenic states in childhood.

Regarding the incidence of schizophrenia in the relatives of young schizophrenics, particularly in their siblings, an increased expectancy was found in a number of family studies. A sample of preadolescent index cases, both twin and single-born, was collected by Kallmann and Roth and reported in 1956. Unlike the case of hospitalized adult schizophrenic patients, there was a considerable excess of males in both the twin and single-born index cases. An increased vulnerability of the preadolescent male seemed also to be indicated by an earlier age of onset among the boys as compared with the girls — 8.8 vs. 11.1 years for twin index cases, and 7 vs. 9.7 years for single-born index cases. Very young children who presented a clinical picture of psychosis with mental deficiency, "perhaps simulating a severe intellectual de-

ficit, as the result of a schizophrenic process” were not included in the sample. It is of special interest in connection with the matter of chronological effects to observe the concordance rates among the cotwins of the DZ and MZ pairs in this study. For total schizophrenia the uncorrected rate was 22.9% for the DZ and 88.2% for the MZ cotwins. Of these, most presented themselves as preadolescent schizophrenia — the rates for preadolescent schizophrenia being 17.1% for DZ and 70.6% for MZ cotwins. In considering the other siblings of the index cases of this study the total schizophrenia rate without age correction was 9%, most of these again presenting as preadolescent cases, so that the preadolescent schizophrenia rate for sibs was 8% with only 1.7% of the sibs having their onset in adulthood. In this connection Kallmann speculated in 1956 that even with some possible difference in the ability to trace the onset of clinical symptoms in older schizophrenic patients, “it cannot be precluded that the sibs and dizygotic cotwins of preadolescent index cases tend to develop an early form of the disease more frequently than those of adult cases.” Kallmann therefore raised the question of a biological etiology (probably mediated through polygenic resistance factors) to the tendency for the early development of schizophrenic phenomena, just as there might be a biological tendency to explain the increased incidence in boys when the age of onset was in childhood.

If one turns to schizophrenia in adult life one finds again evidence of correlation between symptomatology and age of onset. In early adulthood one is apt to find hebephrenic symptoms, with catatonic episodes appearing in the middle twenties. On the other hand paranoid symptoms, involving projective mechanisms and organized delusions and hallucinations, are apt to occur in those cases where onset occurs in the middle thirties rather than in the early or middle twenties.

In these adult forms of schizophrenia one again finds close correlation between the age of onset among twin pairs. Kallmann (1946) noted a difference of 3.5 years in onset between MZ cotwins as well as the fact that “significant dissimilarities in symptomatology are observed only in twin partners who show a definite variation in age of onset.” In Slater’s study reported in 1953 the ages of onset in MZ twins taken in pairs yielded a correlation coefficient of 0.54 while that between the age of onset in pairs of schizophrenic sibs was 0.39. (The correlation given for the concordant DZ pairs, to be sure, was strikingly high, 0.74, but Slater felt this was based on a small number of 13 pairs and could not be regarded as reliable.) In the study of Kringlen (1967) based on schizophrenic twins in Norway, the average age of onset in the MZ twin pairs differed by about four years; in 3 out of 17 cases there was practically no difference in age of onset, while 50% became concordant within less than five years, 76% within less than ten years. Kringlen noted that these figures were in accordance with those of Kallmann and Slater reported above as well as with Luxemburger’s findings of 1936, in which 84% of concordant MZ twins had an interval between onsets of less than six years. In the study of Gottesman and Shields (1966) done on schizophrenic twins at the Maudsley Hospital, the intrapair differences in age of onset between MZ cotwins was less than five years for 9 out of 10 pairs.

Lastly, in the clinical descriptions of schizophrenia, there is included an illness termed late paraphrenia, a schizophrenic-like illness, first appearing in old age (Roth, 1955). Symptoms are largely of a paranoid nature, the condition is mainly confined to women and the risk among relatives is less than that among those of earlier onset schizophrenics.

In summarizing the various data on schizophrenia as they pertain to questions of chronology, one is struck by relationships between clinical distinctions and genetically programmed variables such as age, sex, and family loading.

In childhood there appear to be some cases, very early in onset, whose symptomatology is either of the oligophrenic nature or that associated with early infantile autism. After the third, and prior to the seventh or eighth, year of life, there is a heterogeneous group which includes many with neurological symptoms. Finally, after the eighth or ninth year one begins to see withdrawal, hebephrenic symptoms, and other characteristics of the more adult varieties of schizophrenia.

Adult schizophrenia according to the age of onset seems to progress from hebephrenic to catatonic and then, especially in those with later onset, to the paranoid type of symptomatology. The latter extends into the presenium and senium in a small number of instances.

Without biochemical evidence, it cannot be certain that all of these clinical conditions can be subsumed under the same etiology, and, to be sure, many believe that childhood cases with neurological symptoms may be different in nature from those without, and that adult cases with acute onset and good prognosis (reactive, atypical, or peripheral types) may be different from those with slow onset and poor prognosis (process, typical, or nuclear types). But, these very distinctions have largely been supported on the basis of family history and degree of genetic loading. Children with very early onset of psychosis have affected parents much more rarely than those with later onset of psychosis and those with neurological symptoms have fewer familial cases than those without (Meyers and Goldfarb, 1962). In adults, concordant MZ twins have been described by Rosenthal (1969) as more apt to have a positive family history and a chronic course than discordant ones; also typical (unfavorable course) schizophrenia has been described by Mitsuda (1967) as having a recessive form of inheritance; and atypical (acute, good prognosis), to be equally dominant or recessive. Total life span in schizophrenia is usually considered to be lower than for the general population.

There are enough consistencies therefore, in the relation of clinical symptoms, age of onset, length of course, and family and twin findings, to warrant the supposition that chronology is one of the phenotypic manifestations of the genetic system necessary for the development of schizophrenia in the many ways in which it presents itself. Whether this genetic vulnerability is due to a toxic or deficiency state controlled by a single gene or operon, or whether it is determined by inadequate protection mediated by a polygenic system, leading to vulnerability of the central nervous and other systems to particular kinds of disorganization, the biological consequences include those related to the chronological periods throughout life at which

illness appears and runs its course. The environment may certainly influence these processes, but of course one way in which this influence is mediated may be through genetic feedback systems also controlled by informational macromolecules. Predictive longitudinal studies of high-risk children now in progress both at our Institute and elsewhere will eventually shed more light upon the etiology, the heterogeneity, and the chronology of schizophrenia.

Affective Disease

In affective psychoses — depression and manic-depressive illness — there has also been noted a relationship between the degree of genetic loading and the age of onset of the disease. The incidence of depression is lower in families of index cases with a later onset — specifically, the risk for affective disorders among first degree relatives is lower if the first episode occurs after the age of 50-60 (Price, 1968). Conversely, in a recent study done by us on manic-depressive psychosis with and without a family history among first degree relatives, those who have such a family history showed a significantly earlier age of onset than those who have not (Mendlewicz et al, 1972). Similarities between parent and child in the age of onset and course have been reported in the case of some of the rare instances of affective disease in childhood (Campbell, 1953). Twin and family concordance studies, biochemical and pharmacological investigations, and longitudinal observations should throw further light on the genetic etiology of affective disease and its various chronological manifestations as related to severity and symptomatology as well as periodicity.

Huntington's Chorea

If one turns to central nervous system disorders inherited in a single autosomal fashion, there are various patterns of age-dependence, for example the very early onset and vulnerability of the central nervous system in phenylketonuria, or the late onset of clinical symptoms in Huntington's chorea. Huntington's chorea (Myriantopoulos, 1966), inherited in a single autosomal dominant fashion with complete penetrance, involves neuropathological lesions in basal ganglia and the frontal lobes of the cerebral cortex. The mean age of onset in Huntington's chorea is generally considered to be about age 35 with a standard deviation of about 12 years. Put another way, the age of greatest risk is usually between the ages of 35 and 40 years with a considerably smaller risk under 25 and over 55 years.

The correlation between the age of onset in sibs has been found to be significantly higher than that between sibships, and sporadic pairs of twins have been reported including a number of MZ pairs in which the symptoms appeared within a short time of each other. The correlation between the age of onset in the parents and in the child has been reported as 0.59 by Penrose and 0.50 by Bell. Similarity in onset among closely related individuals has been considered by some to be due to similar

background genes, though earlier the concept of biotype or the existence of various strains of the disease was invoked.

Huntington's chorea coming on in childhood is rare and the symptoms are usually those of spasticity, tremor, early mental deterioration, and seizures. In spite of the deviant clinical picture, these cases are born to parents with Huntington's chorea. According to a number of reports it is generally the father who has been affected in the early cases of Huntington's chorea (Barbeau, 1970; Jones and Philips, 1970). No satisfactory explanation for this phenomenon has been advanced, although it has been suggested that males may be more fertile than females in families where the onset appears earlier, although female choreics are in general more fertile than males. In general the symptoms are more severe and more rapidly progressing with early onset of disease; in later cases emotional disturbance often precedes and is more prominent than choreiform movements.

In a study by Reed and Chandler (1958) the age of onset and the age of death show greater similarities within sibships than between sibships. The authors indicate the possibility of there being similar background genes in the family, or several different particular genes for Huntington's chorea, at one or more loci. Byers and Dodge present a family in which a choreic man had two sons, both with childhood form of Huntington's chorea, both by a different wife, with the implication that the other unaffected parent was not responsible genetically for the age of onset in the offspring (Byers and Dodge, 1967). In a family long known to us, a pair of DZ twins were first seen at the age of 15 when one of them who had febrile convulsions as a baby began to show incoordination at age 10, was institutionalized at 11, and died at 18. She had increases in all her deep reflexes, with ankle and patella clonus, marked intention tremor, strabismus, disarthria, and rigidity of her legs. Her cotwin showed only slight unsteadiness at the age of 15, but clinical manifestations of chorea in her speech and movements by the age of 17. This second twin married, had a child, and died two years later at the age of 26. At the age of 8 her child was seen and showed active reflexes, bilateral Babinski, difficulty in balance, wide-gait walk, difficulty in rapid alternating movements, and questionable tremors. The twins' father, a grandmother, two uncles, and some cousins also suffered from Huntington's chorea. In all cases onset was before the age of 20 with frank chorea by the age of 30, but all survived at least until the age of 38. The twins' father died at the age of 41. There seems, therefore, from various reports, to be some clinical correlation between the age of onset and type of symptomatology within members of the same family in Huntington's chorea, representing another connection between genetic parameters and chronology of illness.

Sexual Development

The clinical importance of age of onset is evident in all variations and disorders of personality development, but perhaps no more so than in those involving sexual choice and sexual identification. From a psychodynamic point of view, for example,

homosexuality is usually considered to be the result of excess fear generated during the childhood relationships to male and female parents. Having presented some twin data indicating a genetic contribution to the development of male homosexuality, Kallmann (1952) wrote:

“Apparently only two males who are similar in both the genotypical and the developmental aspects of sexual maturation and personality integration are also apt to be alike in those specific vulnerabilities favoring a trend towards fixation or regression to immature levels of sexuality. The most plausible explanation of this finding is that the axis around which the personality and sex function takes place is so easily dislocated that the attainment of a maturational balance may be disarranged at different developmental states and by a variety of disturbing mechanisms... .”

In line with this formulation it may be that a normal rate of maturation of personality development in a heterosexual choice is distinguished by the ability to perceive and respond to sexual stimuli of a pleasurable nature, to recognize and feel satisfaction and success and to utilize these experiences as integrating forces and guides to future action (Rainer, 1962). Hutchinson (1959) had speculated that the genotype responsible for homosexuality may operate on the rate and extent of development of the neurophysiological mechanisms underlying the identification processes and other aspects of object relationship in infancy. Comfort (1959) pointed to the possible significance of the time when castration anxiety begins, an adaptation phenomenon in animals protecting immature males from competitive harm during the period between the achievement of sexual maturity and the attainment of adequate size and strength. Early or excessive castration anxiety might result in homosexuality. One may consider this alternative type of behavior as a dynamic process which develops across time in a person's biological life.

No abnormal chromosomal findings have been found in male homosexuality. There are certain disorders of sex chromosomes however, where the timing of the onset of symptomatology as well as biological changes is important. Here one is dealing with the effects of entire chromosomal imbalance. In ovarian dysgenesis or Turner's syndrome (45,X), Cohen (1962) addressed himself to the question of when to initiate estrogen therapy to induce femininity by artificial means. In many cases physical characteristics of Turner's syndrome are not noted prior to age 6. At that time, the individuals begin to fall behind their contemporaries in height but their development before puberty otherwise is roughly that of a normal child. This author found that some girls appeared to have reached a stage of readiness for biological adulthood in terms of their identification with the female sex role before biological changes actually took place, whereas other girls remained more infantile and it was felt needed more preparation for the feminine role before hormonal treatment was to begin.

In Klinefelter's syndrome (47,XYY), there has been described a decrease in plasma testosterone levels with age, whereas there is no striking decline in men with normal karyotypes (Paulsen et al, 1968). In the case of Klinefelter's disease the role of key age periods is also illustrated by the fact that testosterone treatment before the age

of 25 may increase the process of physical maturity but delay the increase in sexual libido, while testosterone treatments started after the age of 25 may increase sexual libido but not potency and lead to aggressiveness, mental disturbance, and perhaps sexual aggressivity in predisposed cases (Nielsen, 1969).

The complex interaction of hormonal, psychological, and social forces in the development of sexuality is illustrated in the above examples in which imbalance seems to have an effect which in many ways is tied to the chronological development of personality crystallization and integration at key critical periods during life.

Down's Syndrome and Presenile Disease

The complexity of the relationship of complex genetic equilibrium in life chronology may be illustrated in another typical chromosomal anomaly, i.e., trisomy-21 or Down's syndrome. Increased mortality in early years due to infection and congenital heart disease is matched by a higher mortality experience for Down's syndrome patients of all ages (Lilienfeld, 1969). Jervis (1970) has pointed out that even following the introduction of antibiotics and the doubling of the life-span of the Down's syndrome patient, the percentage of survival is still strikingly abnormal and it has become more apparent that patients with Down's syndrome age prematurely. Senile disease is eight times more frequently a cause of death in Down's syndrome than in the general population. Intellectual deterioration is difficult to assess in these mentally defective patients. Emotional deterioration takes place along with changes in personal habits and onset of minor neurological signs.

Pathological evidence has been found in these patients of specific morphological changes; namely, senile plaques, Alzheimer's neurofibrillary degeneration and granulovacuolar degeneration of nerve cells, which ordinarily represent signs of senile or presenile psychosis, but occur in Down's syndrome at a much earlier age (Solitare and Lamarche, 1966). Olsen and Shaw (1969) studied 26 consecutive cases of Down's syndrome who came to autopsy; 3 of them died over the age of 35 and all had neuropathological changes of Alzheimer's disease.

In the presenile and senile diseases themselves, these changes may represent specific genetic factors, possibly recessive in nature (Constantinidis et al, 1962).

Aging

Turning from these various pathological considerations in mental illness and deficiency, it is possible to consider the role of genetics in the more normal processes of aging. With respect to the genetic contribution to the life span, experimental studies by Raymond Pearl (1928) indicated that certain *Drosophila* mutants were marked by short duration of life and a characteristic form of life curve, and that these characteristics behaved in simple Mendelian nature in cross-breeding experiments. Pearl hypothesized a capacity, "inherent vitality", which he defined as the total potential capacity of an organism to perform vital actions in the complete ab-

sence of exogenous derivation of matter or energy. He believed this inherent vitality was a function of the organization of the individual as determined by inheritance, and that there was an inverse relationship between the rate of growth and the duration of life, both of which were expressions of this inherent vitality.

Further evidence for the relationship of life span to genotype in *Drosophila* have been provided by the experiments of Gedda and Brenci (1969), who believe that the influence of a gene on life span may be either direct (primary effect of the gene) or secondary (interaction with other structural and/or functional genes). The investigators gave the term “*chronon*” to the temporal dimension of the gene exemplified by these experiments. These authors also studied the decreasing manifestation of genic information throughout life as measured by the decreased alkaline phosphatase activity in different strains of *Drosophila*. They surmised that this gradual extinction of genic information depended upon the existence of a type of energy which becomes degraded with time, and they termed the degree of stability of a gene “*ergon*”.

In human populations there were a number of early studies relating life span of offspring to that of their parents. In Pearl's work, longevity (“regarded as a single numerical expression of the graded effects of all the forces that operate upon the individual, innate and environmental”) was investigated by comparing the ancestors of two groups of persons, one a group of persons still living at age 90 and above, and the other a random group of individuals. The sum of the ages at death of the six immediate ancestors of the index cases were significantly greater in the longevous group than in the comparison group (Pearl and Pearl, 1934).

The most extensive and carefully followed investigation of aging has been that conducted in the Department of Medical Genetics of the New York State Psychiatric Institute since 1945 by Franz J. Kallmann and various colleagues and continued at the present time by L. F. Jarvik and associates (Kallmann, 1961). Starting with 1,603 twin index cases over the age of 60 in the years 1945-1948, a group of 584 pairs was ascertained where both twins qualified as index cases. Mortality of these pairs were followed, particularly of same-sex pairs. By 1959, 192 pairs had two deceased partners. Considering the length of time between the death of the first twin and the death of the second twin, this span was consistently greater in the DZ pairs than in the MZ pairs. Of course for those dying earlier this difference was more marked, but was evident even in those dying over the age of 80.

In these studies Kallmann and his colleagues confirmed the relationship between the mean life span of the twins and their siblings and the age of death of their parents. The investigators felt that life span potential was demonstrated to have a genetic basis which could be assumed to follow the multifactor type of inheritance.

Also studied were intrapair differences in psychometric test scores, which were larger for DZ than for MZ twins. There was some indication that stability of intellectual performance was associated with survival (Jarvik et al, 1957; Blum et al, 1970; Jarvik et al, 1972).

In the search for possible biological concomitants of aging, Jarvik and her colleagues speculated on the possible role of chromosome loss in dividing cells, particularly

glial cells which might in turn bear some relation to aneuploidy in lymphocytes of peripheral blood (Jarvik and Kato, 1970). Chromosome examinations of peripheral blood lymphocytes in 61 twins ranging in age from 77 to 93 years were carried out to determine whether there were increasing deviations from the normal chromosome number with increasing life span. These twins were from among the survivors of the previously described longitudinal study. As compared with a group of young individuals, an excess of chromosome loss was found in the aged women but not in the aged men. In the small number of intact pairs available there was no greater similarity in chromosome number between the MZ twin partners than for the members of the DZ pairs. The chromosome loss among aged women was random and not limited specifically to C group chromosomes; in the aged males, although they showed no greater frequency of overall chromosome loss than young males, the chromosomes that were lost were largely in the G group.

Finally, a higher frequency of chromosome loss has been found by Nielsen et al (1968) and by Jarvik et al (1971) in the peripheral leukocytes of women with organic brain syndrome compared with women of comparable age. In the New York study there was a significant increase in the frequency of chromosome loss in the women with organic brain syndrome, but without evidence of cerebral arteriosclerosis, when compared with women without organic brain syndrome. The relationship between chromosome loss and organic brain syndrome in males, however, appeared to be purely random. In women, a positive association between chromosome loss and memory loss was also demonstrated by psychological testing. While the concordance in degree of chromosome loss was no greater among the MZ than among the DZ twins in this series of aged twins, it was suggested by the investigators that this lack of similarity is due to their advanced age, that some possibly genotypic contributions to chromosome loss that may have manifested themselves in such loss at earlier ages were incompatible with long survival.

From these findings one may not deduce a clear genetic mechanism for aging. The animal experiments and the life span data on man seem to indicate an effect of the genotype upon the length of life. However, the role of the environment in inducing somatic mutations, particularly chromosome loss, in susceptible individuals has also to be taken into account. The mere fact that the aging process seems to follow a certain program has been taken to indicate an effect controlled by the organism's genotype. Szilard, using some of the data of Kallmann regarding the heritability of length of life, assumed that the mechanism involved the chromosome rather than the gene as the unit of inheritance, vitality, length of life, and the aging process (Szilard, 1959; Bruer and Sacher, 1965). The reasoning was that if there were random assortments of tens of thousands of genes, the spread of ages at death would be very small. Actually, since there is a larger spread, Szilard felt aging depended upon the inheritance of intact chromosomes, on the probability of inactivation of chromosomes or the frequency of chromosome fault. Perhaps relevant is the recent speculation by Mittwoch (1971) that the Y chromosome may speed up the growth and development of the gonadal rudiments during embryonic development.

On a molecular basis it was suggested recently that an accumulation of errors in the specification of enzymes which are involved in DNA synthesis or protein synthesis might result in a snowballing effect in which the cell would pass on to its daughter cells the inability to perform their function (Editorial, *Nature*, 1969). Experiments with *Drosophila* (Harrison and Holliday, 1967) and in fungi (Holliday, 1969) showed a correlation of accelerated aging with increased frequency of mistakes in protein synthesis; it was suggested that the consequence of such accumulation of errors would be the accumulation of abnormal proteins in the cytoplasm of aged cells.

At this stage in the understanding of the mechanism of mental disease and psychological development there is no way to subsume the various clinical and observational phenomena described in this presentation under a single model of genetic interaction. Normal mental development would seem to depend upon the adaptive activities of the nervous system, the perception, processing, and storing of impressions and information, and the arousal and utilization of emotional response, all of these arising at the proper time in human growth, development, and social interaction, and geared to the critical ages and tasks throughout the life span. Genetic contribution to health or disease would have to reside either in individual enzyme-specifying genes, in the balanced interaction of many of these genes as operon systems, polygenic complexes, or chromosome arrangement, and on the synchronized and orderly expression of genetic action throughout life. Somatic mutations or chromosomal loss may be implicated, and the environment, time, and susceptibility may interact in their production. Faulty or asynchronous development may be nonadaptive and the type of maladaptation may depend upon the basic fault as well as the time at which it becomes apparent. Psychiatrists and molecular geneticists operating at different levels of organization and with different types of data and skills have much to offer in supporting each other's investigations into these processes.

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RIASSUNTO

La genetica si occupa dei cambiamenti biologici e diretti nel tempo; la psichiatria, dello sviluppo o della scomposizione, nell'arco della vita umana, di pensiero, sensazioni e adattamento sociale. Con l'accresciuto riconoscimento del contributo genotipico all'individualità mentale ed emotiva, diviene appropriato il considerare i parametri cronologici della malattia mentale in un contesto genetistico. Tali parametri comprendono l'età d'insorgenza della malattia (che a sua volta influenza le caratteristiche cliniche), la successione sintomatologica, la durata della malattia, la sua periodicità, e le relazioni nel tempo fra episodi clinici ed altri eventi biologici. Vengono passati in rassegna studi gemellari e familiari sia retrospettivi che prospettici, che collegano tali fenomeni temporali ai fattori genetici nella malattia mentale. Fra le condizioni da considerare si trovano schizofrenia, psicosi maniaco-depressiva, corea di Huntington, anomalie cariotomiche, malattia senile e psico-senile e lo stesso processo psicobiologico d'invecchiamento.

RÉSUMÉ

La génétique s'occupe des changements biologiques et directs dans le temps; la psychiatrie, du développement ou de la répartition, dans les différentes étapes de la vie humaine, de pensée, sensations et adaptation sociale. Alors que la contribution génotypique à l'individualité mentale et émotionnelle devient de plus en plus reconnue, il est approprié de considérer les paramètres chronologiques de la maladie mentale dans un contexte génétique. Ces paramètres comprennent l'âge de début de la maladie (qui à son tour influence les caractéristiques cliniques), la succession symptomatologique, la durée de la maladie et sa périodicité, et les rapports dans le temps entre épisodes cliniques et d'autres événements biologiques. L'auteur passe en revue les études gémellaires et familiales rétrospectives ou perspectives, qui relient ces phénomènes temporels aux facteurs génétiques dans la maladie mentale. Parmi les conditions à considérer se trouvent schizophrénie, psychose maniaco-dépressive, chorée de Huntington, anomalies caryotypiques, maladie sénile et pré-sénile, et même le procès psychobiologique du vieillissement.

ZUSAMMENFASSUNG

Die Genetik befasst sich mit den biologischen und zeitlich ausgerichteten Veränderungen; die Psychiatrie hingegen beobachtet, wie der Gedanke, die Gefühle und die Anpassung an die Gesellschaft sich im Laufe des menschlichen Lebens entwickeln oder spalten. Nachdem immer mehr erkannt wird, dass der Genotyp wesentlich zur geistigen und seelischen Individualitätsbildung beiträgt, müssen auch die chronologischen Parameter der Geisteskrankheiten vom Erbstandpunkt aus betrachtet werden. Zu diesen Parametern gehören: Auftrittsalter einer Krankheit (von dem dann wieder die klinischen Merkmale abhängen), die Reihenfolge der Krank-

heitssymptome, die Krankheitsdauer, ihre Häufigkeit sowie die zeitlichen Beziehungen zwischen den Erkrankungen und anderen biologischen Ereignissen. Es werden sowohl in die Vergangenheit als in die Zukunft gerichtete Zwillings- und Sippen-untersuchungen bei Geisteskrankheiten aufgeführt, wo eine Verbindung zwischen diesen zeitlichen Phänomenen und den Erbfaktoren festgestellt wurde. Die Forschungsgebiete umfassen: Schizophrenie, manisch-depressive Psychose, Huntington'sche Chorea, karyologische Anomalien, senile und psychosenile Leiden sowie den psychobiologischen Altersprozess selbst.

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