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# **BIOLOGICAL RESEARCH IN SCHIZOPHRENIA**

**Report of a WHO Scientific Group**

**WORLD HEALTH ORGANIZATION**

**GENEVA**

1970

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RESEARCH IN SCHIZOPHRENIA

Geneva, 13-17 October 1969

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## **BIOLOGICAL RESEARCH IN SCHIZOPHRENIA**

### **Report of a WHO Scientific Group**

#### **1. INTRODUCTION**

A WHO Scientific Group on Biological Research in Schizophrenia met in Geneva from 13 to 17 October 1969. The meeting was opened by Dr L. Verhoestraete, Director, Division of Health Protection and Promotion, on behalf of the Director-General.

The first meeting of a WHO Scientific Group on Mental Health Research, in 1964, pointed out the lack of firm knowledge on the etiology and pathogenesis of mental disorders. Following the recommendations of the Group, WHO developed two research programmes, one on the diagnosis, classification, statistics and epidemiology of mental disorders, and the other on biological psychiatry.

As part of the first programme, a series of annual international seminars on the diagnosis, classification and statistics of mental disorders has been organized, the first of which, held in 1965, concentrated on schizophrenia. An International Pilot Study on Schizophrenia (IPSS) was initiated in 1965 and involved collaborating research centres in nine countries.

Four scientific groups were convened between 1965 and 1968. These considered : genetics in psychiatry;<sup>1</sup> neurophysiological and behavioural research in psychiatry;<sup>2</sup> research in psychopharmacology;<sup>3</sup> and the biochemistry of mental disorders.<sup>4</sup> Certain recommendations made by these scientific groups are being implemented. A network of international and regional reference centres on psychopharmacology has been established.

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<sup>1</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1966, No. 346.

<sup>2</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1968, No. 381.

<sup>3</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1967, No. 371.

<sup>4</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1969, No. 427.

Research projects initiated include studies on groups with a high risk of developing mental disorders and an investigation of the influence of malnutrition on intellectual growth and emotional maturation. Problems of methodology in psychiatric and particularly psychopharmacological investigations have come under detailed discussion.

After the first phase of relatively independent development of the two research programmes, it was considered feasible to investigate the extent to which biological methods of research could be applied in collaborative studies of specific mental disorders, and on the other hand to study the applicability of epidemiological research methods to biological studies in psychiatry. Both possibilities are discussed in this report.

Many meetings on biological and other research in schizophrenia have been held in different parts of the world. The literature on this subject is voluminous and intensive investigations are being carried out. This report concentrates on selected aspects of such research, reviewing the more important methods of research in genetics, neurophysiology, psychopharmacology, and biochemistry that hold promise for application to investigations of schizophrenia. Biological investigations into the schizophrenic disorders are undertaken with the general aims of throwing light on etiology, understanding the mechanisms underlying the formation and change of symptoms, measuring severity, monitoring response to treatment, and predicting the course and outcome. This report also considers the extent to which past work has contributed to knowledge of the etiology, prevention, treatment, and prognosis of various subgroups of schizophrenia and has suggested lines of work that are likely to be productive in the future.

One of the main obstacles to such research is the fact that schizophrenia is not a well defined entity and presents itself in very different ways; indeed, considerable disagreement exists between different schools of psychiatry and individual psychiatrists as to the connotation of the term. However, the WHO International Pilot Study of Schizophrenia (IPSS) provides an example of how investigators with different clinical backgrounds and training can collaborate in the collection of standard data about schizophrenic patients, while preserving their own points of view. The methods used in the IPSS, and the experience of the groups of investigators in the 9 centres taking part in it, could contribute towards the success of any of the study programmes recommended in this report.

Section 2 of this report outlines some of the major areas of biological research in schizophrenia. Section 3 considers some problems of design and method and includes an outline of the IPSS as an example of how some of them can be overcome. The training of research workers for work in international projects is considered in section 4, and section 5 makes recommendations on promising lines of biological study in schizophrenia, affective disorders, and mental subnormality.

## 2. MAJOR AREAS OF BIOLOGICAL INVESTIGATION OF SCHIZOPHRENIA

The nosological entity "schizophrenia" is made up of many dissimilar and even contrasting behaviour modes, symptoms, and patterns of development of clinical events. Inhibition is marked in catatonic stupor, whereas increased psychomotility is evident in states of paranoid belligerence; there is profound affective lameness in states of asocial withdrawal, such as those seen in "simple schizophrenia" — yet all these dissimilar clinical conditions have been called schizophrenia. For this reason it is generally more appropriate to use the term "schizophrenic illness", or to refer in the plural to "the schizophrenias". To break down schizophrenic phenomena into sets of characteristics that can be defined facilitates observation and analysis at many levels of biological and social investigation. This approach, which does not view symptoms, behavioural states, or other biological phenomena in isolation from their clinical context, facilitates the study of specific syndromes and of their interrelationships.

### 2.1 Genetic research

A number of different genetic techniques have been used in the study of schizophrenia. These are outlined below.

(1) The genealogical method, widely used in earlier times, frequently gave insignificant or even misleading results. The starting point of such studies was usually families in which an accumulation of mental disorders had been found, and since such accumulations were often socially determined or arbitrary, and were frequently quite heterogeneous, accurate genetic interpretation of them was impossible.

(2) When, later on, the search for Mendelian inheritance in schizophrenia started it became obvious that representative samples were necessary. As no clear Mendelian mode of inheritance could be demonstrated, a period followed during which the method of determining the "empirical prognosis" was widely applied, yielding many important results. It was necessary to compare the life-time expectancies for mental disorders found during such studies with the corresponding expectancies in the general population. As a result, geneticists developed a special interest in psychiatric epidemiology, an interest that was later shared by "environmentalists". The interpretation of results was for some time hampered by an "either-or" attitude, but an unbiased approach to the study of the interaction of genes and the environment gradually developed.

(3) The study of schizophrenia in individual pairs of twins led to an over-representation of concordant cases, and it became clear that the study of unselected twin series was a necessary condition for obtaining valid results. Despite the introduction of this principle, the results of investigations of twins are still somewhat controversial. Differences in concordance rates for schizophrenia in different series of twins show variations that cannot at present be fully explained. However, most of the evidence suggests the presence of a genetic factor in schizophrenia, although it seems to be less potent than was previously reported. Furthermore, concordance of mental traits is less informative than concordance of physical characteristics, since the former may arise partly from the sharing of the same environment. Twins reared apart are therefore of special interest; however, the number of such cases that have been reported is quite insufficient to allow definite conclusions to be drawn in relation to schizophrenia. At present there is general agreement that differences between monozygotic twins are of special interest, since they are the best existing clue to the influence of environmental factors.

(4) Studies of children reared in separation from their biological relatives permit a relatively sharp distinction to be made between the effects of nature and those of nurture. The results of the first extensive investigations of this kind have confirmed the importance of genetic factors in the etiology of schizophrenic illnesses.

(5) Chromosome studies have not yet given information of relevance to schizophrenia research. Chromosome aberrations do not seem to be more frequent in schizophrenic persons than in the general population. Among patients with the XXY-constitution there is an over-representation of mental deviations; a few investigators have claimed that schizophrenia is relatively frequent among such patients, but other investigators have been unable to confirm this.

(6) There have been reports that the fertility rate in schizophrenic patients is now increasing towards more normal levels. The establishment of the validity of this finding — and, if it is valid, the study of its origins and consequences — would be important.

## 2.2 Biochemical research

Biochemistry has been applied increasingly in recent years to the study of schizophrenic illness. This has been encouraged by the formulation of several new biochemical hypotheses on the causation of schizophrenia and by a growing appreciation of the importance of genetic factors, since it is known that genetic effects are coded and expressed through biochemical mechanisms.

*Biochemical hypotheses*

Many biochemical studies in schizophrenia in the past decade have concentrated on the possibility that either an abnormal amine in the central nervous system (CNS) or an abnormal protein in the blood plasma is significantly related to schizophrenia. Neither hypothesis has been completely discredited or completely confirmed.

The amine hypotheses are based on the known presence and distribution in the CNS of amines that are chemically related to certain psychotomimetic drugs. Three important amines are found in the brain together with the enzymes needed for their synthesis and breakdown: dopamine (the precursor of norepinephrine), norepinephrine, and serotonin. The latter 2 amines are concentrated particularly in brain regions involved with affect and with the higher control of learning, motivation, and behaviour. Many drugs (e.g., mescaline, lysergic acid diethylamide, dimethyltryptamine, and psilocybin) that produce florid psychotic symptoms in certain subjects are either *N*-methyl or *O*-methyl derivatives of these 3 amines. Both *N*-methylation and *O*-methylation are known to occur.

Based on these observations, the following main hypotheses have emerged: (1) the catecholamine hypothesis (that an abnormal psychotomimetic catecholamine metabolite is produced in the body); (2) the tryptamine hypothesis (that a psychotomimetic derivative of tryptamine is produced); and (3) the transmethylation hypothesis (that the basic biological defect in schizophrenia is a disorder of the methylation process).

Attempts to test these hypotheses have led to the following findings:

(1) As predicted by the first hypothesis, there have been reports that schizophrenic patients excrete an abnormal catecholamine metabolite (dimethoxyphenylethylamine) and that normal subjects do not. Some groups have reported confirmatory evidence, but others have failed to reproduce the original findings. A relationship to dietary intake has been demonstrated.

(2) It has been reported that various amines, particularly tryptamine, are excreted in increased amounts during the exacerbation of a schizophrenic psychosis, with a return towards base-line levels during remission. However, it has been suggested that such changes are related to non-specific factors (e.g., changes in food intake and nitrogen balance).

(3) Several investigators have reported that the administration of large doses of the major methyl donor, methionine, together with MAO inhibitors causes exacerbation in a minority of schizophrenic patients. The administration of other methyl donors has given similar results. However, the extent to which such exacerbations are toxic reactions superimposed on a schizophrenic psychosis is not clear.

A number of different hypotheses have led to a search for abnormal substances in the blood plasma of schizophrenics. Most such studies have sought evidence of an abnormal protein that can be identified by (a) its effects on animal behaviour (e.g., the disruption of learned responses); (b) its toxic effects and the development of pathological lesions following its injection into animals; or (c) its effect on some biochemical "test system", such as the ratio of lactate to pyruvate formed in the medium after chicken erythrocytes have been incubated with a patient's plasma. Some workers have reported the detection of increased levels of macroglobulins and other proteins in schizophrenic patients, and the production of schizophrenic symptoms in human volunteers to whom these proteins were administered, but other workers have failed to reproduce these findings. There have also been reports of the presence of an abnormal protein that is believed to alter the permeability of nerve cells to precursors of neurotransmitters, but the evidence is conflicting. The reported findings may depend on factors other than schizophrenia.

New lines of inquiry, reports of positive findings, and new hypotheses continue to appear. Each of these requires adequate critical evaluation.

#### *Biochemical techniques*

The application of biochemistry to the study of schizophrenia has also been stimulated by the development of a number of new techniques for measuring the concentration of metabolites in the tissues and body fluids of patients. Some of the ways in which biochemical investigations can be carried out — depending on the type of information that is required — are outlined below.

(1) *Measurement of static concentrations of metabolites in body fluids and tissues.* The metabolites that can be studied include inorganic ions, trace elements, vitamins, and many compounds concerned in carbohydrate, lipid, and protein metabolism. Measurements of enzymic activity can also be made. The samples that are normally obtainable for study include urine, blood serum, blood cells, saliva, sweat, sebum, and cerebrospinal fluid. Biopsy samples of brain tissue are not generally available, but they have been investigated in some special cases. Sometimes it may be advantageous for frozen samples to be transported to centres where special investigations can be carried out.

The significance that can be attached to a single experimental finding, such as the level of a plasma metabolite, depends not only on the validity of the method but also on the extent to which the level changes in a given patient from time to time. A preliminary study to establish these facts is usually necessary before the investigation of an experimental series is undertaken.

(2) *Post-mortem studies.* The availability of fresh autopsy material varies widely in different countries, and this is an area in which international co-operation can be helpful. In some countries the regulations are relatively favourable, and brain tissue can sometimes be obtained shortly after death. Deep-frozen specimens can then be sent long distances by air.

Investigations of fresh autopsy material tend to be slow and difficult to organize. Generally they are best arranged at centres where special techniques are in use for other purposes and are therefore available for use at any time. In addition to the determination of compounds in endocrine and other organs, further studies are needed of metabolite levels (e.g., biogenic amines) and enzymic activity in localized regions of the brain. A number of new histochemical methods are now available and could be applied to this problem; these include combined examination by light and electron microscopy and the use of fluorescence techniques.

(3) *Loading tests.* The performance of a metabolic system *in vivo* can be studied by a tolerance test in which the changes are measured after administering a test dose of a metabolite. This approach gives more information than the measurement of static levels, but it requires the attendance of the patient over a period of time. Measurements of glucose tolerance and tryptophan tolerance are examples of tests that have been widely used.

(4) *Radioisotope techniques.* Radioisotope-labelled compounds are becoming increasingly available and they can be used for measuring rates of metabolite turnover, rates of transport, rates of hormone secretion, etc., *in vivo*. A useful application is the measurement of tissue fluid volumes by the isotope dilution method. The use of metabolites labelled specifically in certain positions (e.g., 5-hydroxy[carboxy-<sup>14</sup>C] tryptophan) enables special aspects of metabolism to be studied. The application of these techniques to the study of mental illness has become possible with the development of counting equipment that is sufficiently sensitive for the measurement of minute quantities of radioisotopes, so that safe doses can be given.

(5) *Response to endocrine factors and drugs.* Useful information may be obtained by measuring the metabolic changes produced by certain drugs (e.g., reserpine and monoamine oxidase inhibitors). In phenothiazine treatment, the level of the drug itself in the tissues and body fluids is of interest. Basic biochemical research on the mode of action of psychotomimetic and other drugs is also relevant. There are interesting relationships between widely used neuroleptic and psychodysleptic (hallucinogenic) agents, and these could be further explored.

Further information can be obtained by the use of specific enzyme inhibitors that block certain pathways and thus change the levels of meta-

bolites. The effects of endocrine factors, such as insulin and thyroid hormones, are also of interest, as are the effects of administering amino acids (e.g., methionine) that affect the mental state.

### 2.3 Neurophysiological and behavioural research

Neurophysiological and behavioural studies are concerned mainly with the analysis of the mechanisms underlying psychopathological disturbances, and only indirectly with questions of etiology. The early work in this field concentrated on the analysis of in-going stimuli and out-going responses, but the recent trend has been to consider central mechanisms, such as memory and recall, also.

Studies on animals have led, in particular, to the accumulation of data on the functions of the reticular activating system and the limbic system (or "visceral brain"), and a number of hypotheses concerning schizophrenia have been put forward on the basis of such work. It has been suggested, for example, that some schizophrenic patients are in a state of hyperarousal because of a dysfunction in the reticular activating system and that certain tranquilizing drugs act to correct this state. It has also been suggested that the reticular activating system may be the basis for the behavioural and subjective phenomena encountered in sensory deprivation, sensory overload, and sensory distortion which are analogous to some of the symptoms of schizophrenia.

#### *Studies of "arousal"*

Hypotheses concerning "arousal" have also given rise to investigations of schizophrenic patients. For example, it has long been known that the autonomic reactions in acute schizophrenia are exaggerated and are similar in some respects to those of highly anxious individuals. In schizophrenic patients who have been ill for many years, there have been several observations indicating a state of high arousal, as indicated by a high level of skin conductance, a high heart rate, a high sedation threshold, a low variability of the EEG, a low threshold of fusion of two consecutive clicks or flashes, and the improvement of behaviour following the injection of amobarbital sodium. It has also been found that over-arousal is closely correlated with social withdrawal in patients with certain types of chronic schizophrenia.

It is important both to repeat these studies using reliable techniques of measurement under standard environmental conditions, and to discover how the findings are related to various clinical syndromes and to the time course of the schizophrenic disorders. Other important questions that require further investigation are the influence of drugs and the

extent to which elevated levels of substances such as monoamines, adrenal steroids, or abnormal metabolites are related to various states of arousal.

#### *Electroencephalography*

Much of the previous work on abnormalities of the EEG in schizophrenic patients has been vitiated because of a lack of precision in diagnosis and in the definition of what constitutes a deviation from normal, and because allowance has not been made for the effect of various types of biological treatment. There is at present no evidence that an abnormal EEG occurs more frequently in the schizophrenic disorders, but further studies, particularly of temporal lobe function, in untreated patients would be worth while. There is also some indication that the pattern of the waking EEG may be related to the outcome of the condition, a slow regular rhythm indicating a poor prognosis and an irregular rhythm a good one. Quantitative analysis of the EEG, using a digital computer, may be a useful technique of measuring drug effects in the treatment of schizophrenia. The technique of evoked potentials has not yet been sufficiently explored in the study of the schizophrenic disorders, but it might well repay attention. Telemetric studies are also likely to prove valuable.

#### *Conditioning*

Conditioning methods have been successfully used to give a subtle and detailed description of the behaviour of schizophrenic patients under laboratory conditions. Data concerning disturbances in conditional reflexes have been correlated with changes in clinical state. Early studies of higher nervous activity led to useful general concepts, but much greater precision is required to cope with the complex data on various brain structures afforded by modern electroneurophysiology. Behavioural therapies, now regarded as forms of psychotherapy, have been elaborated on the basis of conditioning. Of these, operant conditioning is the most promising for the treatment of schizophrenic patients.

It is possible to investigate the relationships between motor, autonomic, and central responses to a stimulus using polygraphic recording. One finding that deserves further investigation is the observation that retarded patients who show a diminished motor response but an increased autonomic response to a stimulus have a relatively good prognosis. Some such patients also seem to show poor central conditioning of the arousal reaction. Another interesting report is that some schizophrenic patients become habituated to stimuli more slowly than non-schizophrenic patients.

Conditional reflex studies may be helpful in providing objective criteria for evaluating the quality of remission and the prognosis in schizophrenic disorders. However, few systematic studies have been carried out in this area.

*Sleep studies*

The observation that deprivation of sleep can give rise to psychotic symptoms in normal subjects has led to the study of sleep in schizophrenic patients. The only agreed finding has been that some schizophrenic patients sleep less deeply than non-schizophrenic subjects, but a number of other results deserve investigation. For example, it has been suggested that borderline schizophrenic patients show an increase in the paradoxical stage of sleep and that schizophrenic patients deprived of the paradoxical stage, with or without rapid eye movements, do not show the ordinary rebound phenomenon.

The value of all these studies would be enhanced if the clinical symptoms, stage of illness, conditions of observation, and drug or other treatment were controlled.

**2.4 Psychopharmacological research**

Psychopharmacology makes use of the methods of pharmacology, physiology, biochemistry, and other biomedical sciences. Clinical psychopharmacology contributes to research in schizophrenia by assessing the clinical effectiveness of drugs and the relevance of drug mechanisms to the study of theories on the etiology of schizophrenic disorders.

In our present state of knowledge the clinical effectiveness of a given drug for treating schizophrenic disorders can best be defined on the basis of the extent to which it modifies symptoms and syndromes. Thus, concepts of the clinical mode of action are possible only on the level of symptomatology and social functioning. The administration of neuroleptic drugs has become the treatment of choice for schizophrenic patients. Experience with this therapy throughout the world can be expected to yield extensive data on changes in clinical epidemiology during the past 15 years.

However, although the literature on drug investigation is both extensive and voluminous, there remains considerable disparity in the findings and opinions on the action and effectiveness of drugs in schizophrenic disorders. Consequently, attention should be focused on the problems and lacunae in knowledge that still exist despite the steady refinement of methods of research and data analysis. Several major problem areas can be identified, as follows.

(1) High priority should be given to the monitoring of drug usage. It is estimated that 20 % of in-patients and 40-50 % of out-patients do not take drugs as prescribed, do not take them at all, or add other drugs of their own choice. As long as drug intake cannot be ensured, clinical evaluations must remain presumptive. Monitoring is essential with

the recently introduced lithium treatment, owing to the complications that can arise from dose-dependent toxicity. However, monitoring also has other uses — e.g., it can identify modes of drug metabolism that account for variations in response. Further knowledge of the interaction between drugs and individual constitutional differences will undoubtedly contribute to a better understanding of such variations.

Clinical monitoring, furthermore, should determine drug effects in relation to changes and fluctuations in psychopathology. Just as the dosage of insulin and digitalis in the treatment of diabetes and cardiac failure, respectively, must be adapted to the severity of the pathological condition, the dosage of psychoactive drugs must be adapted to evidence of adverse effects and changes in the pathological condition and in social functioning.

(2) The definition of therapeutic objectives is another problem area. Schizophrenia is a set of illnesses of unknown etiology and it is inappropriate to use terms such as “anti-schizophrenic” drugs. The use of such terms might lead physicians to subject all schizophrenic patients to drug treatment. The concept of “target symptoms” has been widely used in decisions regarding drug treatment. Investigation of the action of drugs on these symptoms should lead to increased understanding of schizophrenic psychopathology.

At present the majority of patients are kept on drug treatment for prolonged, if not for indefinite, periods regardless of the onset and history of their illness. Prolonged medication may be given either to treat continuing symptoms or, in patients who do not show symptoms, to prevent future psychotic episodes, and these two objectives should be clearly distinguished. The treatment of periodic mood disorders with lithium has both therapeutic and preventive goals. Schizophrenic patients have been divided into subgroups on the basis of the periodicity of their symptoms. Continuous treatment that disregards such periodicity may obscure the nature of the clinical manifestations.

(3) A satisfactory answer has never been given to the question of which schizophrenic patients should not be treated with drugs. Patients in the “therapeutic failure” category have been classified as non-responders or as refractory. This would seem to imply that a new drug may succeed where others have failed. Continual substitution of one neuroleptic compound for another has been the practice for many years. However, if, neuroleptics are syndrome-specific it would seem unlikely that all schizophrenic patients could benefit from neuroleptic treatment. It is more probable that the condition of patients with certain characteristics would be worsened. There is, therefore, a need to know whether such patients are non-responders because of a psychopathological condition that should for the present be regarded as not treatable with drugs.

(4) Clarification of the differential effects of neuroleptic compounds is necessary. It is probable that the neuroleptics (and, for that matter, other psychoactive drugs, such as antidepressants) act specifically on certain symptom constellations, and studies should be undertaken to demonstrate such selectivity and specificity.

(5) In evaluating the effects of drugs, much work has been done on changes in the patient's symptoms, but little attention has been given to the way in which the patient functions in society. The aim of modern treatment of many disorders of unknown etiology is the restoration of full functional capacity. The aim of chemotherapy of schizophrenic disorders can be thought of similarly. Successful restoration of function is a major therapeutic achievement, regardless of the lack of knowledge of etiology. However, schedules for measuring socio-functional capacity on the basis of standardized scales have not yet been evaluated for use in comparative international studies. The further development of such rating schedules would be an important aid to longitudinal evaluations of the effectiveness of drug treatment.

The problem areas outlined above merit high priority if clinical psychopharmacology is to make significant contributions to research in schizophrenia. If this goal is to be achieved, hypotheses that take into account the complexity of schizophrenia are necessary. The formulation of such hypotheses is most likely to occur if psychopharmacological research moves from isolated projects to internationally designed collaborative studies. (The relevance of some of these areas to the IPSS is noted on page 32.)

## 2.5 Other biological research

### *Constitutional attributes*

The human constitution is the sum total of an individual's morphological, psychological, and physiological characteristics, all determined by the interaction between heredity and environment.

Physique lends itself more readily to exact measurement than do other constitutional attributes, and it provides a convenient starting point for the study of correlations between various aspects of human constitution, including susceptibility to diseases such as schizophrenia. Many different methods have been used for assessing physique, including somatotyping, the factorial analysis of body measurements, the assessment of relative development of tissues (e.g., muscle, fat, and bone), and the measurement of the proportions of the masculine and feminine components of physique (androgyny).

Recent studies using all the above methods have shown that 80 % of the variation in human physique can be accounted for by 3 factors :

body size, body shape, and androgyny. It is now possible to assess these factors by taking 4 body measurements (stature, transverse chest diameter, biacromial diameter, and bicristal diameter), and from these to obtain indices of body size, body shape, and androgyny.

There is some evidence that body type may be related to predisposition to schizophrenia, to the form under which it appears, to the age at which it appears, and to its course.

There is a need for further studies of these relationships in groups of patients from different parts of the world and on the correlations that may exist between various aspects of schizophrenia and other constitutional factors such as body size and androgyny.

#### *Other areas*

Other fields of biological research in schizophrenia include neuropathological studies employing newly developed histological and electron microscopy techniques, and the study of other constitutional attributes such as blood groups, cardiovascular characteristics, abnormalities in the leucocytes, and immunological processes. Further investigations are required to find a biological explanation for the known effects of age and sex on the course and clinical manifestations of different forms of schizophrenic illness.

### **3. DESIGN AND METHODS OF RESEARCH**

#### **3.1 General methodological principles**

General methodological principles may be drawn from the numerous conflicting findings, and failures to reproduce findings, of earlier biological studies of schizophrenia. Not all of these will be equally applicable to every study, but the Group suggests that careful attention be given to each of these points before studies are undertaken.

(1) Primary emphasis should be placed on the essential need to have, for each patient studied, not only a nosological diagnosis but an adequate, quantified description of his present clinical state. This should include symptoms that are relevant to psychopathology and also more general aspects of the patient's observed behaviour. Clearly it is necessary to define precisely (a) the patient's present clinical state, (b) the course of his illness, and (c) the many conditions, other than his mental condition, that may influence his present state: diet, medication, activity, and the like. It should be possible to derive quantitative descriptions of the patient's condition from the individual items in an evaluation schedule. The IPSS Present State Examination schedule described in section 3.6

is an example of such a schedule and it could be used by centres collaborating in a co-ordinated international programme of biological studies. If further analysis of IPSS data shows that the Present State Examination schedule and related schedules function satisfactorily, the training and experience that have made such international agreement possible in measuring a most difficult set of clinical phenomena should be recognized as a most valuable research resource, and these schedules should be given careful consideration for possible use in biological studies.

(2) Despite our inability to deal with all variables, every effort should be made to control and/or to measure or rate factors known to influence biological systems involved in current hypotheses on schizophrenia. It is normal to assess the patient's clinical status, but other factors that affect such systems should also be taken into account, including the following :

- (a) the patient's past and present drug intake;
- (b) other treatment that the patient has received;
- (c) the patient's medical history (a complete medical examination should be given, and all nonpsychiatric findings and diagnoses should be recorded);
- (d) the composition of the diet and the patient's nitrogen balance and weight changes (where feasible, the weight should be measured periodically and frequently);
- (e) the patient's use of common stimulants (coffee, tea and tobacco);
- (f) the patient's activity level;
- (g) social and other environmental factors; and
- (h) the patient's biological cycles (e.g., sleep record).

An attempt to control or measure the above factors involves complex problems, some of which — e.g., the monitoring of drug intake — are considered in other sections of this report. If a collaborative study were to be planned, it would be necessary to reach agreement on the methods to be used for control and measurement and for different groups of patients (e.g., in-patients and out-patients).

(3) At present it is not possible to identify any single area for schizophrenia research that seems more promising than others. Consequently, it is desirable that biological investigations of schizophrenia be widely based so as to include neurophysiological, biochemical, psychopharmacological, genetic, and other studies. It is possible to obtain significant information when data from multidisciplinary sources are collected and analysed by correlation, cluster, multivariate, and other techniques.

(4) Clear and definitive negative results as well as positive findings are important in making progress in the understanding of schizophrenia.

(5) Careful consideration must be given to the statistical as well as to the behavioural and biological techniques to be used. Certain scales may facilitate correlational analysis better than others. Provision should be made for dealing with incomplete data, since there will be few variables for which all centres can obtain data for all patients. The data system should enable simple rapid tests to be made of hypotheses involving 1 or 2 variables and should also be suitable for more complex cluster and factor analyses. A large number of data from multidisciplinary sources on large populations can overwhelm an investigation team that has not made adequate provision for periodic data reduction and analysis.

(6) It is desirable that all teams in different centres engaged in a collaborative study be equally reliable in the application of methods. No data should be entered in the central data file for procedures that have not been adequately standardized. Only centres that are able to collaborate in the necessary training and standardization operations should participate.

(7) Biological and statistical methods should be planned so as to facilitate the periodic review of techniques and data analysis and so as to make possible modification without the necessity for discarding previously obtained data.

### 3.2 Diagnosis

Biological studies of schizophrenia have produced a number of findings that subsequent investigation has failed to reproduce. One reason for this is that biological techniques have been applied to patients about whom there is inadequate diagnostic information. This report does not discuss such questions as the reality of the concept of "schizophrenia", the limits of "schizophrenia", or whether the condition represents one or many sub-syndromes. The essential problem is the adequate definition of the patient's condition, which can be done in a number of different ways. If it is possible to obtain an accurate, detailed description of the patient's behaviour and present state and of changes in these factors over a period of time, it would appear to be unnecessary to insist on obtaining rigid agreement among different investigators on a precise diagnostic classification. The main requirement is that collaborating investigators in different centres should establish empirically that, despite theoretical differences, they can use the same clinical measuring instruments and arrive at similar quantitative conclusions concerning aspects of a patient's present state, such as pressure of speech, agitation, presence of delusions, and hallucinatory activity. Given a sufficient number of reliable indices of this kind, correlations can be sought between individual clinical symptoms or syndromes and biological data. Agreement on a system of clinical diagnosis can then become a goal rather than a pre-condition for collaborative biochemical studies of schizophrenia.

An alternative approach to the problem of diagnosis rests on a different assumption — that the major problems in the diagnosis of schizophrenia are boundary problems : the limits within which it is agreed that a patient is schizophrenic and beyond which that he is not. (It is assumed that there is a group of schizophrenic patients who would be similarly diagnosed by psychiatrists the world over.) If this approach is used in selecting subjects for biological studies, a panel of psychiatrists representing different points of view and backgrounds is necessary, and patients should be selected only when this panel is unanimously agreed on the diagnosis. A similar criterion — unanimity concerning the absence of psychosis — can provide an effective control group. This approach has the disadvantages that criteria for inclusion and exclusion may not be clear and that certain possibly important sub-groups are excluded.

There are a number of approaches to research that do not require unanimity in diagnosis. If the clinical judgement of a diagnostic panel can be quantified — e.g., if the probability of schizophrenia were to be rated on a 7-point scale from 1 (definitely not schizophrenic) to 7 (definitely schizophrenic) — and if the other variables can also be quantified, correlational analysis can reveal significant relationships even though the patients represent a diagnostic continuum rather than a “ pure-culture ” group. There are many problems in which the presence of a heterogeneous group, with wide variation, renders the likelihood of finding relationships greater than it would be if an entirely homogeneous population were studied. However, there may be other situations in which the selection of patients showing great similarity of course and clinical status will maximize the possibility of finding relationships.

### 3.3 Research methods

#### *Statistical analysis of homogeneous groups*

The most commonly used method is the statistical comparison of groups of schizophrenics, and the comparison of such groups with control groups. This technique is appropriate for testing the characteristic features of a group that is homogeneous for any chosen variable, but it is unsuitable for a group that is heterogeneous. The choice of controls is as important as the choice of patients, since they must be matched for all controllable factors that can influence the feature under investigation. In addition to matching for age and sex, it is usually desirable to match for diet, exercise, drugs consumed, concurrent infections, stress, and “ hospitalization ”. Artefacts can be introduced by differences in diurnal rhythm, parasitic infection, previous drug therapy, and many other variables.

It should be emphasized that an apparently negative finding, in which the experimental group shows no statistically significant difference from the control group, is not necessarily without value. A larger standard deviation in the experimental group may be of interest in revealing a greater degree of individual variation. Results in which individual values differ from the mean by several standard deviations suggest that the group may be heterogeneous, and individuals showing a large variation of this kind from the mean should generally be followed up in a special study.

It is known that a number of different pathological conditions can lead to schizophrenia-like psychoses, and in the past a number of these conditions were included as sub-groups of the illness described as schizophrenia. A group of patients with schizophrenic illness may be homogeneous with respect to the clinical features that are used as diagnostic criteria, but it cannot be assumed that the underlying causal factors are the same in every case. In fact, some investigators believe that schizophrenia is not a homogeneous condition and that the definition of further sub-groups should be an important objective of further research. Among the sub-groups of this kind that have been proposed are a form of "rheumatic schizophrenia" and a "post-encephalitic schizophrenia". The recent finding of a relationship between the development of prepartum schizophrenia and the absence of male offspring has suggested the existence of a further sub-group of "puerperal schizophrenia" attributable to a specific interaction of a hormonal or allergic kind between mother and fetus. Schizophrenia-like psychoses are also known to be induced by certain forms of malnutrition and by various kinds of toxic state.

In some schizophrenic patients the psychosis appears to vary in severity, being sometimes more "aggravated" and sometimes more quiescent. The metabolic changes are again of interest, but their significance is not clear. The extent to which the hypothetical underlying "schizophrenic process" continues during the quiescent period is unknown, as are the biological correlates, if any, that may then be present.

Most patients undergo considerable changes in the course of time. The early acute schizophrenic presents a very different picture from the same patient in remission or from the patient who has suffered from a long-standing schizophrenic illness, and such changes are likely to be reflected metabolically. It would appear that for investigations intended to elucidate causal factors, every effort should be made to obtain patients at an early stage of their illness, before they have been subjected to drug therapy or other forms of treatment. Nevertheless, there are other constitutional features, such as those depending mainly on genetic factors, that are unlikely to be much changed by methods of treatment. For investigations of such features, the more readily available populations of chronic patients can be used.

*Statistical analysis of heterogeneous populations*

An alternate method to the comparison of homogeneous groups involves obtaining a large number of data from multi-disciplinary research by different investigators on the same group of subjects who represent a heterogeneous population ranging from the normal to the schizophrenic. After the data are pooled in a quantifiable form, correlational and multi-variate analysis techniques can be used to define significant relationships between any two variables or groups of related variables. In such a design the heterogeneity of the population, if quantifiable, increases rather than decreases the likelihood of obtaining significant correlations. This type of design is particularly appropriate for problems where it is difficult to select a major promising hypothesis, and where it is possible to pool data from large numbers of patients studied with common research techniques. This design is also easily applicable to longitudinal studies in which variations over time can become one of many variables to be considered.

**3.4 Longitudinal studies**

The interpretation of the results of a great number of biological studies in psychiatry has been hampered by the fact that the investigations have been limited to brief periods of time. In such cases it is impossible to know whether the findings are correlated to the underlying disease process or whether they are due mainly to irrelevant environmental factors prevailing at the time of the investigation. For this reason longitudinal studies are urgently needed as a supplementary research approach. The investigations should be repeated over a long period of time and, should the symptomatology be of a changing nature, during each different type of stage. If possible, the investigations should also be carried out under different environmental conditions — e.g., during hospitalization as well as after discharge — and under different therapeutic circumstances. A classical example of a thorough longitudinal study is the investigation of so-called “periodic catatonia”, in which patients were intensively followed for many years. In this way it might be possible to discover which biological changes are related (*a*) to the disorder itself, (*b*) to different stages of the disorder, and (*c*) to environmental and therapeutic factors. Manic-depressive psychosis is a disorder in which such distinctions might well become possible.

In other disorders, such as schizophrenia, more complicated interaction of factors may make the interpretation of even thorough longitudinal studies difficult. If, for example, schizophrenia should be partly caused by a metabolic disorder, this might be active only intermittently. During periods of metabolic crisis direct manifestations in the form of halluci-

nations might arise. This might give rise to secondary psychological "chain reactions", continuing for a long time after the initial somatic crisis was over. The secondary, psychologically determined, mental symptoms might well be even more conspicuous than the initial metabolically determined symptoms, although the initial biochemical changes might no longer be measurable. The possibility of such paradoxical incidents must always be borne in mind when seemingly meaningless sequences of results are to be interpreted.

The statistical evaluation of results obtained in longitudinal studies can be performed in two different ways. If the number of observations of individual patients is sufficiently large, the correlation between symptomatology and biological changes can be calculated. If the number of patients is large enough, the observations can be pooled and similar correlations can be sought.

### **3.5 High-risk and other groups**

In addition to matched homogeneous groups and heterogeneous groups, described above, other subject groups of special interest can be defined — e.g., subjects at high risk of the development of schizophrenia or other mental disorders. Such a group can be selected in different ways. One approach is based on selecting the children of schizophrenic parents or the nonpsychotic co-twins of monozygotic twins with schizophrenia. Nonbiological approaches would include the use of epidemiological studies, particularly socio-economic indices, or the presence of childhood maladjustment for identifying a high-risk population.

Initial studies along these lines are under way, and appear to show that this is a promising research approach, but in view of the time that may elapse before the development of a psychosis, such studies must be carried out over a long period of time.

### **3.6 International Pilot Study of Schizophrenia**

In all the studies that have been mentioned in this report, certain problems seem to be relevant to the reported results. These include the description and classification of symptomatology, the stage of the illness at which the patient is investigated, and the conditions under which he is living and the treatment he is being given. It is seldom clear when different findings are brought about simply by different research conditions. It is no longer acceptable merely to designate a group of patients as "schizophrenic". Future studies, if they are to be taken seriously, must indicate that a minimum of relevant information has been obtained and used in selecting cases and interpreting results.

The International Pilot Study of Schizophrenia (IPSS) is a multi-centre project that is seeking a solution to such problems of clinical definition. The following description of the project is given as an example of one way in which clinical variability can be reduced.

The IPSS is the first of a series of research projects organized by WHO on the epidemiology of mental disorders. Its main purposes are as follows:

- (1) to develop reliable techniques for describing the psychiatric condition of patients suffering from the "functional" psychoses, particularly schizophrenia, in 9 countries of widely differing social and cultural characteristics;
- (2) to train psychiatrists and other workers in the use of these techniques and in participation in a major international research project;
- (3) to discover whether certain central sub-syndromes of schizophrenia occur in all 9 areas; and
- (4) to compare the 2-year course and outcome of 9 groups of early schizophrenic patients.

The 9 centres taking part are situated in Aarhus, Denmark; Agra, India; Cali, Colombia; Ibadan, Nigeria; London, England; Moscow, USSR; Prague, Czechoslovakia; Taipei, Taiwan (China); and Washington, D.C., USA.

#### *Schedules and forms*

A standardized form of clinical examination for eliciting and describing "present state" symptomatology, which had been developed and found reliable in previous studies, was adapted for use in the IPSS. All psychiatrists in the 9 centres received some training in its use, and it was found that translations of the examination schedule into different languages were usable. The schedule contains about 320 items, each of which can be coded numerically. The items are then combined in various ways to give summary indices of the patient's "present mental state".

Another schedule covers the course, symptomatology, and treatment of the present and previous episodes of illness, and information concerning personality, use of drugs and alcohol, and other clinical data. There are also forms for the collection of social data, for recording physical abnormalities, and for overall diagnostic assessment. Follow-up schedules covering clinical and social data have also been produced.

#### *Training and reliability*

The psychiatrists were trained in the use of the "present state" examination by visiting the centre where it had been developed, by rating

patients on the basis of video-tape-recordings of standard examinations, by visiting each other's centres, by meeting together regularly, and by simultaneous and consecutive examinations conducted by different members of the same team. After an initial phase, during which experience was obtained in all the techniques to be used, reliability was found to be reasonably high and the main project was started. Simultaneous ratings by two psychiatrists continue to be made at regular intervals on a sample of patients in order to check that reliability is being maintained.

#### *Selection of patients*

Patients were selected by a screening procedure in which all those who satisfied certain criteria concerning age, residence, and absence of organic conditions and who showed certain symptoms at the time of admission (e.g., excitement, delusions, hallucinations, and severe withdrawal) were interviewed, together with an informant where necessary. The examiner's diagnosis was not a condition of selection. Approximately 100 schizophrenic patients and 25 patients with other "functional" psychoses were examined in each centre, together with a number of patients without psychotic symptoms, making over 1200 in all.

#### *Data collection and analysis*

As each patient was examined, the set of schedules was sent to WHO, where the data were stored on magnetic tape. So far the main analyses have been concerned with reliability and with the classification of clinical condition (using "clinical" methods, numerical taxonomy, and factor analysis). It is already clear that "typical" schizophrenic patients are to be found in all 9 areas.

#### *Follow-up study*

Patients in the study are being interviewed 1 year after admission and will again be seen 2 years from the date of first examination, beginning in April 1970.

#### *Diagnostic procedures*

Variation arising from the clinician's diagnostic preconceptions and from observer error during the interview is minimized by selecting patients on the basis of certain behavioural characteristics and symptoms rather than by diagnosis, followed by the use of a standardized form of examination.

The numerical ratings of symptoms and signs are then analysed centrally and can be summarized and classified in various ways. A promising technique is to combine the ratings of individual items into fewer clinically similar groups and then to combine these groups into syndromes that seem of particular importance for the diagnosis. For example, a "nuclear schizophrenia" syndrome is composed of item-groups representing voices talking about the patient, voices commenting on the patient's actions, delusions of control, thought echo, thought broadcasting, and allied symptoms. Item-groups and syndromes can then be handled statistically in various ways, or they can be presented as profiles for various sub-groups (e.g., according to age, sex, social or cultural grouping, and length of illness).

A standardized way of combining the syndromes of special diagnostic importance, making decisions according to clinical rules but incorporating these into a computer programme so that the procedure is carried out in identical fashion for all cases, has been developed and applied to the examination schedules of the first 750 patients. The resulting classification shows that a substantial group of patients showing the symptoms comprising the "nuclear schizophrenia" syndrome exists in each of the 9 areas investigated. In all centres there are also patients showing typical examples of other schizophrenic sub-groups, delusional depression, mania, and other conditions. In due course, clinical data concerning previous episodes and possible etiology will also be used for this procedure, so that the process of diagnosis will be even more closely mimicked; however, the methods will still be applied in exactly the same way to each set of ratings.

Other classification techniques being investigated include numerical taxonomy and factor analysis.

In addition, each investigator, acting in his role as clinician, makes a diagnostic assessment after he has completed the examination of the patient. This diagnosis is, of course, affected by the fact that the clinical data-gathering has been standardized (and may therefore be more complete than usual) and by the extensive contacts investigators from the 9 centres have had with each other. The diagnosis is made in terms of the nosological system ordinarily used by each investigator, which varies considerably from one centre to another. Comparison of this set of diagnoses with those reached using the computer programme (which is applied in exactly the same way for all centres) will help to throw light on differences between the various psychiatric nosologies.

It is thus possible to retain the advantages of both individual and standardized diagnostic procedures in the IPSS.

#### 4. TRAINING FOR RESEARCH

Two principal types of training are of interest in connexion with co-operative research.

(1) Training may be necessary to improve co-ordination of the work of experienced scientists already working on their chosen fields. For example, biochemists and neurophysiologists will need no training in theories and methods connected with their own fields. However, it is uncommon to find psychiatrists who are acquainted with these fields, who are able to make precise observations of symptoms and course independently of their diagnostic preconceptions, and who can conduct scientific projects in collaboration with specialists in other fields. It would be a major contribution to research if teams of biochemists, neurophysiologists, and clinicians could be brought together to facilitate the detailed planning of international collaborative studies, to provide statistical assistance, to help with the administrative problems that inevitably arise in collecting and handling large numbers of data, to co-ordinate efforts, and to standardize techniques. This process is one of mutual education and no international study can be undertaken without it. It cannot be too strongly emphasized that this form of training is essential to large-scale collaborative work.

(2) If a number of centres were to bring together such interdisciplinary teams, an opportunity for a second type of training would be created. In many parts of the world (e.g., in some of the centres collaborating in the IPSS), there are university departments of psychiatry with developing scientific programmes. The scientists and technicians in such departments would require further specific training to enable them to undertake many of the studies recommended in this report. Ideally, such training would be obtained in one of the centres mentioned above, which would also provide subsequent supervision to ensure the maintenance of high standards.

At first, the investigations carried out in the developing centres could be relatively simple (e.g., ECG, plethysmograph, polygraphic registration of EMG, the collection of body fluids for examination elsewhere, and simple biochemical estimations), the main purpose being to train the interdisciplinary teams. The training of psychiatrists in standardized techniques of clinical recording, selection of patients, and experimental design would also be extremely important, and this has already begun in the IPSS centres.

As the teams became more experienced, more complex investigations could be introduced and the teams would themselves be able to take

on a teaching function in their own university departments. It would be reasonable to balance the research and training aspects in the early part of such a project, in the expectation that well-trained research teams would ultimately be able to form their own hypotheses and to design and conduct scientific projects to test them, thus adding to the general fund of scientific knowledge of mental disorders.

## 5. RECOMMENDATIONS FOR COLLABORATIVE STUDIES

### 5.1 General recommendations

(1) In view of the need for studies of the type outlined in section 2, and the demonstrated feasibility of collaborative international studies of schizophrenia in the clinical area, as shown by the IPSS, the Group strongly recommends that biological aspects of schizophrenia be investigated in an international multidisciplinary programme carried out in a number of different centres. Such a programme would be of great help in improving the treatment of schizophrenia and in clarifying its pathogenic mechanisms.

(2) Some of the genetic, biochemical, neurophysiological, and psychopharmacological studies recommended below would be suitable for inclusion in studies such as the IPSS, and the Group suggest that these be brought to the attention of the participating centres.

(3) The success of international collaborative studies depends on the development and coordination of teams of specialists and clinicians, and the suggestions in section 4 concerning the training of such teams are strongly recommended.

(4) Should it be necessary to arrange international meetings or conferences for training purposes, it is recommended that, where feasible, some of these be held in the developing countries.

(5) Future scientific work and reports should be continually evaluated for their relevance to the specific recommendations made in this report. Similarly, there should be continuing efforts to improve techniques and the technical abilities of participating investigators.

### 5.2 Biological studies of schizophrenia

#### *Genetic studies*

In studies similar to the IPSS it would be of great importance to include, from the very beginning, thorough genetically oriented family studies of the distribution of psychopathology. In this way unique

material could be collected, with sharply and uniformly defined index cases, derived from quite different cultures. Other such collaborative genetic investigations might include (a) study of the "high-risk" group of children of schizophrenic women included in studies such as the IPSS, and (b) an attempt to verify (or disprove) the recent findings on the correlation between schizophrenia arising during pregnancies and the sex of the children resulting from such pregnancies.

More general recommendations for genetic studies related to schizophrenia include the following :

(1) Studies of the incidence of mental disorders in whole population groups in different cultures should be undertaken, with special attention to isolated communities in which recessive abnormalities are likely to be frequent.

(2) Research on the distribution of chromosomal abnormalities within the general population would provide a sound basis for interpreting the occurrence of mental deviations in individuals with chromosomal aberrations. Biochemical correlates of such aberrations should be searched for.

(3) Although systematic registration of twins has been organized in a few countries, most publications on psychiatric twin investigations are still based on samples of uncertain representativeness. A WHO international survey of twin registers and studies was made in 1966 to permit transcultural comparisons of twin studies. A special search should be made for monozygotic twins who have been raised separately.

(4) Studies of adopted children and of their biological and adoptive families should be especially encouraged.

(5) Genealogical studies of the classical type will probably not yield definitive results until distinctive physiological and biochemical findings have been made in individuals with mental abnormalities.

(6) Too few genetic studies, combined with long-term follow-up investigations, of mental disorders of childhood have been carried out, and further studies should be encouraged.

(7) Teams conducting genetic studies should comprise specialists from a number of fields, thus making a multidisciplinary approach possible.

(8) The 1965 WHO Scientific Group on Research on Genetics in Psychiatry noted that "WHO projects on standardization of psychiatric diagnosis, classification and statistics" then in progress were "highly relevant to research in its own field", and strongly recommended that this work be continued. The Group also pointed out that "improvement of the techniques employed in establishing . . . national registers of psy-

chiatric cases, and a wider recognition of their value could greatly facilitate the collection of source material for psychiatric genetic studies".<sup>1</sup> The present Group strongly endorses these recommendations, and looks forward to the completion of the WHO projects mentioned, which will provide an indispensable basis for transcultural studies of an epidemiological and genetic nature.

#### *Biochemical studies*

*Simple procedures.* The following relatively simple procedures should be considered for use in studies of groups of mental patients.

(1) *Urine.* The association of metabolic disorders with mental retardation is now well established, but the extent to which they occur in populations of patients with schizophrenic illness is unknown. It would be of interest to know whether such disorders occur more frequently in schizophrenics than in the general population. This could be determined by applying a routine chromatographic test for aminoacidurias, including homocystinuria, for which a special relationship to schizophrenia has been reported. Tests for amphetamine derivatives in the urine would be useful in urban areas where amphetamine abuse is common, in view of the occurrence of schizophrenia-like mental disturbance attributable to amphetamines. For similar reasons, tests for barbiturates, bromides, and other drugs might also be used. Porphyrinuria, which is often associated with mental symptoms, could also be detected by a relatively simple test.

(2) *Blood.* The erythrocyte sedimentation rate gives a valuable indication of chronic infective conditions, such as a septic focus, and it should be applied routinely whenever possible. The fasting blood glucose level is sometimes affected by phenothiazine treatment and in various forms of spontaneous hypoglycemia. Plasma protein levels can give an indication of protein malnutrition, which can affect the mental condition. The level of protein-bound iodine in the plasma is of special interest as an indication of thyroid disease and in areas where there is iodine deficiency. The eosinophil count is relevant in areas where heavy infestation with parasites is prevalent; positive findings should be followed-up by testing the stool for ova. Each of the conditions listed above can significantly affect — and occasionally initiate — a psychopathological state.

(3) *Cerebrospinal fluid.* The measurement of proteins would help to clarify reports from several centres of raised levels in a significant proportion of patients diagnosed as suffering from schizophrenia. In some

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<sup>1</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1966, No. 346, p. 19.

cases this finding has been attributed to a form of subacute viral encephalitis, which may be of etiological significance in some subgroups of schizophrenia.

*Specialized procedures.* The following procedures are of more limited applicability. The estimation of urinary or plasma steroids and monoamine metabolites, although demanding in time and equipment, could be considered in suitably equipped centres, since the levels of these substances are of interest in relation to gonadal function arousal levels, and the mechanisms for coping with stress. Tryptophan tolerance and blood pyruvate tests can be used to indicate deficiency of B-group vitamins.

At present there are no biochemical factors known to be associated specifically with schizophrenic illness. Nevertheless the search for biochemical abnormalities continues. Studies such as those related to biochemical hypotheses of schizophrenia described in section 2.2 require special training and equipment that are available in relatively few centres at present. It is possible that investigations now in progress may suggest new lines of research and further investigations that can be carried out on a wider scale.

#### *Neurophysiological and behavioural studies*

A number of the lines of enquiry mentioned in section 2.3 could be investigated using relatively simple techniques, although specialized training would be necessary.

It would be useful to undertake studies aimed at clarifying (1) whether schizophrenic patients are in a state of abnormal "arousal" compared with normal persons or patients suffering from other conditions (e.g., anxiety, excitement, or stupor); (2) whether abnormal states of "arousal" are associated with patterns of schizophrenic symptomatology; (3) whether such abnormal states change over a period of time (e.g., in chronic schizophrenia compared with the acute phase); (4) the influence of drugs on degree of "arousal"; and (5) the relation between "arousal" level and the presence of certain substances thought to be significant in schizophrenia. Studies of the other problems noted in section 2.3 would require rather more complicated equipment—e.g., central measurements of arousal such as two-flash or two-click thresholds, evoked potentials, quantitative analysis using a digital computer, studies of deprivation of the paradoxical stage of sleep, conditioned reflex studies, and investigations using telemetry. Such techniques would not be suitable for use in a study such as the IPSS. However, peripheral measurements would be quite feasible.

It would be profitable to undertake investigations of the electroencephalogram in untreated patients. Such studies might help to clarify the problem of whether there are abnormalities of temporal lobe function,

and whether the pattern of the waking EEG is related to the outcome of the illness. In a large-scale study in many parts of the world it might be possible to collect a sizeable group of untreated patients.

Investigations should be undertaken of the possibility that patients with psychomotor retardation who show a diminished motor response to a stimulus, but an increased autonomic response, may have a relatively good prognosis.

All the studies outlined above could be conducted with fairly simple laboratory equipment, including devices for the polygraphic recording of the EEG, EMG, ECG, heart rate, skin conductance, and plethysmogram. The level, size, and latency of response to stimuli and habituation could all be measured.

#### *Psychopharmacological studies*

(1) Methods for monitoring the intake, plasma levels, saliva levels, and urinary excretion of drugs should be introduced. Determinations should be made at regular intervals so as to detect relationships between dosage, metabolism, and excretion. Special attention should be given to individual differences, particularly in persons in whom there is therapeutic failure.

(2) The selective therapeutic effects of neuroleptic compounds should be investigated. Of the 3 types of phenothiazine, the aliphatic and piperidine groups have predominantly sedative actions, whereas the piperazine group is more potent weight for weight and is said to have greater stimulating action. Consequently, it is customary to use the aliphatic and piperidine derivatives for schizophrenics who are overactive or disturbed in behaviour or who exhibit more agitation or emotional distress. It is believed that the condition of schizophrenics who are inert and apathetic and who lack drive and energy may be worsened by the aliphatic and piperidine phenothiazines, and for such patients the piperazine derivatives are usually preferred. Many physicians also believe the piperazine phenothiazines are especially effective in paranoid forms of schizophrenia. However, a scientific basis for these widely held beliefs has never been demonstrated. It is therefore recommended that a study of the differential effects of the aliphatic, piperidine, and piperazine drugs at varying dosage levels be included in the IPSS. Such a study could be expected to provide information on the advantages and limitations of these phenothiazines for treating different forms of schizophrenia.

(3) Studies should be made of (a) the general effectiveness of drug treatment and (b) the effect of termination after prolonged treatment. The IPSS, with its standardized recording of symptoms and envisaged standardized follow-up, offers a unique opportunity for a psychopharmacological study. It would necessitate detailed recording of the pres-

cribed and the obtained treatment on a record sheet included in the follow-up psychiatric history. The analysis of pharmacological therapy within the IPSS could cover:

- (a) the relation between the prescribed treatment and types of symptom, psychiatric history, social functioning of the patient, and diagnostic assessment of the patient;
- (b) the effectiveness of the adopted treatment schedules, as determined by changes in the symptoms and social functioning of the patient; and
- (c) studies of patients on prolonged treatment. Two groups of subjects are suggested for such studies : chronic schizophrenic patients in hospital who have been on psychopharmacological treatment for at least 2 years and out-patients who have been on psychopharmacological treatment for at least 1 year. Patients from whom drugs have been withdrawn and replaced by a placebo could be compared with those undergoing treatment in terms of grade of improvement, length of remission, rate and time of relapses, changes in social functioning, etc. Such ratings should be made by independent observers who are not involved in the treatment procedure, and appropriate controls should be used.

#### *Constitutional studies*

Measurements of stature, transverse chest diameter, biacromial diameter, and bicristal diameter could easily be included in a study such as the IPSS.

### **5.3 Biological studies of other mental disorders**

#### *Affective disorders*

The manic depressive group of psychoses could afford ample opportunity for international collaboration in biological study and research. Standardization of the criteria for assessing the affective psychoses, so as to differentiate them from other psychoses, particular the schizo-affective, toxic, reactive, and organic psychoses, is indispensable for such work.

The selection of affective disorders as the second major form of mental illness for international study is based on the following considerations: (1) the high frequency of depression in the general population, and its consequent public health implications; (2) the availability of more biochemical information on affective states than on other psychopathological phenomena; and (3) the fact that there appear to be substantial

differences in the incidence of these disorders in different countries, whereas this is not true of schizophrenia. Study of these problems might help to clarify the interaction of social, genetic, and biochemical factors in the pathogenesis of both groups of psychoses.

Biochemical investigation could concentrate on monoamine metabolism by means of longitudinal studies of blood and urine levels of serotonin and catecholamine derivatives at different phases of the illness — e.g., the manic, hypomanic, and depressive phases. Research in other areas, such as the mechanism of action of lithium salts and their prophylactic use, should be encouraged.

Neurophysiological studies to determine the anxiety level and sedation threshold may prove of great value in clinical diagnosis and in prognosis. It would be of great value to carry out similar investigations of schizo-affective and other psychotic disorders and to compare the results. The methods recommended for genetic studies of schizophrenia would also be applicable in such investigations.

#### *Mental retardation*

About 0.4 % of children can be classified as moderately, severely, or profoundly retarded. Including those in special schools and those who are mildly retarded, 1-3 % of the population may be regarded as mentally retarded. Owing to advances in medical and social care, these handicapped persons now have a higher expectancy of life than formerly, so their numbers can be expected to increase. Advances in research in the past 10 years have thrown light on some of the causes of and possibilities for preventing mental retardation, as well as on means of early case-finding and stimulation that may prevent deterioration. Relevant research should be periodically reviewed and co-ordinated international research should be encouraged. The Group make the following specific recommendations :

(1) There is a need for international standardization of tests for early case-finding, such as biochemical screening (e.g., tests for phenylketonuria), chromosome analysis, and somatic indices of genetic defects.

(2) Standardized tests for defined cultures or populations should be developed — e.g., (a) diagnostic tests of the level of retardation that are applicable to populations of pre-school and school age (i.e., psychometric, including nonverbal, tests), and (b) psychological tests that would permit the early detection of developmental retardation (i.e., tests of psychomotor development and of cognitive and verbal functions).

(3) Electroencephalographic investigations should be undertaken of disturbances in electrical cerebral maturation.

(4) Methods for the central examination of specimens and results should be established. For example, specimens from newborn infants could be sent to an international centre for chromosome and biochemical analysis.

(5) International co-operation in specific research projects — e.g., in areas where there is a scarcity of suitable cases for investigation — should be encouraged. An example noted by a 1965 WHO Scientific Group on Research on Genetics in Psychiatry is “research connected with the frequency of chromosome abnormalities, the relationship between these abnormalities and . . . mental retardation, and the search for their biochemical correlates”.<sup>1</sup> A 1968 WHO Scientific Group on the Biochemistry of Mental Disorders pointed out the need for “research . . . on the feasibility of, and methods for, mass screening of populations” for inborn errors of metabolism and “on the reversibility of the mental effects of different forms of malnutrition”,<sup>2</sup> and international co-operation in such research would be advantageous. The use of operant conditioning techniques for training the moderately, severely, and profoundly retarded has given promising initial results and should be encouraged on an international scale.<sup>3</sup> International studies of psychopathology in relation to mental retardation would be of interest.

(6) In future international research on mental retardation, the epidemiological and social aspects should be considered together with the biological aspects.

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<sup>1</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1966, No. 346, p. 19.

<sup>2</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1969, No. 427, p. 36.

<sup>3</sup> See *Wld Hlth Org. techn. Rep. Ser.*, 1968, No. 392, p. 51, and 1968, No. 381, p. 6.

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