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**RESEARCH ON GENETICS  
IN PSYCHIATRY**

**Report of a WHO Scientific Group**

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WORLD HEALTH ORGANIZATION

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WHO SCIENTIFIC GROUP ON RESEARCH ON GENETICS  
IN PSYCHIATRY

Geneva, 8-13 November 1965

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# RESEARCH ON GENETICS IN PSYCHIATRY

## Report of a WHO Scientific Group

### 1. INTRODUCTION

A WHO Scientific Group on Research on Genetics in Psychiatry met in Geneva from 8 to 13 November 1965. The meeting was opened by Dr F. Grundy, Assistant Director-General, on behalf of the Director-General. Professor E. Inouye was elected Chairman and Professor N. E. Morton Vice-Chairman; Dr D. W. Kay was nominated Rapporteur.

After reviewing the present state of knowledge on genetics of mental disorders, the Group discussed the research areas where international collaboration (as opposed to research within national frameworks) is likely to be most productive.<sup>1</sup> At present direct comparisons of the data provided by workers in different countries is difficult, and clearer definitions, classifications and terminologies are highly desirable. Consideration was given to suitable means of collaboration, including the establishment of a permanent working group concerned with research on genetics in psychiatry.

In order to define the scope of the discussions more precisely, the Group decided to focus attention mainly on mental retardation and the functional and organic psychoses.

### 2. PRESENT STATE OF KNOWLEDGE ON GENETICS OF MENTAL DISORDERS

#### 2.1 General considerations

Psychiatric genetic research has endeavoured, through family and twin investigations, to examine the role of genetic factors in the occurrence and development of certain mental disorders—such as schizophrenia and manic-depressive psychosis—of mental retardation and epilepsy, of certain rarer mental diseases and, to a lesser extent, of psychopathy and neurosis.

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<sup>1</sup> The Group took into consideration the recommendations of a WHO Scientific Group on Mental Health which met in April 1964. No report of this meeting was published, but its work was reviewed in *WHO Chronicle*, 1964, 18, 380.

Genealogical statistical methods have been used in family, cohort and census investigations to produce empirical risk figures for the various psychiatric disorders. Attempts have been made to bring these results into agreement with the figures that could be expected if the diseases in question followed one of the well-established Mendelian laws of heredity.

The results of the many investigations in different countries show close agreement and, despite various theoretical objections, the familial appearance of certain mental diseases suggests that genetic factors are of considerable importance. With regard to the modes of inheritance it must, however, be admitted that—apart from certain diseases like Huntington's chorea and the various monomeric syndromes found among the mentally retarded and a few other groups—the results are not in accordance with simple Mendelian laws, although a number of additional hypotheses can be brought into play in order to explain the discrepancies. The interpretation of results has remained disputable, and it is a prevailing opinion that there is unlikely to be much further progress until results of other research, for instance in biochemical genetics, can be incorporated in psychiatric genetic investigations.

The more or less sensational morbid pictures upon which attention is usually focused, such as schizophrenia, manic-depressive psychosis or epilepsy, can hardly be said to represent the main expressions of the respective genes. Perhaps some of them can be regarded as more or less accidental exacerbations of some much more constant manifestation of the gene, a manifestation that it is not yet possible to recognize.

## 2.2 Clinical aspects

### (a) *Huntington's chorea*

This condition has long been known to be due to a single dominant autosomal gene with a penetrance of nearly 100%. Pathologically, the condition manifests as vacuolation and degeneration of neurones, with a marked local incidence (basal ganglia, especially globus pallidus, and cerebral cortex). Nothing is known of the biochemical basis of the disorder. A feature of great interest is the immense range in the age of onset, which extends from early childhood into the late sixties, with a mean about the age of 40 years. Another feature of considerable theoretical importance is that a proportion of cases begin with a psychosis, usually paranoid in quality, which is clinically indistinguishable from schizophrenia. The schizophrenic picture may persist for years before recognizable neurological symptoms appear.

### (b) *Other pre-senile organic disorders*

*Paralysis agitans*, when it appears spontaneously (and not, for instance, on a basis of cerebral vascular disease) may be due to an autosomal domi-

nant gene of rather low penetrance. Mental symptoms were quite common in one systematic study.

While *Alzheimer's disease* is usually considered to be due to an autosomal dominant gene, recent systematic work has led to the conclusion that it is more likely to be determined by polygenic inheritance. In *Pick's disease*, an autosomal dominant of much reduced penetrance is considered probable.

(c) *Senile dementia*

While the prevailing opinion has been that senile dementia is a variant of normal aging processes and therefore polygenically determined, a recent large-scale study provided a number of arguments indicating that a single dominant autosomal gene is involved, with penetrance increasing almost linearly with age from about 70 years. There seems to be no excess of Alzheimer's disease, Pick's disease, arteriosclerotic psychosis or affective disorders of old age among relatives of patients with senile dementia.

(d) *Epilepsy*

Polygenic inheritance is compatible with older investigations carried out in this field, including a number of twin series. However, there is also evidence strongly suggesting the operation of a dominant autosomal gene in some families. Of course, purely exogenous cases also exist.

(e) *Schizophrenia*

It is beyond doubt that the risk in relatives of schizophrenics is considerably raised as compared with the average population. Moreover, the risk is clearly higher, the closer the relationship, being at its highest in monozygotic twins. These findings constitute the background for assuming important genetic factors in schizophrenia.

The mode of inheritance has been subject to much discussion. The single gene hypothesis with either a recessive or a dominant autosomal gene, as well as a hypothesis of polygenic inheritance has been considered.

Sometimes schizophrenics occur in the families of manic-depressives, and conversely, but the prevailing impression is that the disorders are separate genetic entities. A basic problem, however, is the questionable genetic homogeneity of schizophrenia itself. Several attempts to identify subgroups with different modes of inheritance have been made. Generally, schizophrenia with favourable outcome has a lower risk of classic schizophrenia (dementia praecox) among the relatives than classic schizophrenia itself. Some of the atypical schizophrenias are instead related to epilepsy; others again have an increased risk of neurotic and psychopathic reactions among relatives. Thus, several genetic entities are involved. Schizophrenia-

like psychoses may occur in connexion with diversified organic conditions, genetic or non-genetic, as well as with psychogenic reactions.

So-called schizoid personality is seen preponderantly in the relatives of classic schizophrenics rather than in those of atypical schizophrenics.

*(f) Manic-depressive disorder*

Almost without exception, workers who have studied the genetics of manic-depressive psychosis have tended towards a hypothesis of dominant inheritance with a partial manifestation of the gene.

The problem of heterogeneity is again present here. Certainly, a distinction should be made between manic-depressive disorder and so-called reactive and neurotic depressions.

It is an interesting finding that the type of response to certain anti-depressant drugs, either positive or negative, seems to run in families.

*(g) Neuroses and personality disorders*

This is a difficult field for genetic research because environmental factors are obviously very important; nevertheless, it is likely that genetic factors do play some part in etiology. For instance, obsessional character traits have been found to be common in the first degree relatives of patients suffering from obsessive-compulsive neurosis.

On the whole, even if neurotic reactions are often environmentally conditioned, twin studies suggest that there are genetic factors underlying personality structure.

*(h) Mental retardation*

While the variation of "normal" intelligence is largely due to polygenic inheritance, the "pathological" variants and low-grade subnormality are often due to the effects of exogenous noxa, single gene substitutions, or chromosomal abnormalities. During the last decade, rapid progress has been made in this field. Thus, several circumscribed genetic entities are now known, and in some of them the nature of the metabolic disturbance has been revealed and proved amenable to treatment at least to some degree.

### **2.3 Biochemical and biological aspects**

In many branches of medicine, studies in the fields of biochemistry and genetics have often been mutually reinforcing: pathognomonic biochemical characteristics have provided useful and objective diagnostic criteria which have been applied in genealogical studies to yield information on the mode of inheritance. In psychiatry, a similar use has been made of biochemical information in certain forms of mental deficiency, but in

the case of the major psychoses this approach has not yet been made with success.

Significant biochemical abnormalities have been identified in mentally retarded subjects, their genetic basis being demonstrated along with crucial etiological or pathogenetic roles. Phenylpyruvic oligophrenia, one of the earliest to be recognized, has been the subject of extensive investigation.

Although the benefit that reportedly attends the withdrawal of phenylalanine from the diet suggests that the accumulation of this amino acid or its products is responsible for the mental defect, the identification of a substantial number of individuals with phenylketonuria but with normal intelligence argues in the opposite direction. Heterozygotes for the defect have been identified by means of phenylalanine-loading studies, and the development of simple urinary tests has permitted widespread screening of newborns for this rare disorder. Other genetic metabolic errors, some only recently identified, that are associated with mental defect include: galactosaemia, leucinosia (or maple syrup urine disease), Hartnup's disease, Tay-Sachs disease, and homocystinuria. The last-named is notable for being the first in which an enzyme deficit (cystathionine synthase) has been demonstrated in the brain.

Unlike some types of mental retardation, neither schizophrenia nor any of its major subgroups has been shown to be associated with a well-defined biochemical abnormality. One hypothesis receiving current attention postulates the transmethylation of normal metabolic products and the accumulation of abnormal amounts of psychotomimetic methylated derivatives. Exacerbation of a psychotic state in chronic schizophrenics upon the administration of large doses of methionine or betaine, two important biological methyl donors, is compatible with the hypothesis. The presence in the urine of a dimethylated congener of dopamine (3,4-dimethoxyphenylethylamine) has been reported by a number of groups to occur more frequently in schizophrenics than in normals, but several investigators find it to be equally common in normals, and some have adduced evidence that it is of dietary origin.

With regard to the affective psychoses, considerable research has been done on alteration in adrenocortical hormones, which represent at least an important secondary response of the adrenals to psychological stress. There is some evidence that alteration in electrolyte metabolism in the central nervous system plays a central role in affective states, and there is some inferential support for hypotheses relating biogenic amines in the central nervous system to normal and abnormal affective states. Thus reserpine has marked effects upon a number of amines in the brain, and monoamine oxidase inhibitors, which increase cerebral amine concentrations, are useful antidepressant drugs. There is evidence that implicates noradrenaline or serotonin as amines of special significance in affective disorders.

The list of psychoses associated with biochemical disorders is at present relatively small. Pellagra, a nutritional deficiency of nicotinic acid, is often associated with psychosis. Porphyria is sometimes associated with psychotic manifestations of various kinds. Wilson's disease, in which there is a deposition of copper in the brain as the result of a genetic deficit of ceruloplasmin synthesis, is frequently accompanied by severe neurosis or psychosis. Hypothyroidism and hyperthyroidism are quite often associated with neurotic or psychotic reactions. In addition, hypoglycaemia, acidosis, uraemia, and cerebral anoxia, brought about by a number of somatic disorders, may sometimes be responsible for psychotic states. A number of drugs and toxic agents are capable of causing a psychotic reaction. Of particular interest are those (amphetamine, iproniazid, reserpine, etc.) which produce psychoses in a relatively small proportion of individuals exposed to them.

Recent evidence supports the idea that in a substantial proportion of cases senile psychosis is due to cerebral ischaemia, and the degree of interference with normal mental function correlates well with decreased cerebral blood flow and oxygen consumption. Other processes associated with aging, however, may lead to mental deterioration for different reasons.

In a series of interesting experiments on rabbits it was shown that a stress response obtainable in these animals by the intravenous injection of normal human sera did not take place when the rabbits were challenged with sera from patients with Pick's disease, nuclear schizophrenia or general paresis.

Work done with sera from irradiated animals showed that such sera contained metabolites with antimutagenic activity, and that similar effects could be obtained using sera from some schizophrenic patients. These sera were haemolytic and the metabolites were apparently derived from substances like adrenochrome, dopamine, etc. It was speculated that the variability of schizophrenia as opposed to the static course of mental retardation might be related to the waxing and waning of these metabolites.

#### 2.4 Cytological aspects

Chromosome abnormalities now known affect almost 1% of newborn infants. In a proportion of people they are associated with abnormal mental function. About half the anomalies affect the autosomes and half the sex chromosomes.

##### (a) Autosomal aberrations

The commonest of these is caused by 21-trisomy, determining a condition sometimes referred to as Down's syndrome. An approximate incidence of 1.5 per thousand live births can be accepted as generally valid.

Psychological testing of persons with 21-trisomy has been extensively carried out, but young children and infants with this disorder have been studied very little and longitudinal investigations have not been completed, though a number are in progress.

The other trisomies have too short a life-span to allow development of psychiatric disorders. Mental retardation is, however, always observed. Conditions related to partial deletion of genetic material are now known: for example, deletion of part of the short arm of chromosome 5 ("cri du chat" syndrome) produces severe mental retardation. The same is true in the case of deletion of the short arm of chromosome 18.

Generally speaking, all the quantitative changes of autosomes now recorded (deficiencies, duplications and so on) are associated with mental retardation in the affected individual.

Biochemical consequences of these changes are not precisely known, the current hypothesis underlying research being that excess of genetic material produces an excess (or a deficiency) of biochemical reactions normally controlled by the genes located on the chromosomal fragment involved.

Biochemical studies in 21-trisomy were carried out even before the demonstration of the chromosome anomaly, but have received considerable impetus from the hope of locating genes on the trisomic chromosome. Thus observations have been made on the level of serum calcium, on the urinary excretion of  $\beta$ -amino isobutyric acid, on the urinary output of tryptophane metabolites, and on serotonin levels in the blood.

Work has been done on a number of enzymes of leucocytes or red cells of 21-trisomy subjects, and on gamma-globulins in their blood.

No definite data are now available concerning the three other autosomal syndromes: 13-trisomy, 18-trisomy, and deletion of chromosome-5 ("cri du chat").

(b) *Sex-chromosome aberrations*

The commonest anomaly of the sex chromosomes is Klinefelter's syndrome. Males with this syndrome are almost invariably chromatin positive, usually XXY and often chromosome mosaics. The frequency of XXY is about one in 600 newborn and that of XXY mosaics about one in 1600, an over-all frequency of chromatin-positive newborn males of about 2 per 1000. By contrast among mentally retarded males in institutions, the prevalence of chromatin-positive subjects is perhaps two to four times as great, little difference being observed whether severe or milder forms are studied. The same order of frequency has been found among chronic institutionalized male schizophrenics.

Triplo-X females have an apparent frequency of the order of one per 1200 liveborn girls. Among samples of the mentally abnormal in insti-

tutions, however, the prevalence of this group appears to be somewhat higher. Somatic abnormalities are generally absent in this condition.

Women with ovarian dysgenesis (O.D.) often have sex chromosome abnormality. There are three cytological groups: women with an XO sex complement, women who carry a structurally abnormal X chromosome, and finally those who are mosaics, with one XO cell line and one line which contains structurally normal X's.

It has been noticed by many workers that O.D. tends to be associated with only a slight degree of intellectual retardation. The proportion of XO females found among severely defective patients in institutions appears to be no greater than that expected in the general population.

In conclusion, a striking difference is observed between the effect of excess or lack of autosome material as compared with excess or lack of sex-chromosome material.

While autosomal imbalance always produces severe mental retardation and possibly leads to other psychological disturbances, most of the sex-chromosome imbalances, unless they are extreme, are not associated with marked mental retardation. Even in the relatively well-tolerated abnormalities (XXY, XXX, XO, etc.) there does, however, seem to be a greater susceptibility to functional psychiatric disorders.

### 3. RESEARCH TRENDS

#### 3.1 General considerations

Profound differences in the state of genetic understanding are to be found in the two categories of mental illness — defect and disorder. Several techniques are yielding good results in the study of mental defect, and the tempo of productive research has accelerated markedly in the last decade. On the other hand, the genetic study of the mental disorders has advanced very little as yet, but a consideration of the results obtained in the study of mental defects may also shed some light on mental disorders.

As regards "mental retardation of unknown etiology", the methods of population genetics are helpful in a way that is quite different from the familiar role of pedigree analysis in establishing the mode of inheritance of a well-defined entity. It has been shown, for instance, that the occurrence risk in sibs is sharply bimodal, the low-risk (sporadic) group having a normal inbreeding coefficient, while the high-risk group has a segregation frequency approaching one-quarter and a marked excess of parental consanguinity. Thus it appears that single, highly penetrant recessive genes are responsible for a large part of the high-risk group, which also includes at least one chromosomal anomaly. Recessive genes do not appear to play an important role for low-risk cases, which must represent

exogenous causes, chromosomal aberrations, polygenic inheritance, and other mechanisms.

Psychiatric diagnosis, based essentially on mental symptoms, is not always valid as an instrument for discriminating genetic entities. The delayed age of diagnosis for many mental disorders is an additional impediment to genetic analysis. Because of these difficulties, recessive inheritance has seldom been demonstrated, but several dominant disorders have been recognized through large pedigrees (Huntington's chorea, Pick's disease, and perhaps Alzheimer's disease). Dominant inheritance has been suspected in some cases of idiopathic epilepsy, but the evidence is inconclusive.

Psychiatric diagnosis should, as far as possible, be based on a phenomenological approach as well as on an independent consideration of questions of etiology.

Consideration of a variety of aspects is to be recommended also in genetic research. It may be advantageous to collect the basic material not only according to phenomenological criteria but also according to prognostic, physical or etiological criteria. Whatever the starting point, it must be kept in mind that homogeneity in the other aspects is not to be expected, and that pathoplastic factors, individual and cultural, will always influence the clinical picture.

There is indeed a need for genetic assistance in the endeavour to understand nosologic affinities across conventional classifications. Certainly it is of importance to establish empirically the risk of relatives of mentally disordered subjects being similarly affected and even to attempt to clarify the mode of inheritance. However, these cannot be the sole aims of genetic research. Quite as important as similarity is variation.

Genetic studies are helpful, somewhat paradoxically, in the search for environmental etiological factors. Monozygotic twins discordant for mental disorder, either in degree or quality, furnish ideal material for retrospective research on precipitating or contributory factors of an environmental nature, and perhaps in the near future for a biochemical approach. In this connexion it is important to remember that the concept of environment, as opposed to genetic equipment, is not confined to the psychological sphere but includes also the physical. Prospective twin studies have been made by selecting pairs of identical twins discordant for a particular environmental factor, such as cerebral concussion or alcoholic abuse, and trying to ascertain the effect of this factor in the one twin using the other twin as a control.

### **3.2 Clinical and epidemiological investigation**

It appears that a truly clinical approach using a wide variety of appraisal techniques is desirable in psychiatric genetic research. It is in the nature of

such an approach that observations and results vary according to the aspect of the problem on which the main emphasis is placed. This kind of diversity and divergence probably has to be accepted, and not restricted by an overzealous standardization. Instead, generous publication of case histories, not only of figures, should be facilitated. Central collection of psychiatric case-histories for genetic studies should be considered, as well as exchange of both material and research workers. The value of the work of certain investigators has been considerably reduced owing to lack of adequate clinical descriptions which others could evaluate. WHO could assist psychiatric genetic research by enabling full case histories of probands and secondary cases to be made available to other workers. Further, if more elaborate methods of recording interviews are developed, such as by the use of magnetic tape or videotape, this would be of considerable value in psychiatric genetics. The possibility of reviewing the original diagnosis may lead to increased understanding of the nature of psychiatric syndromes.

In an effort to improve diagnostic comparability for purposes of collaborative genetic studies, further consideration should be given to the use of standardized questionnaires on which to base case-histories. Psychiatrists and geneticists involved in such studies should co-operate in drawing up the questionnaires and subsequently in reviewing their usefulness. Establishment of working definitions of the diagnostic categories under investigation will be a prerequisite for collaborative studies. Cognizance should be taken of any findings available at the time from the work being carried out by WHO on the standardization of psychiatric diagnosis, classification and statistics, or from its programme of research on specific mental disorders.

In interpreting the results of family studies, the psychoses as opposed to mental retardation present certain special problems since they occur later in life, and in the latent period there is wide scope for various factors to interact with or modify gene action. Even when familial aggregation is found, there may be difficulty in proving that a genetic component exists, owing to the shared environment, physical as well as psychological.

The question of homogeneity of the material raises difficult problems of interpretation. There is evidence, for instance, that the phenotype may show considerable variation despite presumed genotypic homogeneity.

In studying the genetics of the psychoses of old age it is very important to recognize the need, as in younger ages, to collect material that is, as far as possible, diagnostically homogeneous. Twin studies, and other studies of families showing the condition to be investigated, are probably the most practical and economical methods available.

Huntington's chorea, with its clear genetic basis, might be regarded as the most favourable condition for intensive study, the detection of carriers being the immediate aim. However, the most pressing problem in the

whole field of mental disorder is to find a model capable of throwing light on the nature and mode of interaction of the genetic and environmental factors operating in the causation of schizophrenic illness.

The likelihood of a breakthrough that would revolutionize knowledge of schizophrenia—for example, in the field of biochemical genetics—now seems more remote than it did a few years ago, and long-term studies should therefore be encouraged.

One method that might throw light on the genetics of schizophrenia would be the retrospective study of twins discordant for this disorder. Another method, which has the advantage of being prospective and might be particularly fruitful, would be to make longitudinal studies of children having either one or two schizophrenic parents. The yield of information should be higher than in pedigree studies generally, since the children of affected parents are a high risk group. Although such a study would take some years to produce any results, it would be particularly relevant to the special problem of the interaction between genetic constitution and environment.

It is of considerable value to determine the incidence of mental illness under different cultural conditions, provided that common protocols and nomenclatures are used. A very complete recent study of a special area (Iceland) may be noted where, however, no appreciable divergencies in psychiatric morbidity from the situation compared with other Scandinavian countries came to light. For comparative purposes national registers should, as far as possible, be organized so as to give comparable data.

### 3.3 Investigations using twins

The classical twin method involves a comparison of the *rates of concordance* between monozygotic and dizygotic pairs.

In the initial stages of psychiatric twin research it was assumed that twin studies would answer the question of whether a normal trait or disease is determined by heredity *or* environment. It soon became evident, however, that heredity and environment contribute jointly to a major part of mental disorders, and also that the “choice” of environment is frequently determined by the genotype.

Even when concordance for psychosis is present, complete similarity in monozygotic twins is rare, although certain basic characteristics of the psychosis are usually similar. Thus, by arranging the symptoms according to the degrees of intra-pair similarity, a means is provided for judging nosologic relationships and the validity of certain diagnostic concepts and principles of classification.

In any study of concordance the method of ascertainment of twins requires close attention. Reliable consecutive sampling can be achieved by identifying individual cases suffering from psychosis in registers with

registered twin births, whereas a simple questioning of those patients who are known to be twins, or of twins who volunteer for investigation, easily leads to an over-representation of concordant cases.

The definition of the matrix population from which samples of twins are drawn is of equal importance. Recent investigations indicate that concordance rates may be higher in a population of chronic psychotics than among psychotics who are admitted for the first time, or who have never been admitted. It is recommended that, in future research, twin series should be drawn directly from birth registers.

Of even greater importance than the study of concordance is that of discordance in monozygotic twins. In fact this method affords the possibility of adducing a genetically identical control. Such cases constitute an ideal material for retrospective research into precipitating or contributory factors. Monozygotic twins may be used in prospective studies when one of the twins has been exposed to the influence of a well-defined psychological or physical experience.

Of special interest in this respect is the work on monozygotic twins who have been separated in early childhood and exposed to different socio-psychological environments. In some cases of this kind, marked dissimilarity in personality has been found, while in other cases the personality of the twins remained very similar despite wide differences in environment. This finding suggests that the influence of environment differs according to the particular genotypic background, a question that should be subjected to further investigation. In view of the rare occurrence of separated monozygotic twins, international collaboration in studies of this type is recommended.

The Group noted with interest the work already carried out by WHO on the methodology of twin studies, in connexion with the collection of information on twin material available in different parts of the world.

### 3.4 Genetic analysis

Genetic analysis of variability can proceed in either of two ways: by identification of the specific contributions of major genes, or by statistical manipulations based on the assumption of an indefinitely large number of genes with individually imperceptible effects. After a period when the second approach was in the ascendancy because of its practical application to plant and animal breeding, the major-gene hypothesis has received new impetus from the identification by biochemical, cytological, statistical, and experimental breeding techniques of genes with substantial effects on quantitative traits, leaving only a small proportion of cases for which the traditional methods of quantitative genetics are suited.

In the light of this work, we may predict that, in the future, major genes (perhaps as many different ones as have been identified in mental

defect) will be found to account for many cases of mental disorders, leaving a component due to polygenes and non-genetic mechanisms that will defy analysis. On this assumption, genetic analysis of mental disorders, as of other heterogeneous traits, should be directed to the characterization of major genes, rather than to elaboration of non-disprovable hypotheses about the residual cases.

In order of increasing seriousness, the principal obstacles to rigorous genetic analysis are :

- (a) incomplete ascertainment ;
- (b) etiological heterogeneity ;
- (c) incomplete penetrance (i.e., failure to identify clinically normal carriers of major genes).

With careful attention to the ascertainment procedures, especially the identification of probands and independent ascertainment, modern methods of segregation analysis are adequate to control biases due to incomplete ascertainment. Etiological heterogeneity is a more disturbing complication, but "sporadic" cases (with low recurrence risks in relatives) can be separated from "high-risk" cases (with a high recurrence risk in relatives) and the latter submitted to segregation analysis. In this way cases of more direct genetic etiology, even if they constitute only a minor fraction of the total, may be studied.

However, any hypothesis that claims that a large fraction of the susceptible genotypes is unrecognizable must remain highly speculative. To prove such a hypothesis it is necessary to reveal a clear bimodality among the unaffected relatives of probands, one mode corresponding to normal genotypes and the other mode to susceptible genotypes that are not penetrant as clinical disease ("the carrier state"). The use of discriminant functions to establish differences between relatives and controls is one method of combining relevant objective criteria into an index that might reveal this bimodality. Among the possibly useful criteria for such analysis are drug responses, scales of subclinical severity, EEG records, and scores on psychometric tests.

Discriminant analysis (and multiple regression analysis) has been employed to determine the best predictors of final diagnosis in 21-trisomy (Down's syndrome). In order to make use of this method in adult psychoses, some grouping criterion is necessary. Possibly, follow-up results, response to treatment or family aggregation might be used for this purpose.

Considerable advantages are at times to be gained from studying areas with high consanguinity rates, as has been shown in the case of mental retardation. There is, however, little evidence of high consanguinity rates among the mentally ill, although the data on this point are not very extensive. Since isolated communities are becoming rare, psychiatric genetic

studies among them will have to be done in the near future, if they are to be done at all. Where isolated communities are already included in genetic surveys, it would therefore be of advantage to include studies of psychiatric disorders.

Among less traditional genetic methods, the analysis of diallele crosses between different populations may be helpful and justifies the study of these populations. In this way, possible differences in prevalence and expression among ethnic groups could be explored, using the methods developed by geneticists for incomplete ascertainment, and these differences clarified by the great variety of interpopulational matings.

### 3.5 Cytogenetic studies

In addition to research on the deleterious effects of autosomal imbalance leading to severe mental retardation, investigations are at present being carried out on whether various chromosomal changes increase susceptibility to other psychiatric conditions.

In cases of sexual imbalance (XXY, XO, XXX and others), the recognized high frequencies among mental defectives indicate that long-term follow-up study of these persons would be of utmost interest. The detection of most of these conditions is feasible by the simple nuclear-sexing technique, and it would therefore be within the bounds of possibility to undertake longitudinal studies of the occurrence of psychiatric disorders in a large population of affected people. A possible correlation between these conditions and psychotic behaviour—schizophrenia, for example—could thus be directly detected.

In autosomal imbalances like 13-trisomy or 18-trisomy, such a follow-up study does not seem feasible. In 21-trisomy, however, the need for such inquiries is particularly obvious on two grounds, first to determine the speed of mental development of 21-trisomics, related to their actual age or IQ (progressive deterioration), and secondly to find how frequently such patients develop psychosis (e.g., schizophrenia) in adult life.

Special investigations could be made on the recently recognized "reciprocal syndromes". In these disorders some subjects suffer from the lack of a given portion of the heredity patrimony (deletion of the short arm of chromosome 5, for example) while others suffer from excess of that same portion (for example trisomy for the distal part of the short arm of chromosome 5).

These rare instances should be specially scrutinized for their psychiatric symptoms. The somatic stigmata observed in these reciprocal symptoms are mirror-images or counter types of each other. It would be valuable to study and compare psychiatric disorders associated with these reciprocal syndromes.

The general interest of psychiatric investigations in cases of known chromosomal aberrations, whether autosomal or sexual, is that they would permit study of rather large and homogeneous groups of patients in which the genetic aberration is precisely known.

Finally, it must be stressed again that investigations of biochemical effects of genetic imbalance are among the most urgent needs.

These studies can be achieved either by direct examination of individuals or by *in vitro* methods taking advantage of tissue culture techniques. The availability of theoretically unlimited numbers of cells carrying specific chromosomal changes permits an experimental approach, which would otherwise be impossible.

Close co-operation between laboratories is essential for the collection and comparison of very rare cases that are of great potential significance. An attempt has been made to achieve this on a regional scale in France. The organization undertaking this research<sup>1</sup> has a triple objective :

(a) pooling of technical knowledge, training of research workers and exchange of experts ;

(b) central collection and analysis of clinical, psychiatric and cytogenetic data on "exceptional cases" ;

(c) preservation by refrigeration of stem cells from patients with a rare chromosome anomaly (having such a "bank" would enable biochemical and cytogenetic comparisons to be made of cases too rare for collection in a single laboratory).

It might be considered feasible to carry out such a co-operative attempt on an international scale.

### 3.6 Biochemical studies

Continued and increased emphasis should be placed upon the search for biochemical abnormalities, with great attention to the necessity of ruling out alternative explanations and of demonstrating with rigour the specificity of the biochemical finding for the disorder in question. Attention should be given to devising techniques for the study of biochemical defects within the brain.

The question arises as to what clinical parameters correlate best with the biological criteria. Probably the most satisfactory parameter is the course that the disease takes (e.g., remitting, cyclic, recurrent or chronic).

It is most important in this respect to find out which of the many biological changes in the organism of schizophrenics and other psychotics are related to their genetic peculiarities, and which are directly related to

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<sup>1</sup> Recherche coopérative sur programme : cytogénétique humaine, CNRS, Paris.

the current pathological process. For these purposes it is necessary to organize a long-term and thorough investigation of a population potentially liable to schizophrenia or other psychoses. Such investigations should be combined with a detailed study of the families of the schizophrenic patients. Such forms of investigation are long and difficult, but in view of the relative unfruitfulness of previous investigations, they appear inevitable.

The genetic information already available may help to make the search more rational. Thus, research can be improved by comparing populations having a strong familial history of the disorder with those having a weak familial history, or by examining populations at high risk for the disorder.

The identification of some clinical subgroups of mental retardation, e.g., phenylketonuria or homocystinuria, has followed the discovery of a biochemical abnormality. Although this usually comes about by chance, an increasing number of examples of chemical abnormalities are detected among a large group of undifferentiated patients by screening procedures. The biochemical findings have served as the basis for more precise and objective genetic studies and have motivated the study of the fundamental biochemical mechanisms involved in the disorder. Studies on the families of patients have then readily yielded information on the genetic transmission of the disorder.

Human somatic cells cultured *in vitro* (for example, cells from organs and tissues of schizophrenic patients) may be used for genetic investigation.

Tissue culture experiments on foetal neuroglial cells, which are apparently primitive spongioblasts, should be continued. Human embryonic material from foetuses obtained at interruption of pregnancy were used in these studies and a comparison is now being made between tissues from non-schizophrenic controls and material from embryos where both parents were schizophrenic.

It is possible that drugs, or the chemical alterations that produce psychosis in only a limited number of subjects, may do so by potentiating a genetic vulnerability. This hypothesis could be tested by examining the incidence of psychosis in the families of those individuals who have shown a psychotic reaction to one or another of these drugs.

The possibility should be carefully explored of identifying the major genes determining the metabolism of psychomimetic drugs, antidepressants, mono-amines, methylated hydrocarbons and other substances that may be of etiological significance for psychosis. A model for this is the polymorphism determining the inactivation rate of isoniazid which was discovered in tuberculosis therapy but might be relevant to psychosis, since slow inactivators are much more prone to side effects after chronic administration of isoniazid. Both the identification of major genes in these systems through family studies and the comparison of gene frequencies in psychiatric groups and controls are important. Conceivably, the major polymor-

phisms, such as blood groups and serum proteins, affect the risks for psychosis, just as, for example, the ABO types have been shown to vary in risk of stomach cancer and duodenal ulcer. A possible association between sex-linked glucose-6-phosphate dehydrogenase deficiency and schizophrenia has been reported. Studies to confirm and extend these findings are desirable.

Finally, the biochemical basis of psychoses associated with chromosomal anomalies should be investigated in man and in experimental animals (for example, the XXY mouse and cat, and the XO mouse). In general, mutants in laboratory mammals with effects on behaviour provide valuable opportunities for biochemical studies.

#### 4. SUMMARY AND RECOMMENDATIONS

The Group emphasizes that advances in psychiatric genetics are likely, to a considerable extent, to be linked with advances in psychiatry as a whole and puts forward the following recommendations :

##### **Standardization of psychiatric diagnosis, classification and statistics**

The Group notes the on-going WHO projects on standardization of psychiatric diagnosis, classification and statistics as highly relevant to research in its own field, and strongly recommends continuation of this work. Since increased knowledge in psychiatric genetics should eventually make its own contribution to problems of classification, the two approaches can be regarded as interdependent ; it would therefore be an advantage if the exchange of information between workers in the two fields could be improved. The Group also points out that improvement and modernization of the techniques employed in establishing the existing national registers of psychiatric cases, and a wider recognition of their value could greatly facilitate the collection of source material for psychiatric genetic studies.

##### **Topics for international research**

A number of topics on which further research is needed have been mentioned in the body of the report.

The following are some examples of projects where the scarcity of suitable cases for investigation makes it highly desirable for interdisciplinary research to be conducted on an international scale :

(i) Research connected with the frequency of chromosome abnormalities, the relationship between these abnormalities and mental disorder or retardation, and the search for their biochemical correlates.

(ii) Family studies of patients who have experienced psychoses induced by drugs.

(iii) Studies concerning genetic-environmental interactions, especially those requiring an unusual combination of circumstances, e.g., study of twins separated early in life, of monozygotic twins discordant for mental disorder, and of adopted children and their families in relation to mental illness.

(iv) Collection of histologically confirmed cases of certain rare diseases, such as Pick's disease, with a view to carrying out family studies.

A different type of approach involves the psychiatric study of whole populations. Since the presence of recessive genes is brought to light by inbreeding, there is a case for undertaking comparative studies of isolated communities and of communities with a high degree of racial admixture. In this way, further examples of recessive disorders in the field of mental retardation or of mental disorder might be identified. Since isolated communities are becoming increasingly rare, studies of this kind will have to be done in the near future if they are to be done at all. The Group points out that where isolated communities are already the subject of genetic or epidemiological surveys, it would be an advantage if a psychiatric geneticist were attached of the team conducting the survey.

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