GENETICAL ETIOLOGY IN MENTAL ILLNESS[1]

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IN this paper I do not intend to present a complete survey of genetically orientated psychiatric research from its beginning or during a specified period of time. I should like, rather, to stress a few general principles and, by way of a limited number of examples, bring out some of the pros and cons and weaknesses of the genetical argument. A comprehensive review was, in fact, published quite recently by Cowie and Slater [1].

Unfortunately, a great deal of contemporary psychiatry is based more on beliefs than on actual biological facts. Many psychiatrists even appear to discover "facts" that are actually inherent in their own hypothetical constructions. In other words, they forget the pieces that they had put into the bag and get enthusiastic when, at a later date, these same pieces are extracted through some cumbersome operation. This characteristic is, I think, true for many extreme and dogmatic schools of psychiatry, whether organic or psychodynamic, environmental or genetical. I do not, of course, think that I have the skill to master more than a few small corners of this intriguing field. However, my general medical and biological background together with my fragmentary experience of psychiatric research work has led to the tentative conclusion that any unitary explanation of the etiology even of what is now considered to be a special type of mental illness, or a clinical entity, will not contribute to the advancement of psychiatric research. It is true that most psychiatrists, at least theoretically, recognize a multidimensional etiology in almost every form of mental illness, but very often, in research as well as in practice, some variables are minimized or left out of consideration as universally constant.

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It is well known to all biologists of man that man's evolution is unique as compared to other species insofar as it is regulated by an additional variable, namely culture, and not just by the usual two, *i.e.* heredity and environment. Culture, although part of our environment, has such a great importance in this context that it must be mentioned and thought of as a special, third variable.

It is rather natural to find that for centuries the explanation of mental illness, as well as for all kinds of human misery, was sought in environmental influences ranging from direct physical causes to witchcraft. Only relatively recently has there come understanding of the potentialities of genetical differences in creating individual variation.

Of the three variables, two, environment and culture, may and have been, studied extensively without regard to the third variable, heredity, although this is far from ideal. Genetic variables, however, cannot be extracted unless all the components of the variation are accounted for. In most of the common types of mental illness, *e.g.* the psychoses, there is one pattern of cultural variables, another of environmental and a third of genetical ones. Furthermore, when dealing with such complex problems the background, personality, and interests of the scientist is important. Yet little attention has been paid to the biases introduced by the personalities of those who carry out research in psychiatry. Considering all these difficulties one might easily take quite a pessimistic attitude as to the chances of getting anywhere at all. However, this is not justified. Practically all human diseases were once quite as mysterious as, for example, schizophrenia is today—perhaps even more so—but the advances in medical research are indisputable.

The possibilities for systematic research exist. We have highly trained and specialized research workers who can record and evaluate a vast number of variables belonging to the three groups; we have electronic computors to calculate any number of correlations in a short time; statisticians to deal with the meaningful interpretation of the figures, and so forth. The real

problem, of course, is to get all these fine skills to join forces. I imagine this would require the sacrifice of some personal prestige so that here again the personality of the scientist comes into the picture. Unless such systematic research in teams can be materialized, we will probably have to wait for the rare genius who can put his finger on the correct association without the aid of the electronic computor.

The point of my preceding argument is that unless we make an honest effort to understand what the other scientist is trying to do in psychiatric research, at least in essence, a lot of the meaningless argument about what is thought to be more or less important will continue. We should also remember that the present situation most likely is due to the discrepancy between the small number of established and generally accepted facts and the enormous demands placed upon our mental health programs.

After this introduction in which I have tried to place the general background, I should like to discuss a few principles of genetics as applied to medical research today.

Medical Genetics

An inquiry into the nature and significance of genetic variables in any disease is always legitimate. At first glance these variables may sometimes seem to be remote, as in malaria. Nevertheless it has now been shown that a specific gene, when it occurs alone, is associated with an increased resistance against this disease.[3] Thus both the individual reaction to the parasite as well as the epidemiology of the disease is influenced by this gene. In other so-called purely environmental diseases, while genetics may add little or nothing to the understanding or cure of the individual, it still may be significant from the epidemiological viewpoint. For example, our present knowledge of the associations between blood groups and disease indicates that few, if any, genes are entirely neutral from the standpoint of evolution. They may have positive or negative selective values for survival and propagation. "Negative" here does not imply

[3] In homozygous form the gene causes sickle cell anemia.

association with disease: in genetic terminology "fitness" is defined in terms of effective fertility. Nevertheless a great deal of this "negative fitness" carries epidemiological significance. I should like to stress this point because our group has been called together to discuss epidemiological issues with regard to mental illness. For if in many common and apparently environmental conditions we can afford to ignore genetics in the individual case, to do so in terms of populations might be a mistake.

In a strict sense medical genetics is concerned with diseases in which specific genes cause a major part of the variation. Its main targets in clinical research can be outlined schematically under the following four points.

a. *Identification of Genetic Diseases.* Special methods for family and twin research have been developed by which the causes of individual variation can be grouped into environmental and genetical components. The genetical components may be polygenic, *i.e.* due to many genes which combine freely and give continuous distributions (for example the genetical components of stature and intelligence). However, in human pathology it is more common that the genetical components consist of major or single gene differences which give rise to discontinuous distributions in families as well as in populations.

When it is said that specific genes are instrumental in a pathological condition, the statement is to be understood in the following way. Individuals who carry these genes in their chromosomes may or may not develop the disease depending on a variety of circumstances; those who do not possess these genes will under no circumstances get the specific condition. However, the latter may develop similar or seemingly identical conditions due to combinations of other genetical and environmental variables. While a discontinuous pattern in accordance with Mendelian laws indicates major gene differences, genetical homogeneity of a series of hospital index cases is as a rule questionable. This is especially true in psychiatry where our primitive type of diagnostic instruments require that we exercise great caution on this point.

b. *Epidemiology.* The two main facts to remember in genetical epidemiology is: (1) that the altered (mutated) gene is the agent and (2) that the human germ cell is the vector. In consequence of this, the mechanism of transmission is explained by gene distribution during meiosis and gene recombinations during fertilization; in other words by the Mendelian laws of heredity. Genes are transmitted from parents to children, only. Depending on the type of genes involved (homo- or heterozygous expression) or their location (*e.g.* in the sex chromosomes) different types of inheritance can be demonstrated. The usual way of dealing with such problems is by analysis of family data.

In a wider sense, genetical epidemiology deals with the behavior of gene mutations in larger groups of individuals *i.e.* whole populations—and their consequences for public health. The prevalence of genetical diseases is determined by such factors as: the frequency of new mutations; differential fertility of affected individuals; selective migration; and chance fluctuations of gene frequencies due to small family and population size (*i.e.* genetical drift).

c. *Mutation.* Genetical diseases are primarily due to altered "normal" genes, *i.e.* gene mutation or broadly speaking any kind of chemical or structural changes in the genetical material. Mutations may be caused by chemical or physical agents (induced mutations) or may occur for, as yet, unknown reasons. The most widely known examples are the mutations caused by ionizing radiations. Because mutations are random changes in genotypes which have gone through long periods of selection and adaptation the chances are that the vast majority of the changes will be non-adaptive, *i.e.* harmful or pathological. Investigations on the origin and fate of mutations in human populations are therefore essential to an understanding of the epidemiology of genetical diseases.

d. *Phenogenetics.* A most important issue is the study of the effect of specific gene mutations on the individuals who carry them in all their cells. In other words we ask the question "what does the gene do to this individual?" in the same sense

as the virologist inquires about the effect of a specific virus. Since genes act primarily on a biochemical or, if you like, biophysical, level (in most instances they are believed to regulate the synthesis of enzyme systems) all genetical diseases might rightly be called metabolic defects, or, in Garrod's nomenclature, "inborn errors of metabolism."

There are many lengthy pathways from these original intracellular metabolic defects to the symptoms and signs observed by the clinician or by the elaborated techniques of the laboratory scientist. Particularly in psychiatry, this field of biochemical genetics is largely unknown and invites fruitful exploration.

This concept of genetical diseases implies a spirit of reserved optimism, since in principle metabolic defects ought to be subject to attack by some sort of substitution therapy. Much pheno-genetical research is now carried out because of the important implications it may have on treatment.

Mental Deficiency

Since it has long been customary to deal separately with mental deficiency, psychoses and neuroses, I shall also use this classification though for no other than conventional reasons. While the problems of nomenclature cannot be taken up here, it should nevertheless be stressed that the only type of systematics acceptable from a scientific viewpoint would be based on explanatory etiology. If our existing nomenclatures are largely based on mental symptoms, and are therefore easy to criticize, it is because our ignorance makes it impossible at the present time to suggest major improvements.

The field of mental deficiency is a good example of the enormous diversity and complexity facing the psychiatrist. The use of genetical methods is just one of many approaches he can employ. We can, in fact, picture here some of the most brilliant contributions of genetics to psychiatry.

Mental deficency (oligophrenia) is subdivided into classes marked by different degrees of intellectual inferiority. These are, of course, social or psychological concepts and very poor

substitutes for medical diagnoses. Keeping this in mind, the present general consensus is that there are some types of mental deficiency which are polygenic and represent the tail end of the normal variation of intelligence. This is a quite reasonable explanation and genetical and statistical investigations of families and populations seem to support such a view [2]. As a problem it is a part of the wider question of the heritability of intelligence.

The conclusions about the genetical variables in determining intelligence, operationally defined as responses to specified tests, are based on biometrical analyses using correlations or regressions. As the interparental correlation is quite high, probably close to .50 (assortative mating) one would expect a parent-child and inter-sib correlation of .75 if the trait was due exclusively to polygenes without dominance or recessivity. Some actual correlations reported by different authors are given in Table 1.

The lower than expected figures indicate the considerable influence of environmental and cultural variables. A mathematical expression of the component parts of the variation is not possible. All the geneticist can say is that environmental changes such as social improvement, better education and so forth cannot be assumed to work on infinite plasticity. Just

Table 1. Correlation coefficients for intelligence.

Source	Type of Related Pairs		
	Parent-Child	Sib-Sib	Parent-Parent
Burt *et al.* (1911)	0.34	0.48	—
Thorndike (1928)	—	0.60	—
Willoughby (1928)	0.35	0.42	0.44
Jones (1928)	0.53	0.49	0.60
Herrmann *et al.* (1933)	—	0.32	—
Matthews *et al.* (1937)	—	0.30	—
Penrose (1938)	—	—	0.39
Cattell *et al.* (1938)	0.84	0.77	0.81
Roberts (1940)	—	0.54	—
Halperin (1945, 1946)	0.37	—	0.65

Source: Penrose, L. S.: The Biology of Mental Defect. London: Sidgwick and Jackson, 1954.

where, on the slope of the curve, pleasant physiological stupidity changes into social or medical problematics is a matter of conjecture. More important than such conjectures is the fact that the malignancy of inferior intelligence is a function of technical and social developments and public tolerance.

Turning to the pathological variations, I have suggested [3] the following main operational categories:

1. Genetical diseases with mental defect as an essential symptom.
2. Genetical diseases with mental defect as an occasional symptom.
3. Environmentally caused diseases, in which mental defect occurs as a symptom caused by either physical lesions (such as injuries, prematurity, infections), or by adverse mental mechanisms.

With respect to most patients with mental defect genetical studies have shown a significantly higher incidence of similar defects among close relatives. The etiological meaning of these findings is rather obscure and it would not be wise to use such figures for the calculation of predictions for further generations. It is now recognized that intellectual inferiority is too complex to be subjected to genetical analysis with any degree of efficiency. The possibilities for further advances in genetical studies will depend on more accurate and precise diagnoses and particularly on the finding of physical or biochemical correlates. Several conditions with such pathology have been shown to have a genetical etiology. Well known examples are the amaurotic idiocies, microcephaly, and phenylketonuria, all belonging to group 1 above.

The case of phenylketonuria is particularly instructive. When it was shown by Fölling [4] that some earlier unspecified patients with mental defect excreted phenylpyruvic acid in their urine, a foundation was laid for a more meaningful genetical investigation. It was soon demonstrated by Jervis [5] and others that the inability to transform phenylalanine to tyrosine and the associated mental defect was due to a single gene dif-

ference, the disease occurring in homozygotes. Later it has been shown that the majority of the heterozygous carriers can be identified by special phenylalanine tolerance tests [6].

Thus it has been possible by combined biochemical and genetical methodology to distinguish from the large group of "undifferentiated mental deficiency of unknown etiology" a condition which apparently is a clinical and genetical entity and to explain a great deal of its etiology.

A few other examples could be given but the story of phenylketonuria is sufficient to illustrate in principle how genetics can contribute to etiological research in this field and in clinical medicine.

The identification of juvenile amaurotic idiocy, on the other hand, was based on specific neurological, histological, and genetical evidence [7]. The advances in the biochemical genetics of this disease have been much slower. A recent development is that about 75 per cent of the heterozygotes can be identified by a characteristic lymphocyte morphology [8].

The identification of heterozygotes has been mentioned here not only because it is interesting and of practical importance for clinical genetics, but also because it gives considerable strength to the genetical argument in so-called recessive disorders.

Only one year ago the etiology of mongolism was a complete mystery in spite of the fact that for decades it has been one of the pet targets of psychiatrists and of many other physicians interested in mental defect. The big step towards the solution of this problem materialized not by the statistical type of genetics but by the development of human cell culture cytogenetics. French [9, 10], English [11] and Swedish [12] workers found that the somatic cells of these patients contained in their nuclei 47 chromosomes instead of the normal 46. The extra chromosome is one of the smallest ones and not the Y-chromosome. The findings demonstrate for the first time in man a type of genetical etiology well known in other organisms. The most likely explanation is that on some occasions egg cells or sperms with 24 instead of 23 chromosomes are produced

through a process known as non-disjunction. When fertilized with normal gametes they give rise to children with mongolism. At present some 20 cases have been examined cytogenetically and the results are consistent, but still it is too early to claim that all cases of mongolism are of this type. The interesting question as to whether other types of human pathology including mental defect may be due to chromosomal aberrations is at present being studied in our laboratories and elsewhere.

By briefly discussing polygenic variation, single gene differences, and chromosomal aberrations in relation to mental defect, I have tried to demonstrate how genetical research can profitably collaborate with other types of research concerned with environmental and cultural variables. The discussion has a general validity, the principles being equally true for other psychiatric fields and for clinical research as a whole. I have a strong feeling that, fortunately, the old argument of nature *versus* nurture has been put aside as an unprofitable quarrel and removed to the department of sophistical odds and ends. This should make it much easier for all of us to work together in collecting, correlating, analyzing, and interpreting biological and social facts in mental illness.

Psychoses

Genetical investigations have been concerned mainly with two of the so-called major psychoses, schizophrenia and manic-depressive psychosis. Inasmuch as many of these investigations, particularly in Scandinavia, have dealt with material derived from geographically limited populations, they have been at the same time epidemiological surveys of mental disorder so that all kinds of mental diseases were included. However, sufficient family data were gathered on only the most common diagnostic groups.

From a scientific viewpoint schizophrenic, manic-depressive, involutional, and senile psychoses, are equally poor diagnostic categories as categories of mental deficiency graded by intelligence or performance tests. Consequently what was said above

about the efficiency of genetical analyses based on mental symptoms is valid here, too. Yet in spite of these limitations, genetical studies have contributed significantly to the understanding of these psychoses. Even if this might still be denied by some psychiatrists the important facts about the distribution of psychoses in families and populations have been appreciated and recognized.

In using the terms "schizophrenia" or "manic-depressive psychosis" I do not imply that they are to be thought of as either clinical or genetical entities, since there are reasons to suspect that we are dealing with mental syndromes caused by a variety of different etiologies. Because the diagnoses are based exclusively on mental symptoms the field is open to a variety of interpretations more or less colored by the investigator's own ideas in respect to etiology. Caution must therefore be exerted in the interpretation of differences in incidence between different populations and investigators unless specifically stated that identical diagnostic principles have been used.

Schizophrenia. While the clinical picture will be modified by the cultural background, schizophrenic psychoses have been found in all kinds of human populations that have been thoroughly investigated, irrespective of whether they enjoy a high technical culture or not, e.g., in Bantus in Africa [13], in Chinese on Formosa [14], in the people of Thailand [15].

Schizophrenic psychoses occur in all social strata. There is, however, some evidence which suggests a statistical association between social disorganization and schizophrenic reactions. Hare [16] and Carstairs *et al.* [17] have shown that more hospital patients with this disease came from slums and lower social strata. Pasamanick *et al.* [18] also found an association between psychoses and low economic status. Other investigators [19, 20] failed to show such distributions. The precise significance of these findings (*cf.* also Harris *et al.* [21]) has not yet been worked out. Further studies are necessary to make possible an analysis of the complex interactions of cause and effect and of selective factors in different communities.

The epidemiological studies were initiated by genetically orientated psychiatrists in Germany early in this century. Later a number of Scandinavian geneticists and psychiatrists have made significant contributions (*cf.* Larsson and Sjögren [22]). Recently the interest in this field has spread to people more

Table 2. General morbid risk of schizophrenia.

Data Ascertained By	Corrected Population (Weinberg's Abridged Method)	Schizophrenia Morbid Risk Per Cent	Type of Population
I. Genealogic Random Test Method			
Several Authors Data Compiled by Fremming [39]	6,709	0.72 ± 0.10	Average. Mostly German Populations
II. Birth-Register Test			
Risk-Period 15–45 Yrs.			
Fremming [39]	3,777	0.90 ± 0.15	Bornholm, Denmark
III. Census Method			
Risk-Period 20–40 Yrs.			
Brugger [40]	18,312	0.38 ± 0.05	Thuringia, Germany
Strömgren [41]	429	0.47 ± 0.33	Rø, Bornholm, Denmark
Sjögren [42]	4,800	0.83 ± 0.13	West Swedish Island
Kaila [43]	194,000	0.91 ± 0.02[a]	Finland
Risk-Period 15–40 Yrs.			
Brugger [44]	2,894	0.41 ± 0.12	Allgäu, Germany
Brugger [45]	1,643	0.36 ± 0.15	Rosenheim, Germany
Sjögren [46]	4,390	0.68 ± 0.12	2 N. Swedish Isolates
Essen-Möller [36]	1,515	1.12 ± 0.27	South-Swedish Rural
Risk-Period 20–45 Yrs.			
Strömgren [41]	19,045	0.65 ± 0.05[b]	Bornholm, Denmark
Böök [26]	2,912	2.85 ± 0.31	N. Swedish Isolate
Risk-Period 15–45 Yrs.			
Schade [47]	1,929	0.52 ± 0.16	Schwalm, Germany
Sjögren [46]	3,440[c]	0.87 ± 0.16	2 N. Swedish Isolates
Böök [26]	3,467	2.39 ± 0.26	N. Swedish Isolate

Note: For comparison purposes differences in Risk Periods are not important.

[a] Does not include recovered cases. If these are taken into account, the morbid risk might be estimated at 1.15–1.20 per cent.

[b] With correction for excess mortality.

[c] Recalculated by the writer. Sjögren had no actual age distribution of this population but computed it according to the average Swedish rural population. As shown in this paper, the population of North Sweden differs somewhat insofar as the younger age groups are larger. This calculation was based on the assumption of the same age distribution as persisted in the investigation area in 1935 which probably gives a more correct morbid risk.

exclusively interested in the social and psychiatric aspects of the disease (*e.g.* Eaton and Weil [23], Mayer-Gross [24], Bremer [25], and others).

For genetical purposes it is convenient to compare the morbid risks calculated in different surveys. These figures express the total risk of becoming manifestly ill for all individuals who survive the period during which the disease may appear, roughly from 15 to 45 years of age. In a large number of surveys relatively small differences have been found, the average morbid risk being about 1 per cent (*cf.* Table 2). A notable exception is the figure of about 3 per cent found by Böök [26] in a North-Swedish community.

Support for a genetical etiology comes from a very large number of adequate studies on families and twins. As the results are very consistent there is no need to repeat individual details here. In short the morbid risk figures are: for siblings of schizophrenics, 7–15 per cent, for children of schizophrenics, 7–16 per cent and for parents of schizophrenics, 5–10 per cent. The figures for siblings and children are not significantly different if one compares families with one or no affected parent. Families with two affected parents have recently been studied by Elsässer [27] who calculated a risk of about 40 per cent for the children of such couples.

Attempts to show, by means of genetical-statistical methods, a significant heterogeneity in terms of the common subgroups (simplex, hebephrenic, catatonic, and paranoid forms) have so far been unsuccessful, possibly due to small numbers involved when the data are broken down.

Statistical associations between symptomatic groups among siblings have been reported by Schulz [28, 29], Bleuler [30] and Slater [31]. A striking symptomatic similarity was also found among the schizophrenics of my own North Swedish investigation [26]. This study was in fact planned to ensure a genetically more homogeneous material than the samples surveyed earlier. At present no definite conclusions can be drawn on the basis of these findings since such associations might

equally be due to regional or familial environmental influences. Also I think it would be hazardous to try to make genotypical divisions on the basis of psychological criteria.

Extensive twin studies by Kallmann [32, 33, 34] and Slater [35] have shown a concordance rate of 76 to 91 per cent for monozygotic and 10–17 per cent for dizygotic twins. In conjunction with the analysis of possible environmental causation, these results strongly support the view that genotypical variation is of primary importance for the development of schizophrenic psychoses.

The distribution of schizophrenia in families (collected by proper sampling techniques) can be explained, theoretically, by one or a combination of the following three mechanisms: (a) some sort of infection, (b) distinct physical or mental trauma and (c) genetical variation.

The first alternative has received no factual support and is rather improbable, unless one assumes some unknown virus which would only attack certain predisposed individuals. (This predisposition would then need to be genetically determined.)

The second alternative (physical or mental trauma) is a serious possibility and may occur in association with genetical predisposition. So far, however, proof is wanting. Severe stress situations during wartime, in concentration camps, etc., are not known to have resulted in an increase of schizophrenia. The influence of a particular family environment finds no support in the fact that in only a few families is a second sibling affected. To my knowledge there are no statistical investigations which support a pure psychogenetic theory of schizophrenia. On the other hand no definite proofs against this theory are available.

It is a common misunderstanding that genetical research has failed because no agreement has been reached as to the Mendelian mechanism of inheritance. While it is true that the crucial test must wait for further developments in diagnostic precision, nevertheless the most likely explanation appears to be that the schizophrenic psychoses are basically caused by major

gene differences which express themselves regularly in homozygotes and occasionally in heterozygotes. Since heterozygotes in this hypothesis are quite common this should imply that more psychotics are heterozygotes than homozygotes. The hypothesis of a simple recessive type of transmission does not agree with the data which show that no significant differences have been found between the risk figures for parents (when properly corrected, according to Essen-Möller [36]), siblings, and children with one or no affected parent. Recently Slater [37] has come to the same conclusion.

Any explanation has to include the assumption of what is commonly called "reduced penetrance," at least in heterozygotes. Penetrance is an operational and statistical concept and its nominal value is a function of diagnostic precision. The effect of practically all pathological human genes is subject to considerable modification or suppression by other genes, and environmental and cultural factors.

The concordance rates for monozygotic twins may be used to calculate a penetrance which, however, has another meaning than that based on family data. When a series of schizophrenic twins are collected by an investigator, naturally he is anxious that his *propositi* should raise as little doubt as possible regarding their diagnosis. So he selects "typical," e.g., often severe cases. These cases, in the present genetical hypothesis, may be assumed to belong to special entities with high penetrance or possess genetical modifiers to the same effect. Probably they are a mixture of both. As the monozygotic twin siblings carry identical genes the concordance rate and the derived penetrance will be higher than that calculated from family data. There are also a number of environmental mechanisms which work in the direction to increase the concordance for monozygotic twins, particularly when mental traits are considered. Consequently the high concordance rates for schizophrenic psychoses in monozygotic twins cannot be used as an argument against the tentative explanations given above.

The argument whether one or more pairs of genes are in-

volved will remain an open question. The point is that the distribution of schizophrenic individuals among the relatives of the *propositi* is presently best explained by postulating a major gene difference. The clear-cut difference between psychotic and non-psychotic siblings in the absence of known specific environmental causation is in favor of this interpretation.

It is unlikely that the high morbid risk of 3 per cent in the North Swedish area [26] is associated with general local environmental factors as no risk increase was found for the different categories of relatives of the *propositi.* The findings are best explained as an effect of selective immigration, genetical drift or both.

As in other genetical diseases, the schizophrenic psychoses cannot be caused exclusively by major gene differences. The effect of such genes is modified by other genes and, of course, by so far unspecified environmental factors. The important conclusion which I think is quite justified, is that major gene differences are very likely the basic prerequisites for the initiation of a chain of events which may result in a psychosis. Unless this specific genetical prerequisite exists the illness will not occur, provided we are not dealing with a supposedly rare non-genetical schizophrenic syndrome.

Such a working hypothesis implies an interesting biological basis for further research. With the traditional genetical statistical methods applied to the psychopathological traits we have probably already extracted all useful information. The next step should be to concentrate on approaches which appear suitable for studying somatic and biochemical correlates and subject these to genetical tests.

Whatever may be the final answer to the problem of genetical factors in schizophrenic psychoses there remains no doubt that psychological and social studies are as important as genetical ones. It seems clear that all genetical studies carried out so far have been more or less deficient in special techniques of environmental and interpersonal analysis. In a corresponding way most environmental, and especially psychological studies, have been

deficient in statistical techniques and an understanding of human biology.

Manic-depressive Psychosis. A discussion of this syndrome would follow very closely the same general scheme as outlined for schizophrenia. I will therefore restrict myself to a few remarks. The morbid risks among close relatives of manic-depressive psychotics do not differ significantly from those of schizophrenics. All recent European investigations agree on risks of 10–15 per cent for parents, siblings, and children. Kallmann's figures [32, 33, 34] deviate upwards by some additional 10 per cent in all instances. What exactly this implies must await the publication of his case histories since they may only demonstrate Dr. Kallmann's diagnostic latitude. Nevertheless, for reasons already given above, such figures cannot be expected to be crucial to the genetical argument.

An important finding in all large genetical investigations [38, 34] is that schizophrenic psychoses do not occur with an increased frequency among the relatives of manic-depressive *propositi* and *vice versa.* This fact indicates significant biological differences between the two syndromes.

The question of the heritability of the two major psychotic syndromes is worthy of serious consideration. It carries great importance not only for the problems of etiology and treatment but also for epidemiology. There is one aspect of epidemiology that has only been touched upon and I should like to return to it here. Mental illnesses in which genetical factors are significantly involved, or are strongly suspected to be so, are quite common. We might assume a general morbid risk of at least 2 per cent. There is a very real possibility that the general increase of the mutation rate due to ionizing radiations and chemical mutagens will cause a significant increase in mental illnesses.

In conclusion, I should like to summarize as follows. A crucial proof of genetical etiology is impossible without a diagnostic method that identifies an almost one to one relationship with the causative gene mutation. This is the case in illnesses as phenylketonuria and amaurotic idiocy which have been men-

tioned as examples. In other conditions which are still identifiable in terms of mental symptoms only, no decision is possible. Here the geneticist and his co-workers must proceed to test different biological correlates. The repetition of traditional family and population surveys, although they surely contribute to epidemiology, will never enable the geneticist to prove his case definitely. While genetical studies of the major mental syndromes—schizophrenia and manic-depressive psychosis—have been justified up to the point indicated here, I find the diagnostic difficulties in the field of neuroses to be of such magnitude as to make a genetical approach, while perhaps interesting, definitely not very meaningful.

References

1. Cowie, V. and Slater, E.: Psychiatric Genetics. *In* Recent Progress in Psychiatry. London: J. and A. Churchill, 1959, 3, p. 1.

2. Roberts, J. A. F.: The Genetics of Mental Deficiency. *Eugenics Review,* 1952, 44, p. 71.

3. Böök, J. A.: Oligophrenia. *In* Sorsby, A. (Ed.): Clinical Genetics. London: Butterworth, 1953, p. 322.

4. Fölling, A.: Uber Ausscheidung von Phenylbrenztraubensäure in den Harn als Stoffwechselanomalie in Verbindung mit Imbecillität. *Hoppe-Seylers Zeitschrift für physiologische Chemie,* 1934, 227, p. 169.

5. Jervis, G. A.: The Genetics of Phenylpyruvic Oligophrenia. *Journal of Mental Science,* 1939, 85, p. 719.

6. Hsia, D. Y. Y. *et al.:* Detection by Phenylalanine Tolerance Tests of Heterozygous Carriers of Phenylketonuria. *Nature,* 1956, 178, p. 1239.

7. Sjögren, T.: Die Juvenile Amaurotische Idiotie. *Hereditas,* 1931, 14, p. 197.

8. Böök, J. A. and Rayner, S.: Genetics and Blood Morphology in Amaurotic Idiocy. *Lancet,* 1958, 1, p. 1077.

9. Lejeune, J. *et al.:* Les Chromosomes Humains en Culture de Tissus. *Les Comptes Rendus Hebdomadaires des Séances de l'Académie des Sciences,* 1959, 248, p. 602.

10. Lejeune, J. *et al.:* Étude des Chromosomes Somatiques de Neuf Enfants Mongoliens. *Les Comptes Rendus Hebdomadaires des Séances de l'Académie des Sciences,* 1959, 248, p. 1721.

11. Jacobs, P. A. *et al.:* The Somatic Chromosomes in Mongolism. *Lancet,* 1959, 1, p. 710.

12. Böök, J. A. *et al.:* Cytogenetical Observations in Mongolism. *Acta paediatrica,* 1959, 48, p. 121.

13. Moffson, A.: Schizophrenia in Male Bantu Admissions to Weskoppies Hospital. *South African Medical Journal,* 1954, 28, p. 662.

14. Lin, Tsung-yi: A Study of the Incidence of Mental Disorder in Chinese and Other Cultures. *Psychiatry,* 1953, 16, p. 313.

15. Prasop, R.: STUDIES OF MENTAL ILLNESS IN THAILAND. Bangkok: Phyathai, 1957.

16. Hare, E. H.: Mental Illness and Social Class in Bristol. *British Journal of Preventive and Social Medicine,* 1955, 9, p. 191.

17. Carstairs, G. M. *et al.:* Changing Population of Mental Hospitals. *British Journal of Preventive and Social Medicine,* 1955, 9, p. 187.

18. Pasamanick, B. *et al.:* Mental Disease Prevalence in an Urban Population. *Public Health Reports,* 1957, 72, p. 574.

19. Clausen, J. A. and Kohn, M. L.: Schizophrenia and the Social Structure of a Small City. *Public Health Reports,* 1957, 72, p. 578.

20. Essen-Möller, E.: Individual Traits and Morbidity in a Swedish Rural Population. *Acta psychiatrica et neurologica.* Supplementum 100, 1956.

21. Harris, A. *et al.:* Schizophrenia: A Prognostic and Social Study. *British Journal of Preventive and Social Medicine,* 1956, 10, p. 107.

22. Larsson, T. and Sjögren, T.: A Methodological, Psychiatric and Statistical Study of a Large Swedish Rural Population. *Acta psychiatrica et neurologica scandinavica.* Supplementum 89, 1954.

23. Eaton, J. W. and Weil, R. J.: CULTURE AND MENTAL DISORDER. Glencoe, Illinois: The Free Press, 1955.

24. Mayer-Gross, W.: Mental Health Survey in a Rural Area. *Eugenics Review,* 1948, 40, p. 140.

25. Bremer, J.: A Social Psychiatric Investigation of a Small Community in Northern Norway. *Acta psychiatrica et neurologica scandinavica.* Supplementum 62, 1951.

26. Böök, J. A.: A Genetic and Neuropsychiatric Investigation of a North Swedish Population, with Special Regard to Schizophrenia and Mental Deficiency. *Acta Genetica et Statistica Medica,* 1953, 4, pp. 1, 133, and 345.

27. Elsässer, G.: DIE NACHKOMMEN GEISTESKRANKER ELTERNPAARE. Stuttgart: Georg Thieme, 1952.

28. Schulz, B.: Zur Erbpathologie der Schizophrenie. *Zeitschrift für die Gesamte Neurologie und Psychiatrie,* 1932, 143, p. 175.

29. Schulz, B.: Versuch einer genealogisch-statistischen Ueberprüfung eines Schizophreniematerials auf biologische Einheitlichkeit. *Zeitschrift für die Gesamte Neurologie und Psychiatrie,* 1934, 151, p. 145.

30. Bleuler, M.: Krankheitsverlauf, Persönlichkeit und Verwandtschaft Schizophrener und ihre gegenseitigen Beziehungen. *In* Bostroem, A. and Beringer, M. (Eds.). SAMMLUNG PSYCHIATRISCHER UND NEUROLOGISCHER EINZELDARSTELLUNGEN. Leipzig: Georg Thieme, 1940.

31. Slater, E.: Genetical Causes of Schizophrenic Symptoms. *Monatsschrift für Psychiatrie und Neurologie,* 1947, 113, p. 50.

32. Kallmann, F. J.: The Genetic Theory of Schizophrenia. An Analysis of 691 Twin Index Families. *American Journal of Psychiatry,* 1946, 103, p. 309.

33. Kallmann, F. J.: The Genetics of Psychoses. *In* CONGRÉS INTERNATIONALE DE PSYCHIATRIE. VI: PSYCHIATRIE SOCIALE. Paris: Hermann, 1950.

34. Kallmann, F. J.: HEREDITY IN HEALTH AND MENTAL DISORDER. New York: W. W. Norton, 1953.

35. Slater, E. and Shields, J.: PSYCHOTIC AND NEUROTIC ILLNESSES IN TWINS. Medical Research Council, Special Report Series No. 278. London: Her Majesty's Stationery Office, 1953.

36. Essen-Möller, E.: The Calculation of Morbid Risk in Parents of Index Cases as Applied to a Family Sample of Schizophrenics. *Acta Genetica et Statistica Medica,* 1955, 5, p. 334.

37. Slater, E.: The Monogenic Theory of Schizophrenia. *Acta Genetica et Statistica Medica,* 1958, 8, p. 50.

38. Stenstedt, A.: A Study in Manic-Depressive Psychosis. *Acta psychiatrica et neurologica scandinavica.* Supplementum 79, 1952.

39. Fremming, K.: SYGDOMSRISIKOEN FOR SINDSLIDELSER. [Morbid Risk of Mental Diseases and Other Mental Abnormalities in an Average Danish Population.] Copenhagen: Einar Munksgaard, 1947.

40. Brugger, C.: Versuch einer Geisteskrankenzählung in Thüringen. *Zeitschrift für die gesamte Neurologie et Psychiatrie,* 1931, 133, p. 352.

41. Strömgren, E.: Beiträge zur psychiatrischen Erblehre. *Acta psychiatrica et neurologica.* Supplementum 19, 1938.

42. Sjögren, T.: Genetic-Statistical and Psychiatric Investigations of a West Swedish Population. *Acta psychiatrica et neurologica scandinavica.* Supplementum 52, 1948.

43. Kaila, M.: Ueber die Durchschnittshäufigkeit der Geisteskrankheiten und des Schwachsinns in Finnland. *Acta psychiatrica et neurologica,* 1942, 17, p. 47.

44. Brugger, C.: Psychiatrische Ergebnisse einer medizinischen, anthropologischen und soziologischen Bevölkerungsuntersuchung. *Zeitschrift für die gesamte Neurologie et Psychiatrie,* 1933, 146, p. 489.

45. Brugger, C.: Psychiatrische Bestandesaufnahme im Gebiet eines medizinisch-anthropologischen Zensus in der Nähe von Rosenheim. *Zeitschrift für die gesamte Neurologie et Psychiatrie,* 1938, 156, p. 189.

46. Sjögren, T.: Investigations of the Heredity of Psychoses and Mental Deficiency in Two North Swedish Parishes. *Annals of Eugenics,* 1935, 6, p. 253.

47. Schade, H.: Ergebnisse einer Bevölkerungsuntersuchung in der Schwalm. *Akademie der Wissenschaften und der Literatur. Abhandlungen der Mathematisch-Naturwissenschaftlichen Klassen,* 1950, 16, p. 419.